UK National Screening Committee

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UK National Screening Committee

Screening for Amino Acid Metabolism Disorders Disease

19 March 2015

Aim

1. This document provides background on the item addressing newborn screening for three Amino acid metabolism disorders; Tyrosinaemia Type 1, Argininosuccinic acidaemia and Citrullinaemia

Current policy

2. The current UKNSC policy recommends that newborn screening for the above amino acid metabolism disorders should not be included in the newborn bloodspot screening programme.

3. The last recommendations additionally included screening for Homocystinuria and Maple Syrup Urine Disease (MSUD), which have subsequently been added to the newborn blood spot programme following an evaluation of expanded screening.

4. The current recommendation for all three conditions is based on a HTA study of clinical effectiveness and cost effectiveness (Pandor A et al., Clinical effectiveness and cost effectiveness of neonatal screening for inborn errors of metabolism using tandem mass spectrometry: a systematic review, March 2004).

Current review

5. Bazian were asked to assess the literature published since the previous review, taking in literature from January 2001 to August 2012. The resulting document is attached.

6. The key findings of the review have been summarised for each condition:

Tyrosinaemia

Newborn screening for tyrosinaemia type I could be considered but there needs to be further study into:

- the epidemiology of this condition in Europe
- studies determining the feasibility of screening for tyrosinaemia type I in the UK and
- investigation of the neurocognitive defects observed in some patients treated with NTBC.
- the proportion of tyrosinaemia cases are currently detected through PKU screening

Citrullinaemia

- there are uncertainties over the epidemiology of this condition in the UK
- concerns over the reliability of the test and
- while evidence suggest there may be some value in the early diagnosis and treatment of patients with forms of the condition that develop symptoms later, there were uncertainties over the timing of acute clinical presentation of cases in relation to screening test delivery

Argininosuccinate lyase deficiency

- uncertainties over the epidemiology of this condition in the UK
- concerns over the timing of the test in relation to the presentation of the acute form of the condition
- there could be value in the early diagnosis and treatment of patients with forms of the condition that develop symptoms later
- However, there are uncertainties on whether the treatment for patients with later-onset forms of the condition improves outcomes in terms of preventing the development of neurocognitive deficiencies and liver disease, even if metabolic decompensations are avoided.

Consultation

7. A three month consultation was hosted on the UK NSC website and additionally promoted through the PHE Screening Twitter platform. The following organisations were contacted directly: British Inherited Metabolic Disease Group ,Children Living with Inherited Metabolic Diseases (CLIMB), Clinical Genetics Society, Genetic Alliance UK, Institute of Child Health, Rare Disease UK, Royal College of General Practitioners, Royal College of Midwives, Royal College of Paediatrics and Child Health, Save Babies Through Screening Foundation UK, UK Newborn Screening Laboratories Network, NHS England Specialised Commissioning and the Department of Health Rare Diseases

8. Responses were received from CLIMB, the British Inborn Metabolic Diseases Group, Genetic Alliance UK, Save Babies Through Screening Foundation UK (SBUK)/ the Patient Advocates for Newborn Screening Group (PANS) and the Royal College for Paediatrics and Child Health (RCPCH).

9. Across the three reviews the following themes were highlighted, that screening would help identify research cohorts to address the gaps in the evidence for screening, that reduction of the diagnostic odyssey should be considered as a reason to introduce screening, that screening to inform reproductive choice should, similarly, be considered a reason to introduce a screening programme. A range of mechanisms to address gaps in the evidence relating to the epidemiology, natural history and treatment outcomes were suggested including work to develop a European disease register for rare diseases, pilot programmes and implementation of screening programmes.

10. Consultation responses for Tyrosinaemia Type 1

    - Many respondents commented that the review of Tyrosinaemia Type 1 needed to be reconsidered. This was because: -

        - it was reported that a workshop of users and clinical experts felt that Tyrosinaemia type 1 was the most likely candidate as an addition to the newborn bloodspot screening programme

- several studies from 2012 onwards, which were not included in the review, increased understanding of the: incidence, short and long term outcomes (early treatment with nitisinone leading to reduced need for longer term treatment for problems with the liver) and consensus management guidelines had been published. The RCPCH response (no.5) provides a reference list of suggested studies for inclusion
- a suggestion that the primary screening marker for Tyrosinaemia Type 1 was outdated and that Succinyl acetone is currently the universal screening marker of choice and that studies using this marker should be the focus of the review
- an updated review focusing on these issues was requested prior to a final recommendation being made on this condition.

- The comments from clinicians, voluntary organisations and their members were all supportive of newborn screening for Tyrosinaemia Type 1.

- Several responses acknowledged that further studies were required into the cause of the apparent neuropsychological problems and that this had not been studied in a screen detected population.

- GAUK suggested a meeting with the UK NSC to discuss how the gaps in the evidence for all amino acid metabolism disorders could be closed before the UK NSC next reviewed screening for the conditions. Additionally, PANS also offered a meeting to discuss any inconsistencies in the discussion of Tyrosinaemia Type 1.

- It was suggested that screening enables increased vigilance, and much earlier support and treatment to ensure patients are able to reach their maximum potential.

11. Consultation responses for Citrullinaemia and Argininosuccinate lyase deficiency

- There was acknowledgement of gaps in literature, particularly regarding the natural history of the condition, the optimal utility of current dietary interventions and the timing of the test.

- The BIMDG believed the UK NSC should promote the use of a pan-nation prospective register/ reporting system by metabolic labs and clinical services of metabolic conditions to enable greater, more applicable information on UK incidence/prevalence.

- A Pilot was advocated in several responses to establish: cost-effectiveness, distribution of markers in UK population, treatment efficacy.

- The point was made that the UK newborn blood spot programme already includes conditions that may present prior to the result of a newborn screening sample being known, eg MCADD, MSUD, Isovaleric Acidaemia. However, it is acknowledged in these instances that this can still result in earlier diagnosis and treatment to improve outcome.

- It was suggested that 2nd tier testing could be adopted to improve test performance and screen for other conditions.

- In terms of treatment, it was noted that current screening programmes (eg cycstic fibrosis and sickle cell) do not fully provide effective intervention and the adoption of screening for Citrullinaemia and ASA will lead to advances in treatment.

- A review on the timing of the current UK newborn blood spot programme was suggested in relation to identifying early-onset forms of Citrullinaemia and ASA.

- Studies point to parental approval of screening on the balance of benefit/ harms and it is unlikely that the benefit/harm balance is significantly different from the conditions included in the national programme from January 2015.

- While some patients groups consulted its member's views in relation to these consultations, GAUK expressed their view that the qualitative evidence from the patient voice was not sufficiently incorporated into the UK NSC decision making process.

The full consultation responses can be found in Annexe A.

FMCH March meeting

12. The FMCH approved the following recommendation at its March meeting:

Screening for citrullinaemia and Argininosuccinate lyase deficiency is not recommended

Screening for tyrosinaemia is not currently recommended but this has been identified as a potential candidate for addition to the programme. Further work is required to identify and explore key issues, including the following, to assess this further:

- Current proportion of cases of tyrosinaemia type 1 detected via PKU screening
- A review of studies reporting on the performance of succinyl acetone as the primary marker
- More information on long term outcomes from NTBC in screen detected populations
- A further review of Nitisinone for reduction in cases of liver failure
- Consideration of the options for exploring the feasibility of screening in the UK should the above work confirm that tyrosinaemia is a good candidate for screening

Action

The UKNSC is asked to approve the above recommendation and in brief is as follows;

Screening for citrullinaemia and Argininosuccinate lyase deficiency is not recommended

Screening for tyrosinaemia is not currently recommended but this has been identified as a potential candidate for addition to the programme with further work required.

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UK National Screening Committee
Screening for Amino Acid Metabolism Disorders - an evidence review

Consultation comments

1.

Name:	Mrs Helen Morris	**Email address:**	**XXXX XXXX**
Organisation (if appropriate):	CLIMB – The National Information Centre for Metabolic Diseases		
Role:	**Information Research Officer**		

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.*
Response in relation to Tyrosinaemia type 1		
Page 38	Criterion 15	Further studies are required into the cause of the neuropsychological problems which are apparent. Learning difficulties are seen in up to 35% of those treated with NTBC, based on a West Midlands study. However, we agree with specialists in this condition that screening will enable increased vigilance, and much earlier support and required therapies to ensure patients are able to reach their

		maximum potential. Notably those with early diagnosis and treatment most often do well in mainstream school with some degree of support.
Page 40	Criterion 16	From the recent paper from PJ McKiernan and colleagues, It would appear that Newborn Screening for Tyrosinaemia type 1 and the subsequent early diagnosis and management of the condition with NTBC significantly, or totally, eradicates any need for treatments for liver disease in the patient and reduces the risk of the patient developing hepatocellular carcinoma. The cost of these treatments alone is significantly high along with other symptomatic management, therapies and service provisions.
Page 44	Criterion 21	Climb is currently represented on the Inherited Metabolic Disease (IMD) Screening Advisory Board. Climb takes on board all views from families and professionals and where the data is factually convincing towards the addition of specific conditions to the current Newborn Screening Programme, we will clearly and proactively support their recommendations. In this case, we have gathered experiences and comments from families, reviewed updated papers, and acknowledged the emphatic backing from specialists in this condition. Families supported by Climb have clearly stated that if Newborn Screening for Tyrosinaemia type 1 was available when their children were born, liver failure could have been prevented. This is significant in itself but they also have also shared their experiences of unwittingly feeding their babies protein rich food which resulted in serious irreversible damage, the months of hospitalisation due to liver failure, serious illness whilst awaiting diagnosis and all of the patients and their families' anguish and anxieties that come with this. We feel that the addition of Tyrosinaemia type 1 would be highly beneficial and

		we wholeheartedly recommend the addition of this condition to the current newborn screening programme.

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Screening for Amino Acid Metabolism Disorders - an evidence review

Consultation comments

2.

Name:	**Mike Champion**	**Email address:**	**XXXX XXXX**
Organisation (if appropriate):	**On behalf of the BIMDG**		
Role:	**Consultant in Paediatric Inherited Metabolic Disease**		
Do you consent to your name being published on the UK NSC website alongside your response? **Yes X No ☐**			

Section and / or page number	**Text or issue to which comments relate**	**Comment** *Please use a new row for each comment and add extra rows as required.*
Response in relation to Citrullinaemia/ Argininosuccinate lyase deficiency		
2. The epidemiology and natural history of the condition, including development from latent to declared disease,	Citrullinaemia: Criterion 2 partly met. No studies were identified that reported the incidence or prevalence of citrullinaemia in the UK Argininosuccinate lyase deficiency: Criterion 2 partly	This is a common observation when reviewing metabolic conditions for consideration for newborn screening. There is a finite number of such conditions that might be considered now and in the near future when looking at what is screened for around the world, especially considering Europe, America and Australia). A

should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage P24	met. No studies were identified that reported the incidence or prevalence of argininosuccinate lyase deficiency in the UK	prospective register or reporting system by metabolic labs and clinical services of this group of 30 or so conditions would allow easy resolution of this perennial concern that other country incidence/prevalence data may differ significantly from the UK and therefore would be unreliable to apply to UK decision making. The UKNSC should promote commissioning of such a programme within the NHS to inform future screening decisions.
2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage P24	Citrullinaemia: Criterion 2 partly met. Several studies were identified that reported that infants can develop symptoms before the results of a newborn blood spot screen are available. However, there still could be value in the early diagnosis and treatment of patients with more mild forms of the condition. Argininosuccinate lyase deficiency: Criterion 2 partly met. The duration of the latent asymptomatic period varies between patients in this disorder as well, and symptoms can develop within the first days of life. Although many of the infants identified with argininosuccinate lyase deficiency in newborn screening programs were asymptomatic at the time of diagnosis, one study was identified that reported that an infant developed symptoms (on day four of life) before the results of a newborn blood spot screen were available. However, there still could be value in the early diagnosis and	The UK newborn screening programme already includes conditions that may present prior to the result of a newborn screening sample being known, eg MCADD, MSUD, Isovaleric Acidaemia. However, it is acknowledged that this can still result in earlier diagnosis and treatment to improve outcome, as presentations can be non-specific and easily mistaken for sepsis. We also know from the example of MCADD that clinical diagnoses will be missed (Porfazam Lancet. 2001 29;358:1063-4) and therefore prenatal testing or prospective management of the infant will not be available for those families, risking further morbidity and mortality.

	treatment of patients with more mild forms of the condition.	
5. There should be a simple, safe, precise and validated screening test P28	Criterion 5 not met for citrullinaemia. Several studies reported high false positive rates when screening for citrullinaemia using citrulline levels as a marker, or the arrival of screening results after symptomatic presentation.	False positive results were not reported from the SW Germany study (Lindner et al 2011) which had a 3 way cut off, citrulline, ornithine:citrulline and citrulline arginine ratios demonstrating the test can be 'precise'. Considering the economic argument for group of disorder testing, 2nd level testing for orotic acid on the same blood spot could further secure sensitivity and specificity (Held et al Clin Chim Acta. 2014;436:149-54, Janzen et al Clin Chim Acta. 2014;430:28-32 and is a key metabolite in urea cycle defects distal to carbamyl phosphate (CPS) deficiency.
6.The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed P43	Criterion 6 uncertain. Although an international collaboration has suggested cut-offs for both citrulline and argininosuccinic acid, individual studies have used different cut-offs to screen for citrullinaemia and argininosuccinate lyase deficiency. In addition, the cut-offs proposed by the international collaboration were based on screening for a panel of disorders, which is an issue as citrulline is elevated in a number of conditions. Levels of argininosuccinic acid, a marker specific for argininosuccinate lyase deficiency, were found to vary between sites.	Programmes have been screening for these conditions since the turn of the century in other countries. International collaboration continues to further define cut-offs and improve precision/reliability and is integral to screening programmes. The collection of UK data from screening pilots such as seen for MCADD and expanded NBS (MSUD, GA1, IVA, HCys and LCHADD) has shown the ability of UK labs to develop appropriate cut offs, especially as we screen later than many countries.
6.The distribution of test values in the target population should be	Criterion 6 uncertain The distribution of markers in a UK population after specimen collection at day five of life is unknown.	Only a UK pilot study can answer this question.

known and a suitable cut-off level defined and agreed P43		
10. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment P51	Criterion 10 partially met for argininosuccinate lyase deficiency. It is unclear whether treatment is successful in preventing the development of neurocognitive deficiencies and liver disease even if metabolic decompensations are avoided. It has been suggested that another toxic compound is present in argininosuccinate lyase deficiency in addition to ammonia. Additional therapies/regimes specific for argininosuccinate lyase deficiency rather than urea cycle disorders in general may need to be developed.	It is recognised that the inability to prevent all complications of a condition is not a bar to inclusion in a national screening programme, eg cystic fibrosis and sickle cell anaemia. It is inevitable that as knowledge grows regarding pathophysiology of many metabolic disorders, therapeutic options will broaden, eg the recognition of nitric oxide deficiency in argininosuccinate lyase deficiency (Nagamani et al Am J Hum Genet. 2012;90(5):836-46). Improved detection through newborn screening facilitates evidence based therapeutic advance by greater patient numbers identified for therapeutic trials
13. 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" (eg.	Criterion 13 not met. No randomised controlled trials of screening were identified	No newborn screening RCT for a metabolic condition has been undertaken, but this has not precluded setting up screening programmes with clinical benefit for patients and families.

Down's syndrome, 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 P53		
15. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment)	Criterion 15 uncertain No formal assessments of the balance of benefits and harms of screening were identified. Testing for citrullinaemia and argininosuccinate lyase deficiency can be done on a dried blood spot. There is likely to be some harm caused by the identification of false positives and false negatives.	It is essential to minimise false positives both for the families involved and correct use of health resources. The literature on the balance of benefits of screening continues and the harm of false positives is better understood. Schmidt et al Genet Med. 2012;14(1):76-80 state that 'Most parents did not report long-term negative impacts of the experience'. Dixon et al J Inherit Metab Dis. 2012;35(1):169-76 concluded that 'there is widespread parental support for extended screening in the UK and that the number of false-positives is a relatively small issue'. Further work is needed in this area. It is unlikely that the benefit/harm balance is significantly different from the conditions included in the national programme from January 2015.

16. 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 (ie. 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 P57	Summary: Criterion 16 not met. No UK based studies of cost effectiveness were identified. Analyses that have considered screening for a panel of MS/MS detectable disorders have found screening to be cost effective. However, in the one study that considered screening for disorders individually, screening for argininosuccinate lyase deficiency and citrullinaemia were amongst the least cost-effective disorders to screen	UK data from a pilot study would be needed to decide economic benefit. World experience would indicate an MS/MS panel eg UCD's to be most likely to prove cost effective rather than on an individual disorder basis.
21. Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity	Summary: Criterion 21 uncertain. Climb report that they have been working alongside medical professionals and families to add Inherited Metabolic Diseases to the Newborn Screening Programme, but specific disorders are not mentioned	Engagement with the stakeholders and the various patient charities will help inform the process. Views will be sort on individual conditions and they will also be able to feedback during the consultation process.

of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public P59		

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Consultation comments

3.

Name:	Alastair Kent	**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:	Director		

Do you consent to your name being published on the UK NSC website alongside your response? **Yes X** **No ☐**		
Section and / or page number	**Text or issue to which comments relate**	**Comment** *Please use a new row for each comment and add extra rows as required.*
Screening for Citrullinaemia and Argininosuccinate lyase deficiency		
Page 6	"For this review an updated systemic search has been performed for relevant publications from 2004 to August 2012".	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. We note with concern that in this instance more than half of the literature referenced is between five and 15 years out of date and that the review specifically excludes those studies that may have been published since August 2012. 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. As the national organisation representing those affected by inherited conditions, Genetic Alliance UK would welcome a meeting to discuss where we could assist in this process.
Page 4	"There is no reason for the policy on systematic population screening for argininosuccinate lyase deficiency to change, as there are still uncertainties over the epidemiology of this condition in the UK"	While a better understanding of the epidemiology and the natural history of a condition would enable a well informed decision making process, it is often not possible for this information to be gathered on rare conditions due to the small number of affected individuals and the unpredictable or heterogeneous nature of the condition's presentation and/or progression. Improved diagnosis and systems for recording the incidence of affected children in the

		UK would improve this, and the implementation of newborn screening for citrullinaemia and argininosuccinate lyase deficiency may be a vital first step.
Page 51	"It is unclear whether this treatment is successful in preventing the development of neurocognitive deficiencies and liver disease, even if metabolic decompensations are avoided".	It is important to note that dietary protein restriction, sometimes in combination with a nitrogen scavenging agent, is currently the best and only way of treating those affected by citrullinaemia and argininosuccinate lyase deficiency, regardless of how a diagnosis is reached. It would appear unethical to deprive a child of the treatment that is available for their condition at the earliest opportunity when this is all the treatment that they can hope to expect when a diagnosis for their condition is ultimately achieved. There is also some evidence, as highlighted in the UKNSCs review, that early intervention could be particularly beneficial. Progress in determining whether this is the case for citrullinaemia and argininosuccinate lyase deficiency patients is likely to be best facilitated by a UKNSC supported pilot of newborn screening for these conditions. Identifying more patients with citrullinaemia and argininosuccinate lyase deficiency will, in general, enable better research into new therapeutic options for these patients by increasing the number of individuals that can be recruited into clinical trials.
Page 64	Studies required: "to determine whether the UK bloodspot screening can	One of the factors the UKNSC considers when determining if a newborn screening programme can offer value is whether the

	detect early-onset cases before they are symptomatic. Reports from screening programmes have found that acute-neonatal forms of the disorders can present symptomatically before the results of screening tests are available".	results of the test become available before the child starts displaying symptoms. The point at which a child first displays symptoms, however, is rarely synonymous with when that child is diagnosed with their condition. Due to the rarity of citrullinaemia and argininosuccinate lyase deficiency, and other similar conditions, many clinicians may never have seen a case of these conditions or may not immediately recognise the symptoms. This means that parents could have to watch their child deteriorate for an unnecessarily long time while they wait for a clinical diagnosis, when early diagnosis and intervention could have been facilitated by a newborn screening programme. The UKNSC should engage with the relevant patient community in order to better understand their experience of diagnosis as a more relevant insight into the potential benefits of a newborn screening programme than academic studies of when the symptoms of the condition are likely to first present.
Page 64	"Implications for research The following areas could provide useful avenues for further research: - Large European based epidemiological studies, as uncertainty remains over the epidemiology of citrullinaemia and argininosuccinate lyase deficiency. - Studies determining the feasibility of blood-spot screening for these conditions in the UK,	Genetic Alliance UK recognise that there are significant gaps in knowledge about citrullinaemia and argininosuccinate lyase deficiency, particularly regarding the natural history of the condition, the optimal utility of current dietary interventions and the practicalities of screening for them (the timing of sample collection in relation to when symptoms present, the best markers to use and information on the affect of early diagnosis through screening).

	including: • Studies to determine whether the UK bloodspot screening process can detect early-onset cases before they are symptomatic. Reports from screening programmes have found that acute-neonatal forms of the disorders can present symptomatically before the results of screening tests are available. For these disorders testing earlier than at five days of age may be beneficial. • Studies to determine the distribution of markers in a UK population on day five of life • Studies to determine the predictive value of screening in the UK. - Development of a screening marker specific for citrullinaemia - Development of treatments that prevent the development of neurocognitive deficiencies and liver disease associated with argininosuccinate lyase deficiency - Studies which determine the value of early treatment - Further studies into the long term outcomes of treating citrullinaemia and argininosuccinate lyase deficiency, particularly to determine the value of screening and treating the mild forms of these conditions.”	The UK NSC’s review highlights the absence of peer reviewed and published evidence on these areas, and also emphasises the need for research into more effective treatments for these conditions. While it is clear that a better understanding of the areas highlighted by the UK NSC’s review would be valuable, what is not clear is how this information is likely to be generated within a reasonable time frame. The UKNSC only considers evidence that has been published in a peer reviewed journal, and favours those studies that specifically look at patients in the UK and in the context of the UK healthcare system. Given these limitations, it is unlikely that the types of evidence that the UKNSC rely on using to inform their decisions will be produced without proactive work by the UKNSC and associated stakeholders. We note that of the 42 publications referenced in this current review more than half of the literature referenced is between five and 15 years out of date. 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 this pilot, it would not have been possible for the UK NSC to satisfy their

		evidence requirements and positively recommend newborn screening for these conditions. We would encourage the UKNSC to consider establishing a similar pilot for citrullinaemia and argininosuccinate lyase deficiency in order to address this. As both of these conditions are already part of newborn screening programmes in the USA and six European countries, it is likely that the pilots would be successful and provide the UKNSC with sufficient evidence to support the future introduction of newborn screening for citrullinaemia and argininosuccinate lyase deficiency in the UK.

Screening for Tyrosinaemia I		
Page 2	"Newborn screening for tyrosinaemia type I could be considered".	Genetic Alliance UK supports the implementation of newborn screening for tyrosinaemia I. The fact that no feasibility studies for screening for tyrosinaemia I at birth have been carried out in the UK should not stand in the way of the UKNSC recommending newborn screening for this condition using the most effective screening methodology in line with recent advances in this area.
Page 5	"For this review an updated systemic search has been performed for relevant publications from 2004 to August 2012".	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. We note with concern that in this instance nearly two thirds of the literature referenced is between five and 15 years out of date and that the review specifically excludes those studies that may have been published since August 2012. 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. As the national organisation representing those affected by inherited conditions, Genetic Alliance UK would welcome a meeting to discuss where we could assist in this process.
Page 11	"The duration of the latent asymptomatic period varies, and no marker has been identified that can discriminate between the early and late onset forms. It has been reported that infants with tyrosinaemia type I can develop symptoms before the results of a newborn dried blood spot screen are available."	**The difference between presentation of symptoms and diagnosis** One of the factors the UKNSC considers when determining if a newborn screening programme can offer value is whether the results of the test become available before the child starts displaying symptoms. The point at which a child first displays symptoms, however, is rarely synonymous with when that child is diagnosed with their condition. Due to the rarity of citrullinaemia

		and argininosuccinate lyase deficiency, and other similar conditions, many clinicians may never have seen a case of these conditions or may not immediately recognise the symptoms. This means that parents could have to watch their child deteriorate for an unnecessarily long time while they wait for a clinical diagnosis, when early diagnosis and intervention could have been facilitated by a newborn screening programme. The UKNSC should engage with the relevant patient community in order to better understand their experience of diagnosis as a more relevant insight into the potential benefits of a newborn screening programme than academic studies of when the symptoms of the condition are likely to first present. **Diagnosis to enable informed reproductive decision-making** It is known that the same genetic mutation can cause both late and early onset tyrosinaemia I. By diagnosing an affected child at birth, even before their symptoms present, parents are given the option of considering their future reproductive choices before they have another child who is also potentially affected. The importance of this information to an affected family could be considerable.
Page 47	"Implications for research The following areas could provide useful avenues for further research:	Genetic Alliance UK recognise that there are significant gaps in knowledge about tyrosinaemia I, including the number of children in the UK who are affected and the long term outcomes of treatment with NTBC, as well as on the practicalities of how a

	- Large European based epidemiological studies, as uncertainty remains over the epidemiology of tyrosinaemia type I. - Studies to determine the feasibility of screening for tyrosinaemia type I in the UK, including: • Studies to determine whether the UK bloodspot screening process can detect early-onset cases before they are symptomatic • Studies to determine the distribution of markers of tyrosinaemia type I in a UK population on day five of life • Studies to determine the predictive value of the screening test in a UK population • Studies to determine the number of cases detected through current UK practice - Further studies into the long term outcomes of treatment with NTBC for tyrosinaemia type I, to determine the cause of the neurological effects reported in some studies, and whether these can be avoided.”	screening programme could work. The UK NSC’s review highlights the absence of peer reviewed and published evidence on these areas. While it is clear that a better understanding of the areas highlighted by the UK NSC’s review would be valuable, what is not clear is how this information is likely to be generated within a reasonable time frame. The UK NSC only considers evidence that has been published in a peer reviewed journal, and favours those studies that specifically look at patients in the UK and in the context of the UK healthcare system. Given these limitations, it is unlikely that the types of evidence that the UKNSC rely on using to inform their decisions will be produced without proactive work by the UKNSC and associated stakeholders. 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 this pilot, it would not have been possible for the UKNSC to satisfy their evidence requirements and positively recommend newborn screening for these conditions.

		We would encourage the UKNSC to consider establishing a similar pilot for tyrosinaemia I in order to address this. As tyrosinaemia I is already part of newborn screening programmes in the USA and ten European countries, it is likely that the pilots would be successful and provide the UKNSC with sufficient evidence to support the introduction newborn screening for tyrosinaemia I in the UK, particularly as a treatment for this condition is already available.

UK National Screening Committee

14/362

UK National Screening Committee
Screening for Amino Acid Metabolism Disorders - an evidence review

Consultation comments

4.

Name:	Pat Roberts	**Email address:**	**XXXX XXXX**
Organisation (if appropriate):	Save Babies Through Screening Foundation UK (SBUK) and the Patient Advocates for Newborn Screening Group (PANS)		
Role:	**Executive Director SBUK and Chair of PANS**		

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.*
Screening for Tyrosinaemia Type 1		
General Comment	Tyrosinaemia Type 1 (Tyr 1) - Full Report	We understand that the RCPCH, BIMDG and others are responding to this consultation, alerting UKNSC to several published reports to support different areas of criteria and the argument for screening for Tyr 1 and which are not referred to within this policy review,

		These include the incidence of the disorder, outcomes, consensus management guidelines, We would suggest that further work needs to be done in the review of available evidence before a decision not to recommend this can be made. **See also our comments below.**
General Comment	Full Report	A consensus meeting of scientists, clinicians and patient group representatives, facilitated by PANS was held in the Autumn of 2014 and the current position on screening for Tyrosinaemia was discussed. It is clear from that meeting, that it is now generally accepted that for universal newborn screening for Tyrosinaemia type 1, tyrosine is not a satisfactory marker. Succinyl acetone is the metabolite that accumulates and is the marker of choice. The document should reflect this. The policy review document does not reflect the different studies on screening using tyrosine as primary marker as opposed to studies using succinyl acetone. Indeed many of the studies quoted in the policy review document do not make clear which primary marker is used. The policy review is therefore very confusing. We would be happy to convene a further meeting with UK NSC to try and resolve the many inconsistencies, if that would be helpful. Birmingham IMD team and scientists have done a great deal of work on Tyrosinaemia type 1 and I am sure they would be willing to participate in any meeting. We need to work collaboratively on this if we are to improve the lives of those children diagnosed with

		Tyrosinaemia Type 1.
General Comment	Full Report	PANS members are astounded at the NSC policy review recommendation not to move forward on newborn screening for Tyr Type 1. In speaking to clinicians and scientists during 2013/14, this is the disorder where the consensus seems to be that it is the 'top of the list' for screening in the UK. (There are now 7 EU Member states who already screen for Tyr 1). As per other observations in our response, this policy review appears flawed in terms of the evidence being reviewed. In the meantime there are children being severely disabled due to a lack of an early diagnosis and treatment. We would urge a speedy re-appraisal of this evidence and policy and a speedy move forward to a pilot in the UK.
Page 29 Section 10	An effective treatment	In reading published evidence, we suggest regard should be had to evidence published in the Journal of Inherited Metabolic Disorders (September 2014). Early nitisinone treatment reduces the need for liver transplantation in children with Tyrosinaemia type 1 and improves post transplant renal function. (Bartlett, Lloyd, McKiernan, Newsome).
Page 35-37, Section 13	There should be evidence from high quality randomized controlled trials	Tyrosinaemia type 1 is a life threatening condition. The evidence of efficacy of treating the condition of nitisinone is strong. We understand from scientists and clinicians that random control trials with treatment and non-treatment arms for tyrosinemia type 1 would actually be considered unethical and impossible to conduct in reality. The criterion should therefore be scored “not assessed” rather than “not met”

Page 37-40, Criterion 15, Summary Page 40.	The benefit of screening should outweigh the physical and psychological harm….	In responding to the benefit v harm criteria we have taken advice from our scientific and clinical experts. We believe that it is important to reiterate their observations on this part of the policy review document. No formal studies of false positives and false negatives have been published, but the data is obtainable from current screening programmes. It is stated that "Neurocognitive defects have been observed in patients with Tyrosinaemia type 1 treated with NTBC." This has been reported anecdotally and in small studies in late-treated patients. It has not been systematically studied and in not in the context of early treatment following newborn screening. The improvement in mortality and morbidity with NTBC treatment is dramatic and cognitive deficits in patients **not** treated with NTBC have not been studied. Therefore the implication that this is a potentially harmful effect of screening is unjustified. Formal assessments of the rate of false positives and negatives in the context of the UK screening programme using succinylacetine as the primary marker can only be commented upon if a formal study is carried out, but these are likely to be very low, as opposed to those from screening programmes using tyrosine as a primary marker.

Criterion 16: Opportunity cost	Summary on Page 42	The summary statement is questionable as the studies quoted have used tyrosine as the primary marker for screening. This is an outdated approach which should not be considered for newborn screening for tyrosinemia type 1 in the UK. The criterion should be rated as "not assessed" rather than not met. **There needs to be further review work on more recent published evidence on Tyrosinaemia type 1 which has not been considered or recorded in this policy review i.e. before any assessment of each set of criteria and/or any recommendation is made**.
		The policy review by the UK NSC team has identified a lack of evidence in a number of areas. The review has identified where studies in 3 main areas may assist in driving out the necessary evidence to support screening for Tyrosinaemia in the UK . However no suggestion is made by the UK NSC of what work might be done and by who to obtain this evidence. Without suggestions, on next steps the policy will be boxed forward for review in another few years and the same conclusion will be reached. Something concrete needs to happen to review and provide the necessary evidence
Screening for Citrullinaemia and Argininosuccinate lyase deficiency		
General Comment	Citrullinaemia (CIT)and Argininosuccinate lyase deficiency (ASA): Full Report - Evidence	We understand that the BIMDG are responding to this consultation, alerting UKNSC to published evidence covering different areas of criteria e.g. preciseness of the test, false positive rates and which are not referred to within this policy review. There needs to be further review work on evidence from other European Member States which has not been considered or included in this policy

		review i.e. before any assessment of each set of criteria and/or any recommendation is made. Note currently 6 EU Member states screen for ASA and 5 EU Member states screen for CIT.
General Comment	Full Report – Evidence	There is a huge reliance on peer reviewed published evidence. The robustness of this is important, however all avenues need to be explored before recommendations are made for further work/studies. It is clear that evidence has not been fully identified. Representing the scientific and clinical experts, the BIMDG is making observations and suggestions in this area. We are supportive of their comments.
Page 24 and Page 27 Epidemiology and natural history of the condition	Citrullinaemia and Argininosuccinate lyase deficiency	Symptoms can develop in the first few days of life for both conditions. The UK NBS programme already includes conditions that may well present before the results of the screening test is received. NBS can still can benefit patients with milder forms of the condition. Also screening for these disorders deficiency may benefit from the review of the date on which the bloodspot sample is taken in the UK. This has been raised previously on policy reviews/consultations for other disorders. A promised review of the day of screening in the UK has yet to materialise. We need this review to be commissioned if we are to benefit children. The day of screening in the UK also impacts early diagnosis of children with other disorders. Children can benefit from early diagnosis and in terms of improved care at the earliest opportunity. I had some recent correspondence

		in connection with this policy review from a UK parent who we are in contact with and who has a child with ASA. In her network of families in the UK she advised me of the following. 'I have recently found a family here in the UK whose child has been diagnosed with late onset ASA. Sadly they now have learning difficulties and the family have been fighting for years knowing something wasn't right but no one thought to look at a metabolic condition as they are so rare'.
Pages 28 and 39 through to 44 Pages 48 through to 51	Sensitivity and specificity Effective treatment or intervention	There are a number of conclusions on whether the criteria is met that are considered 'not certain or 'not assessed'. There is an opportunity for resolving these issues through pilot studies and application to the UK population. This also gives an opportunity for collaboration with European countries who have been screening for these 2 disorders for some time.
Page 51	Effective treatment or intervention.	It is recognized that the inability to prevent all complications of a condition is not a barrier to the inclusion in a national screening programme. There are disorders on our current UK programme where some complications will arise despite early diagnosis.
Page 64 Conclusions	Implications for Research	The policy review by the UK NSC team has identified a lack of evidence in a number of areas. The review has identified some useful avenues for further research. These areas of proposed research may assist in driving out the necessary evidence to support screening for these 2 disorders. However no suggestion is made by the UK NSC of what work might be done and by who to obtain this evidence. Without suggestions on next steps the policy will be boxed forward for review in another few years and the same

		conclusion will be reached. Something concrete needs to happen to provide the necessary evidence.

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Amino acid metabolism disorders screening in newborns
Evidence review – Tyrosinemia type 1

5.

Name	A Chakrapani, MA Preece
Position	Consultants in Inherited Metabolic Disordres
Specialty group, special interest group or CSAC Please specify if you are responding on behalf of a group/committee	BIMDG

Section and / or page number	Text or issue to which comments relate	Comments *Please use a new row for each comment and add extra rows as required.*
Introduction, page 5	….relevant publications from 2004 to August 2012	There have been several publications relating to the subject since August 2012. In particular, the following should be included in the review: Larochelle et al Mol Genet Metab. 2012 Sep;107(1-2):49-54 Bendadi et al J Pediatr. 2014 Feb;164(2):398-401 Zytkovicz et al Clin Biochem. 2013 May;46(7-8):681-4 De Laet et al Orphanet J Rare Dis. 2013 Jan 11;8:8. Mayorandan et al Orphanet J Rare Dis. 2014 Aug 1;9(1):107
Page 7	Incidence	More up to date data on incidence is now available – see Mayorandan et al 2014
Page 11	Summary: Criterion 2 partly met	More up to date data on incidence is now available – see Mayorandan et al OJRD 2014 McKiernan et al Archives of Disease in Childhood 2015
Page 27, Section 6: Distribution of cutoff values in target population	Summary: Criterion 6 is uncertain, Distribution of markers in a UK population after specimen	This has not been formally studied, and can be determined quickly once the screening methodology for succinylacetone is agreed.

	collection at day 5 is unknown	
Page 29, Section 10: “There should be effective treatment….”	Entire section	The section should be updated to include recent studies, as they contain important information on outcome: Mayorandan et al Orphanet J Rare Dis. 2014 Aug 1;9(1):107 Larochelle et al Mol Genet Metab. 2012 Sep;107(1-2):49-54 Mackiernan et al Arch Dis Child 2015 (epub)
Page 35, Section 11	Entire section	An up to date European consensus management guideline has recently been published and should be included: De Laet et al Orphanet J Rare Dis. 2013 Jan 11;8:8
Page 35-37, Section 13: There should be evidence from high quality randomized controlled trials…	Entire section	Tyrosinemia type 1 is a life threatening condition and the evidence of efficacy of treating the condition of nitisinone is strong. Hence, RCTs with treatment and non-treatment arms for tyrosinemia type 1 would be considered unethical and impossible to conduct in reality. The criterion should be scored “not assessed” rather than “not met”
Page 37-40, Criterion 15: The benefit of screening should outweigh the physical and psychological harm….	Summary on page 40	No formal studies of false positives and false negatives have been published, but the data is obtainable from current screening programmes. It is stated that “Neurocgnitive defects have been observed in patients with Tyrosinaemia type 1 treated with NTBC.” This has been reported anecdotally and in small studies in late-treated patients. It has not been systematically studied and in not in the context of early treatment following newborn screening. Furthermore, the improvement in mortality and morbidity with NTBC treatment is dramatic and cognitive deficits in patients NOT treated with NTBC have not been studied. Therefore the implication that this is a potentially harmful effect of screening is unjustified. Formal assessments of the rate of false positives and negatives in the context of the UK screening programme using succinylacetine as the primary marker can only be commented upon if a formal study is carried out, but these are likely to be very low, as opposed to those from screening programmes using tyrosine as a primary marker.
42. Criterion 16: Opportunity cost	Summary on Page 42	The summary statement is unjustified as the studies quoted have used Tyrosine as the primary marker for screening. This is an outdated approach which should not be considered for newborn screening for tyrosinemia type 1 in the UK. The criterion should be rated as “not assessed” rather than not met.
Whole document		It is now generally accepted that for universal newborn screening for tyrosinaemia type 1, tyrosine is not a satisfactory marker. Succinyl acetone is the metabolite that accumulates and is the marker of choice. The document should reflect this. Any studies on screening using tyrosine as primary marker should be in a separate section to those using succinyl acetone (or excluded altogether). Many of the

		studies referenced do not make clear which primary marker is used and thus the whole review becomes rather confusing.
Page 2	Key points	Point 2 'The technique used for…' does not state to what technique it is referring.
Page 2	Summary	'Without fumaryl acetoacetase, tyrosine and intermediate breakdown products accumulate, which can damage the liver kidneys…' should read 'Without fumaryl acetoacetase, intermediate breakdown products accumulate, which can damage the liver(causing increased tyrosine concentrations) kidneys…
Pages 2&3	Summary	Reference to screening programmes using tyrosine should be termed as 'historical' or removed
Page 11	Summary	The same genotype can present as early and late onset forms
Page 12	Section 5	The 2004 HTA report….using tandem MS is limited. Again, needs to indicate whether referring to tyrosine or succinyl acetone
Page 27	Summary	The distribution of markers in a UK population… In Birmingham UK we have evaluated succinyl acetone as a newborn screening test for tyrosinaemia type 1. In 1140 specimens we found median succinyl acetone 0.35 umol/L (range (0-2.38, 2 outliers removed because repeat analysis could not be undertaken). A further study of 1799 samples with tyrosine >200 umol/l showed median succinyl acetone 1.33 umol/l (range 0-5) Dowden et al (2008) J Inherit Metab Disease, 31 (Suppl 1), 5 Dowden et al (2012) J Inherit Metab Disease, 35 (Suppl 1), S158
Page 28	Table 10	Abnormal metabolites expected: Tyrosine and methionine are not always abnormal. Other succinyl acetone metabolites may be present in urine at higher concentrations that succinyl acetone itself. Urine 5-aminolevulinc acid is a useful marker.
Page 46	The screening test	Variation of succ acetone levels between sites is more likely due to analytical varables than pre analytical variables. If newborn screening were adopted the laboratories could work together as they have done very successfully for other tandem MS analytes.