UK National Screening Committee Expanded Blood Spot Screening Consultation comments

March 2014

Organisation:	Clinical Genetics Society		
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Section and / or page number	Text or issue to which comments relate	Comment
	General comment from clinical geneticists	As a professional group who regularly interact with families who have children with MSUD, glutaric acuduria Type 1 and homocystinuria, we welcome the decision by the NSC to include these three disorders in the extended newborn blood spot screening programme. Though these disorders are individually rare, most clinical geneticists have experience of seeing and counselling families with these conditions, and the reduction in morbidity offered by extending the programme will be of significant benefit. In addition, identification of index cases within the family will most likely lead to detection of a number of carriers who could benefit from knowing about the reproductive implications.
NSC executive summary	xii. The health economics report prepared by Scharr indicates that newborn screening for each of the five disorders included in the study was cost saving.	We were surprised that extending the bloodspot screening to include isovaleric acidaemia and and LCHADD was not recommended. The studies have shown that screening for these disorders, too , is not only cost effective but cost-saving. In fact it could be more cost-saving even than the health economic study described suggests, as cascade screening of the families involved , whilst very cheap to carry out , could also identify carrier couples at risk especially in consanguineous families.
NSC evaluation	Due to the range in severity and	We note the concerns regarding the false positive results for

report. IVA, section 10, page 110 Health economics report, conclusion	presentation of IVA, it is possible that detection through newborn screening may identify and medicalise patients who would otherwise have remained asymptomatic. The high overdetection estimated for IVA is most probably related to the prevalence of the 932C->T mutation, individuals with which are likely to remain asymptomatic without screening. The model includes management costs for this subgroup in the form of regular clinical appointments, however it is assumed that these individuals are correctly identified and that there are no long term dietary costs.	IVA, which arose because in this condition there is a common benign sequence variant. There is concern that over detection of cases with this mild variant might lead to anxiety. In fact this is not a new situation for those of us who use genetic and other tests on a regular basis. A similar situation may arise when we screen for CF, for instance. We are used to counselling patients about tests where there may be "false positives" in the form of pseudogenes, mild variants or common polymorphisms and we have built up a great deal of experience in dealing with and communicating such findings. With careful pre-test counselling and post-test explanation we do not consider that significant anxieties will be caused for the families concerned. This small risk can easily be outweighed by the advantages of detecting even a small number of screen-positive IVA patients. An alternative strategy which has been suggested would be to alter the cut-off for detection of IVA to reduce the number of mild cases identified and this seems feasible.
Page 5, NSC report 21.11.13	While many countries included additional conditions, there appeared to be widespread agreement that these five disorders (see Table 2) should be included as part of the newborn screening programme. Table 2 - Five conditions and countries that offer newborn screening for these conditions	Adopting screening for all five disorders would bring us further in line with other EU countries. Increased migration across borders means that we increasingly share more population characteristics with other EU countries who have carefully considered the cost-benefits of adopting screening for metabolic disorders, and it seems reasonable that we should be able to offer a similar strategy to other EU countries.
NSC evaluation report page 5	Comparison of the predicted number of cases with data from the clinical phase of the pilot programme shows that they fall within the estimated number for some conditions (GA-1, IVA) and not others, such as	For LCHADD, the length of time of the pilot study has probably not been long enough to give a true picture of the utility of including this disorder in an extended newborn screen. If the decision is not made at this point to include

	in the case of LCHADD. 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.	LCHADD in extended newborn screening, then we would urge the NSC to consider extending the pilot for this condition to gain a better picture.
Economic evaluation page 10	Table 3 presents the estimated costs and quality of life effects of screening for each of the conditions compared to no screening. It can be seen that screening for all conditions is predicted to be cost saving and more effective when compared to not screening for each condition, that is screening for each condition dominates no screening.	We suspect that laboratory costs for screening for all five disorders will vary very little for screening just for the three disorders agreed, as the similar analytes are used for all. Thus, it would seem reasonable to screen for all five disorders at the same time as cost savings have bee demonstrated.

Organisation:	Climb National Information Centre for Metabolic Diseases		
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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	The expanded newborn screening project, outcomes and the NSC	Climb very much welcomed this pilot. The time and commitment given to the successful implementation, operational management and recording/review of this pilot is to be lauded. The specialist scientific and clinical health professionals who have been involved in this project have worked to the highest standards. In particular the subsequent moral and financial support of the National Screening Committee to enable the continuance of this pilot ensured that a full and highly valuable review was undertaken which has been very instrumental in bringing this consultation to the wider public. It is Climb's contention that funding should now be made available to fully implement this screening for all the disorders in all four countries of the United Kingdom.
Report to the UK National Screening Committee.	Screening in Europe and Other Countries	Included in the report to the NSC is a very clear table (para 1b) that clearly shows that all 5 of the conditions selected for the Expanded NBS project are already widely included in the screening programmes of many countries worldwide. 10 European Member States already screen for 10 or more disorders. Whilst the numbers reported are low for LCHADD and IVA it is strongly recommended that neither disorder should be discounted from inclusion in the Newborn Screening register for England and Wales based on the outcome of this project.
Expanded Bloodspot Consultation	Recommendations made by the NSC	Climb fully supports the recommendation to include MSUD, GA1 and HCU in the UK NBS programme. The priority of NBS is to save lives and an early

Document		diagnosis is extremely critical in saving the lives of babies.
Expanded Bloodspot consultation UK NSC recommendations	Expanded NBS Study.	Climb fully supports the inclusion of LCHADD and IVA in the UK NBS programme and as acknowledged by the NSC that ***there is little evidence in any disbenefit*** of screening for LCHADD or IVA. As an autosomal recessive disorder LCHADD/MPT is characterised by early-onset cardiomyopathy, hypoglycemia, neuropathy, pigmentary retinopathy, and potential sudden death and we would suggest that there are a list of benefits to the families whose children are diagnosed with LCHAD/MPT. Experience in countries where LCHADD is currently screened for acknowledge the significant benefit from early detection of LCHADD/MPT . Isovaleric acidemia (IVA) is a rare metabolic disorder in which the body is unable to process certain proteins properly. It is classified as an organic acid disorder, which is a condition that leads to an abnormal buildup of organic acids. Abnormal levels of organic acids in the blood (organic acidemia), urine (organic aciduria), and tissues can be toxic and can cause serious health problems including death. The lack of any disbenefit and the potential cost savings leads Climb to believe that screening for both disorders (LCHADD – IVA) should not be excluded from the NBS register
Health Economic Report	Conclusions on Cost savings Increased QoL.	The Health Economic report clearly states in its opening conclusion that screening for MSUD, HCU, IVA, GA1 and LCHADD are each estimated to be potentially cost saving and result in increased quality of life compared to no screening. The cost effectiveness study clearly demonstrates that all 5 conditions are cost

		saving. Screening for all 5 disorders would not only be cost effective but would show cost savings for an organisation (the NHS) that is very short of funding. We firmly believe that there are no compelling reasons to reject the screening for all 5 of these disorders.
Expanded NBS Study Report to the NSC.	Conclusions	Whilst it is fully acknowledged that there was a larger than expected number of false positives during the screening for IVA we would strongly disagree with the suggestion from the NSC that there is not likely to have been conferred benefits to the patients diagnosed. Indeed as there is no evidence of disbenefit the NBS conclusion is flawed in reaching this outcome. To avoid the false positive outcomes of IVA screening the cut off level should be raised to 2 or even higher which will lead to an improved PPV and show IVA to be more than suitable disorder for inclusion in the Newborn Screening register. The potential to seriously avoid the potential for early death in undetected cases of IVA and improve the outcomes that will be provided by early detection offers significant benefits to both the patient and the NHS. It is to be noted that throughout Europe once screening for IVA has been implemented that it has not been withdrawn.
Climb	Comment	We can think of a no more destructive act for a family than for their baby to die in the first few weeks or months of life and whilst the NSC openly admits that there is no disbenefit for including LCADD/MPT and IVA in the newborn screening programme we cannot understand why the NSC would not include these two disorders. Discussions last week with leading scientists of two labs taking part in this pilot revealed that there are no cost savings to be made by not including them.

		The impact of including all 5 conditions, albeit with a modified IVA cut-off level is highly likely to result in additional, potentially significant, future cost savings. Looking back at the introduction of screening for MCADD in England and Wales the number of newborns identified with MCADD has shown to be over 70% more than was estimated during the pilot project. We have no doubt that the NSC were surprised by these outcomes and we would suggest that inclusion of these 5 disorders (HCU, IVA, GA1, LCHADD and MSUD) to the UK newborn screening programme may well lead to further 'surprises' as other laboratories in England and Wales are included in the screening regime. ***If there are no costs savings to be made if we don't screen and there no disbenefits if we do screen then why are we considering not screening?*** Based on the above, the benefits to families and the lack of disbenefits in implementing screening for all 5 disorders, we would implore the NSC to reconsider their stance and include LCHADD and IVA in the newborn screening programme.

Organisation:	Central Manchester University Hospitals NHS Foundation Trust, and, North West ANNB Quality Assurance Team (and on behalf of screening midwives in the North West).		
Name:	Lesley Tetlow (Newborn Screening Laboratory) Rebecca Al-Ausi (NW QA)	**Email address:**	xxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxx
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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.*
1 10	Consultation document. Report to National Screening Committtee, p10	We strongly support the NSC's proposal to expand the current NBS bloodspot screening programme to include homocystinuria, MSUD, and glutaric aciduria type 1. As one of the areas involved in the pilot we recognise the clear patient benefit from early diagnosis of these conditions. Despite initial concerns regarding the timescale for implementation of the pilot the approach to giving basic information to parents together with the more detailed and excellent resources on the website worked well. Midwives were comfortable with the process and the relatively low numbers of declines is testament to the fact that communication was effective. This approach should provide a model and be embedded within midwifery training for any future programme expansion..
1 46 61/62	Consultation document. – case for IVA not proved Report to NSC page 46, table of true and false positive results for IVA Report to NSC pages 61,62	The UK NSC considered that the evaluation and cost effectiveness study did not make the case for screening for IVA. This decision was reached on the basis of the high number of false positives and 3 mild cases detected. However, as highlighted in the report of the pilot to the NSC, by increasing the blood spot C5 acyl carnitine cut-off from 1 to 2 μmol/L, 13 of the false positives and 2 of the 3 mild cases would be eliminated. Part of the aim of the pilot was to assess the cut-off so we would support the inclusion of IVA with an

11	Health Economics paper page 11	amended cut-off since it is clear that early detection offers significant clinical benefit. The health economic study has demonstrated a cost saving associated with IVA screening. Since the protocols and processes for IVA screening are in place in areas involved in the pilot, if the NSC does not feel it can sanction full roll out at this stage, it should consider approving an extension of the pilot (with the amended cut-off) in the areas previously involved in order to gather more evidence. In the assessment of IVA, has the pilot study addressed the evidence fully that mild cases of IVA were avoided by the correct cut-off accomplishing this?
1 60/61 11	Consultation document –case for LCHADD not proved. Report to NSC pages 60,61 Health Economics paper page 11	The UK NSC considered that the evaluation and cost effectiveness study did not make the case for screening for LCHADD. This decision appears to be based on the lack of evidence of clear benefit. However within the short timeframe of the pilot it is unlikely that benefit could be proven and outcomes are skewed by the high proportion of MTP deficiency cases amongst the positive cases identified. Given that no dysbenefit was shown and that the Health Economic paper demonstrated a likelihood of a cost saving it would appear premature to abandon LCHADD at this stage. Since the protocols and processes for LCHADD screening are in place in areas involved in the pilot, if the NSC does not feel it can sanction full roll out at this stage, it should consider approving an extension of the pilot in the areas previously involved in order to gather more evidence.
	Report on Health economics of expanded newborn screening pg 11	The report on the cost effectiveness concluded that all five disorders were likely to be cost *saving, (*although it is acknowledged that there were uncertainties in the models for various reasons). The additional cost to the laboratory in relation to the inclusion of IVA and LCHADD alongside the other conditions is minimal and it is likely that the inclusion of IVA with an amended cut-off would result in an

		additional cost saving. Given the significant potential clinical benefit and overall lack of dysbenefit we ask the NSC to consider including all 5 conditions in the expanded programme. It would be unfortunate to remove these at this stage from the pilot sites when the work in setting them up has been accomplished and there is an opportunity to build on the data gathered so far – with this in mind if the NSC does not feel it can sanction full roll out at this stage, we would suggest that consideration be given to approving an extension of the pilot for all 5 conditions in the areas previously involved together with a full national roll out for MSUD, GA1 and homocystinuria.
General Comments		1. Will a new refreshed website be available for the proposed roll-out with simplified information about each of the NBBS conditions to aid providers and remind them of the importance of being able to signpost? Some midwives feel they should know all about the metabolic conditions in the realm of informed consent. Others however suggest they need to understand the basics of what a metabolic condition is and then being able to signpost those requesting further information. 2. When will the screen positive qualitative study of parental experiences of receiving positive screening results under the expanded NBBS programme be ready for publication? 3. Carriage of printed materials for midwives healthcare professionals and parent information sheets .Was there any monitoring of feedback for these resources during the pilot?

Organisation:	Central Manchester University Hospitals NHS Foundation Trust –Newborn Screening and Willink Biochemical Genetics Unit		
Name:	Claire Hart, Consultant Clinical Scientist / Head of Service, Willink Biochemical Genetics Lab Lesley Tetlow, Consultant Clinical Scientist / Director of Newborn Screening Andrew Morris, Consultant in Paediatric Metabolic Medicine, Willink Biochemical Genetics Unit	**Email address:**	xxxxxxxxxxxxx xxxxxxxxxxxxx xxxxxxxxxxxxx
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Section and / or page number	Text or issue to which comments relate	Comment
1	Consultation document.	As one of the centres involved in the delivery of the pilot project we absolutely and unreservedly support the NSC's proposal to expand the current NBS bloodspot screening programme to include homocystinuria, MSUD, and glutaric aciduria type 1. We see this as an important and valuable step forward in the quality of care available to patients with these rare disorders and expect that the patients detected will benefit significantly. We would like to thank the NSC for their support of this pilot project which has allowed the screening services the chance to demonstrate that screening for these disorders can be delivered effectively.
1 46 62	Consultation document. – case for IVA not proved Report to NSC page 46, table of true and false positive results for IVA Report to NSC page 62, section 7. The overall case and the case for individual conditions (comments on	The committee did not accept the case for screening for IVA on the basis of the high number of false positives and 3 mild cases, with the one severe case unfortunately dying. However, like the authors of the report on the pilot project we believe that screening for IVA can be delivered effectively without significant numbers of false positives. The outcomes from the pilot project are based on the use of a cut off for C5 of 1 µmol/L. Part of the aim of the pilot was to assess the appropriateness of the cut offs used, and in the case of

	IVA)	IVA the cut off has been shown not to be appropriate. However there is absolutely no reason why the cut off cannot be changed. By simply raising the cut off to 2 µmol/L the false positive problem would be almost entirely eradicated without missing any clinically significant cases. Indeed this would also have reduced the pick up of very mild cases of IVA from 3 to 1 and hence avoided potentially unnecessary medicalisation of these patients. We would find it acceptable if the NSC programme stated that screening is not intended to identify these exceptionally mild cases. International newborn screening experience, and the UK experience of diagnosing IVA in symptomatic patients tells us that IVA patients who would benefit from treatment are unlikely to have a C5 concentration less than about 5 µmol/L and often have levels above 10, so there may be room to raise the cut off still further. In conclusion we believe that to dismiss screening for IVA because the cut off used in the pilot project wasn't quite right is premature.
1	Consultation document –case for LCHADD not proved.	The NSC has concluded that the data from the project does not support the inclusion of LCHADD in the extended panel. However this seems 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.
11	Report on Health economics of expanded newborn screening pg 11	The report on the cost effectiveness concluded that all five disorders were likely to be cost *saving, (*although it is acknowledged that there were uncertainties in the models for various reasons). 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 IVA and LCHADD would be absolutely marginal, so long as false positives are minimal (i.e. cut off for IVA is changed). Therefore there would need to be a very concrete reason to exclude IVA and 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.
	Consultation document –conclusion that case for IVA and LCHADD not made.	The five disorders chosen for the ENBS panel are a conservative selection based on those already widely included on the panels for newborn screening in many other countries worldwide, with some countries having over 10 years experience of screening for these disorders. This was deliberately done so that we could learn from the experience of other countries and because screening for these disorders is uncontroversial in the international NBS community. Therefore we feel that any decision to remove individual disorders from the panel should be undertaken very cautiously and should not be made on the basis of data from a one year feasibility pilot project.

Organisation:	MetBioNet		
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Please tick whether you are making this submission as an individual or on behalf of an organisation. **Individual** ☐ **Organisation** ✓			
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	Background and pilot	MetBioNet welcomes screening for appropriate additional metabolic disorders as part of the Newborn Screening programme. International practice has led to the inclusion of a greater number of conditions than in the UK but the cautious approach adopted here may have avoided some potential dysbenefit and allowed a thorough appraisal. The support for the current pilot offered by the NSC and their close involvement during the study is recognised and welcomed.	
Recommendation of the NSC - in favour	The pilot study findings and the disorders recommended by the NSC	The recommendation in favour of GA1, MSUD and homocystinuria (pyridoxine unresponsive) by the NSC is to be applauded. The benefits for some of these patients is already apparent from the cases diagnosed by screening and successfully treated as part of the pilot.	
Recommendation of the NSC - against	The pilot study findings and the disorders not recommended by the NSC	The concerns expressed in relation to the inclusion of IVA and LCHADD/MTP may be premature or misplaced. The consensus of international opinion within Europe strongly supports the continued inclusion of these conditions. While not a reason to follow suite, the lack of dysbenefit demonstrated for LCHADD/MTP during the study period in a UK context and the proposal to avoid dysbenefit from IVA screening by	

		increasing the cut-off, implies a presumption in favour rather than against inclusion for these conditions. A retrospective analysis of clinically identified cases of IVA from Sheffield suggests that all recent cases (n=6) would have been identified using a cut-off of 2.0 µmol/L for C5 while false positive results would have been substantially avoided resulting in a PPV% > 50%. The close similarity with the German experience offers further re-assurance. The potential for benefit without significant dysbenefit linked with the cost savings outlined in the cost effectiveness study suggests that a decision to cease testing at this stage would be inadvisable. However, without inclusion as part of the national programme, the consent and reporting issues may prove difficult to overcome and it is likely that testing will cease for these two important conditions unless supported. MetBioNet would strongly support the on-going inclusion of these conditions as part the national programme with careful outcome review planned in a further three years. It is likely that international recommendations from Europe may help guide and form policy in that timescale and pressure to include these disorders is likely to mount rather than diminish following these recommendations. Patient groups and professionals alike would question why, without significant evidence of avoidable dysbenefit and strong evidence of cost saving, the UK chose not to build upon existing experience from the pilot study and allow the UK to participate fully in international data collection so that the true situation could be robustly determined.
Expanded Bloodspot consultation UK NSC	The potential resource impact of continuing screening for all five	The sample to be collected is not influenced by the number of conditions included.

recommendations	disorders vs three disorders.	The report outlines that the clinical support services coped well with the introduction of screening during the pilot period. The CRG for IMD's is confident that the referral and treatment implications can be accommodated in both the current screening and future screening regions for all five conditions. The cost of screening for five conditions is likely to be the same as three disorders from a laboratory perspective and the information and reporting flows would be similar in both scenarios.
Expanded Bloodspot consultation UK NSC recommendations	Conclusions	The aim of the pilot study at the outset was to evaluate logistic feasibility and identify, so far as they exist, possible dysbenefits resulting directly from newborn screening for the five disorders considered. It was clear both from the power and the duration of the study that it was not designed to identify or evaluate outcomes as a basis for decision making. Indeed, it is likely that this would require properly constructed international collaboration. The conclusions of the study clearly support the logistic feasibility of screening for these disorders and have failed to show avoidable dysbenefit, it is clear from the aim and design of the study that outcome at one year, cannot be used to guide decision making in this context. On this basis the successful pilot which ran from July 2012 to July 2013 should be adopted as it stands, with modification of the cut-off used for IVA, and offered safely and cost effectively to the rest of the country with on-going data collection and review planned for 2017.

Organisation:	UKNSLN		
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General comment	Background and pilot	UKNSLN welcomes screening for appropriate additional metabolic disorders as part of the Newborn Screening programme. International practice has led to the inclusion of a greater number of conditions than in the UK but the cautious approach adopted here may have avoided some potential dysbenefit and allowed a thorough appraisal. The support for the current pilot offered by the NSC and their close involvement during the study is recognised and welcomed.
Recommendation of the NSC - in favour	The pilot study findings and the disorders recommended by the NSC	The recommendation in favour of GA1, MSUD and homocystinuria (pyridoxine unresponsive) by the NSC is to be applauded. The benefits for some of these patients is already apparent from the cases diagnosed by screening and successfully treated as part of the pilot.
Recommendation of the NSC - against	The pilot study findings and the disorders not recommended by the NSC	The concerns expressed in relation to the inclusion of IVA and LCHADD/MTP may be premature or misplaced. The consensus of international opinion within Europe strongly supports the continued inclusion of these conditions. While not a reason to follow suite, the lack of dysbenefit demonstrated for LCHADD/MTP during the study period in a UK context and the proposal to avoid dysbenefit from IVA screening by increasing the cut-off, implies a presumption in favour rather than against inclusion for these conditions. A retrospective analysis of clinically identified cases of IVA from Sheffield suggests that all recent cases (n=6) would have been identified using a

		cut-off of 2.0 µmol/L for C5 while false positive results would have been substantially avoided resulting in a PPV% > 50%. The close similarity with the German experience offers further re-assurance. The potential for benefit without significant dysbenefit linked with the cost savings outlined in the cost effectiveness study suggests that a decision to cease testing at this stage would be inadvisable. However, without inclusion as part of the national programme, the consent and reporting issues may prove difficult to overcome and it is likely that testing will cease for these two important conditions unless supported. UKNSLN would strongly support the on-going inclusion of these conditions as part the national programme with careful outcome review planned in a further three years. It is likely that international recommendations from Europe may help guide and form policy in that timescale and pressure to include these disorders is likely to mount rather than diminish following these recommendations. Patient groups and professionals alike would question why, without significant evidence of avoidable dysbenefit and strong evidence of cost saving, the UK chose not to build upon existing experience from the pilot study and allow the UK to participate fully in international data collection so that the true situation could be robustly determined.
Expanded Bloodspot consultation UK NSC recommendations	The potential resource impact of continuing screening for all five disorders vs three disorders.	The sample to be collected is not influenced by the number of conditions included. The report outlines that the clinical support services coped well with the introduction of screening during the pilot period. The CRG for IMD's is confident that the referral and treatment implications can be accommodated in both the current screening and future screening regions

		for all five conditions. The cost of screening for five conditions is likely to be the same as three disorders from a laboratory perspective and the information and reporting flows would be similar in both scenarios.
Expanded Bloodspot consultation UK NSC recommendations	Conclusions	The aim of the pilot study at the outset was to evaluate logistic feasibility and identify, so far as they exist, possible dysbenefits resulting directly from newborn screening for the five disorders considered. It was clear both from the power and the duration of the study that it was not designed to identify or evaluate outcomes as a basis for decision making. Indeed, it is likely that this would require properly constructed international collaboration. The conclusions of the study clearly support the logistic feasibility of screening for these disorders and have failed to show avoidable dysbenefit, it is clear from the aim and design of the study that outcome at one year, cannot be used to guide decision making in this context. On this basis the successful pilot which ran from July 2012 to July 2013 should be adopted as it stands, with modification of the cut-off used for IVA, and offered safely and cost effectively to the rest of the country with on-going data collection and review planned for 2017.

Organisation:	Portsmouth Hospitals NHS Trust		
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Section 3.3 page 21	Screening for MSUD	Noting that the incidence is 1/180,000 or so, I'd be expecting a MSUD case every 3-4 years perhaps in my screening area. However, Having seen two babies born in Wessex in the past year with MSUD that may have been aided by an earlier diagnosis, the sooner this is rolled out nationally, the better!

Organisation:	Paediatric Metabolic Team, University Hospital of Wales, Cardiff, UK		
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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.*
	Background Information	This consultation on whether to include additional metabolic disorders to the current panel screened for here in the UK is timely as it complements the vision set out in the **UK Strategy for Rare Diseases.** The aim of this strategy is to identify and diagnose individuals to enable early intervention, of which newborn bloodspot screening is a key process.
Recommendation to screen for 3 of the 5 conditions		The pilot study undertaken is a conservative one that includes a panel of 5 disorders that are already included in newborn screening programmes across Europe and the rest of the Developed World. It should be highlighted that the majority of these countries also screen for several other metabolic disorders in addition to these five. The recommendation by the UK NSC to include screening for MSUD, GA1 and homocystinuria is to be welcomed and

		supported and the recognition of patient benefit is eagerly awaited.
	"The NSC considered that the evaluation and cost effectiveness and study did not make the case for screening of LCHADD."	LCHADD is a rare but serious disorder and the UK NSC acknowledges the fact that screening during a 1 year period was unlikely to demonstrate benefit. International experience indicates that there is significant benefit from the early detection of LCHADD cases. The NSC also acknowledges that there is little evidence of dysbenefit from screening for LCHAD. Therefore without significant dysbenefit it is difficult to reconcile the decision not to include this disorder in the panel to be screened for. Without the evidence for significant dysbenefit and the cost saving of identifying such cases it should be recommended that LCHADD be included/the evaluation time for LCHADD is extended for a defined period of time.
	"The NSC considered that the evaluation and cost effectiveness and study did not make the case for screening of IVA."	The results for IVA from this pilot are similar to those seen by the screening programme in Germany, with the ratio of mild to severe cases (3:1). Fourteen false positive cases were also detected during the pilot. However, as discussed in the report increasing the C5 cut off for the detection of IVA from 1 to 2µmol/L, will decrease the number false positives (14 to 1) and avoid 2 of the 3 mild IVA cases, whilst still being able to identify the severe classical forms of IVA. Detection and treatment of the severe form should avoid the neonatal mortality and prevent severe neurological damage observed in these cases. On this basis of adjusting the C5 screening cut-off to 2µmol/L – IVA should be included in the panel screened for here in the

		UK.
Health Economics		From the Health Economics report undertaken as part of the pilot study it was demonstrated that screening for all 5 conditions was cost effective. The inclusion of IVA and 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. Not including IVA and LCHADD in the extended screening panel or at the very least not to continue to evaluate screening for these 2 disorders for a defined period is out of line with the vision set out in the UK Rare Diseases Strategy. Furthermore, it also leaves the UK behind the rest of Europe and the developed world in terms of the number of disorders screened for at birth.

Organisation:	Addenbrooke's Hospital, Cambridge		
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Please tick whether you are making this submission as an individual or on behalf of an organisation. **Individual**			

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	Proposal to extend screening by 3 conditions.	The recommendation to extend screening to include MSUD, GA1 and homocystinuria (pyridoxine unresponsive) is welcome. There is clear benefit and it is time that UK newborn screening matched that of European counterparts. Screening for these conditions is well-established elsewhere and the pilot study was successful in terms of logistics, cost-effectiveness and clinical benefit.
	Exclusion of LCHADD and IVA	The Committee's decision not to support screening for IVA and LCHADD/MTP seems short-sighted. These screening tests were deemed cost-effective and the NSC concede that there was little evidence of dysbenefit. The report highlights the potential medicalisation of families where mild cases of IVA have been detected. However this problem could be avoided by adjusting the cut-off, whilst still allowing the clinically significant cases the benefit of early diagnosis and treatment. Reliable assessment of LCHADD/MTP screening requires more data and it would seem premature to halt this screening programme after only one year. Prior to the pilot there was much discussion on the potential disorders and LCHADD was considered a good candidate for screening. The consensus within Europe is for continued inclusion of LCHADD and IVA in newborn screening programmes.
	The potential cost screening for all 5 disorders rather than 3 disorders	The amount of sample collected is not affected by the addition of 3 or 5 conditions. The laboratory costs of screening for 3 or 5 conditions is likely to be very similar.

		Clinical services were not overwhelmed by the 5 conditions during the pilot.

Organisation:	Birmingham Children's Hospital - West Midlands Newborn Screening Laboratory		
Name:	Dr Philippa Goddard	**Email address:**	xxxxxxxxxxxxxxx
Please tick whether you are making this submission as an individual or on behalf of an organisation. **Organisation**			
Comment			

The West Midlands Newborn Screening Laboratory has been involved in the Expanded Newborn Screening pilot study since it commenced on the 16th July 2012. We have been screening for the five disorders, MSUD, Homocystinuria, Isovaleric aciduria, Glutaric aciduria type 1 and LCHAD.

We are encouraged with the outcomes of the pilot study and thank the National Screening Committee for their support and funding. All metabolites for the five disorders are now included in our in - house reagents for preparation of blood spot samples and the results are all linked to our screening information management system. There is therefore a seamless mechanism and process in place for each of the five disorders. The method is extremely robust and each of the screening, referral and diagnostic pathways has been followed successfully for each case detected.

We would welcome the recommendation to continue screening for MSUD, GA1 and homocystinuria but would also wish to see the inclusion of LCHADD and IVA. There is little evidence of dysbenefit from screening for LCHADD and it is generally acknowledged from international experience that there is significant benefit from early detection in true LCHADD deficiency. It would therefore be disappointing to exclude screening for this disorder based on the minimal amount of data collected. Screening for IVA did produce too many false positives. However, altering the cut off would prevent the referral of the majority of these cases whilst still picking up severe cases of IVA. By increasing the C5 screening cut-off from 1.0µmol/L to 2.0µmol/L, the PPV% will greatly improve and there would be potential to avoid 13 of the 14 false positives detected in the study period and reduce the number of mild cases identified from 3 to 1. The potential to avoid neonatal mortality and to improve neurologic and cognitive outcome under early treatments for IVA still warrants the inclusion of IVA in the screening programme.

As with all screening programmes, it is important to consider costs and all five conditions were considered to be cost saving by a carefully conducted case effectiveness study.

In conclusion we believe that the inclusion of all five disorders in the expanded newborn screening programme, with a modified cut-off for IVA, would most likely result in additional cost savings, significant potential benefit for patients and little evidence of dysbenefit.

Organisation:	British Inherited Metabolic Disease Group (BIMDG)		
Name:	Dr. Anupam Chakrapani, Chair BIMDG	**Email address:**	xxxxxxxxxxxxxxx
Please tick whether you are making this submission as an individual or on behalf of an organisation. **Individual ☐ Organisation x☐**			

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.*
60-62	The overall case for the individual conditions	We fully support the inclusion of MSUD, GA1 and Homocystinuria in the newborn screening programme. The evidence from the pilot study and the economic evaluation makes a good case for inclusion of these 3 conditions. The clinical benefits from screening for these 3 conditions clearly outweigh the risks and this has also been the experience internationally from other screening programmes. The screening methodology used in the pilot study for these 3 conditions had a reasonable positive predictive value, along with high sensitivity and specificity. Screening for LCHADD/MTP deficiency did not result in any dysbenefit. The number of false positives was low, the incidence was as expected and the programme did not identify any mild cases that would not have required treatment. LCHADD/MTP deficiency is a highly variable condition and clinical experience indicates that ~50% of cases have a very severe phenotype that has a poor prognosis despite early identification and treatment; however the remainder benefit greatly from treatment, which can be life-saving in many instances. The condition is rare, and a longer study should be carried out on order to assess the clinical utility of screening more accurately. As there are patients who would potentially benefit from screening with no obvious dysbenefits, we feel that LCHADD/MTP screening should continue for a few years more in the pilot sites before re-evaluation. The study reported a high false positive rate for IVA. However, it also showed that if the screening cut off value of the primary marker, C5 acylcarnitine, were raised from 1µmol/l to 2µmol/l, the number of

		false positives would reduce from 14 to 1 and the number of mild cases from 3 to 1. From clinical experience and from international experience with IVA screening, there are undoubtedly many cases of IVA that can potentially benefit from early diagnosis and treatment. The specific question of how many such patients exist and whether the UK newborn screening programme will be beneficial in this context cannot be answered in such a short time span and a longer study period is warranted. As the rate of false positives can be greatly reduced by raising the cut off value of the primary marker, we would recommend that screening for IVA be continued in the pilot sites with a cut off of 2.0µmol/l for a few years more before re-evaluation. In the future, newborn screening may be done earlier than day 5, and this would potentially offer further benefit for patients with the severe forms of MSUD and LCHADD/MTP deficiency. Experience from screening programmes in Europe and North America indicate that this would not significantly affect the sensitivity and specificity of the screening programme as a result. From the screening laboratory perspective, the assays and reporting mechanisms ran very smoothly with little impact on the current screening programme. From a clinical point of view, the clinical pathways that were established at the outset worked extremely well and the patients diagnosed on screening were appropriately managed. The information provided to health professionals and parents on the website was excellent and easily accessible when required. Finally, the economic evaluation indicated that screening for these disorders would be not only cost-effective, but also potentially cost-saving in the long run. With such rare disorders, a short period of follow-up and less than complete collection of data in the unscreened parts of the country, it is very difficult to unequivocally establish the benefits of screening. Despite this, the study has been able to show that screening can be done for these disorders without major problems and dysbenefits. This has provided a good model for evaluating further conditions that may be suitable for newborn screening.

Organisation:	Newcastle upon Tyne Hospitals NHS Foundation Trust, Newborn Screening & Metabolic Team		
Name:	Kim Bartlett	**Email address:**	xxxxxxxxxxxxxx
Please tick whether you are making this submission as an individual or on behalf of an organisation. **Individual** ☐ **Organisation** ☒			

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	Background and pilot	The expansion of the newborn screening programme to include five additional conditions requires careful assessment of any possible dysbenefit as well as examination of the technical and logistical issues and the demonstration of benefit. Although accepted in may other countries, it is clearly necessary to make a robust case of need in the context of NHS newborn screening practice and procedures. The pilot was of insufficient power to demonstrate benefit unequivocally for all five of the conditions under consideration but it was well suited to examine the impact of expansion on all other elements of the newborn screening pathway.
Recommendation of the NSC - in favour	The pilot study findings and the disorders recommended by the NSC	I welcome the recommendation in favour of GA1, MSUD and homocystinuria (pyridoxine unresponsive) by the NSC. For those patients diagnosed and entering the appropriate care pathway as a consequence of the pilot, the benefit is self-evident.
Recommendation of	The pilot study findings and the	The case for inclusion of IVA and LCHADD/MTP is less clear on the basis

the NSC - against	disorders not recommended by the NSC	of the pilot and the NSC declined to support their inclusion. I believe this is mistaken or at least premature. The case for exclusion of IVA is presumably because of the relatively high numbers of false positives. This would almost certainly be avoided by adjustment of the cut off to a value which would exclude the false positives but include the true positives – particularly of the severe phenotype. The pilot, although clearly demonstrating the absence of dysbenefit in regard to LCHADD/MTP, was not of sufficient duration to provide evidence of benefit. My recommendation would be to include all five conditions in an expanded national programme and then review when sufficient and statistically robust data has been accumulated.
Expanded Bloodspot consultation UK NSC recommendations	The potential resource impact of continuing screening for all five disorders vs three disorders.	The proposed expanded service would have a minor impact on the laboratory element of the screening pathway. Exactly the same sample would be used as is used for PKU and MCADD, with modification to the analytes detected in software. There would be a commensurate increase in the number of internal standards, calibration curves and QC protocols but this is a straightforward technical matter and the laboratories involved in project reported no difficulties in implementation. The clinical services required to care for screen positive babies would remain as they are now since the only difference would be that affected babies would be simply detected early in life rather than when they present clinically. I won't rehearse the clinical benefit of early diagnosis and institution of appropriate therapy.
Expanded Bloodspot consultation UK NSC	Conclusions	The pilot study, although it was not designed to assess outcomes, clearly demonstrated; (i) the absence of unavoidable dysbenefit, (ii) technical and

recommendations		logistical feasibility, (iii) straightforward integration into existing systems, (iv) very modest increased cost, and in as much as a time limited pilot is able, (v) the predicted number of screen positive babies. I conclude therefore, that all five conditions should be included in the national rollout with review of the outcomes three years after full implementation.

Organisation:	UK Patient Advocates for Newborn Screening (PANS) Group		
Name:	Patricia Roberts	**Email address:**	xxxxxxxxxxxxxxx

Please tick whether you are making this submission as an individual or on behalf of an organisation.

Individual ☐ **Organisation** ☒

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.*
		Thank you for the opportunity to participate in this expanded bloodspot consultation exercise following the pilot for screening for an additional 5 disorders. I am attaching our response. This response is on behalf of the UK Patient Advocates for Newborn Screening Group (SBUK, Climb, MPS Society, AGSD UK, ALD Life) however we have also consulted with the UK LSD Collaborative (representing Krabbe, MPS, AGSD Pompe, Niemann Pick, Battens, Tay Sachs and Gaucher) as there are key points of interest to both groups.
General comment	The operation of the pilot and findings.	PANS has welcomed this pilot, particularly the time and commitment given to the design and operation of the pilot, the efforts of everyone concerned, the work of the health professionals involved, the production of the reports and the consideration of the findings. We were pleased that the National Screening Committee were prepared to give financial support to 31st March 2014 to enable the screening to continue. We hope that funding will now be secured to continue with this programme and for it to be implemented across the rest of the UK.
Report to the UK National Screening Committee. Para1b-Table	The International picture	The 5 conditions selected for the pilot study are already widely included in the screening programmes of the developed world. In the European Member States, 10 countries already screen for 10 or more disorders. Note: Hungary and Iceland have now been added to this table as screening for these disorders (Source: ISNS). This is a conservative list. All countries use the same set of WHO criteria (Wilson and Jungner) in terms of the benefits and harms of NBS. Therefore extreme caution should be taken in discounting any disorder from the list for the UK.

Expanded Bloodspot Consultation Document	Introduction/recommendation.	The recommendation to include MSUD, GA1 and Homocystinuria in the UK NBS programme is welcomed and fully supported by PANS. The opportunity for early diagnosis is critical in saving the lives of babies.
Expanded Bloodspot consultation UK NSC recommendations Expanded NBS Study. Report to the NSC.	Overall case and conclusions. Paragraphs. 6 and 7	We support the inclusion of LCHADD in the UK newborn screening programme. It is acknowledged in the summary from the NSC that <u>there is little evidence in any disbenefits</u> of screening for LCHADD. Inherited Metabolic disorders are rare and we believe that the NSC acknowledges that all data is unlikely to be achieved in isolation in a one year pilot study. We recognize that the cases were MPT rather than LCHADD, however through international experience it is acknowledged that there is a significant benefit from early detection of LCHADD deficiency and in a proportion of MPT patients. Without evidence of significant disbenefit and the likelihood of cost savings we believe that screening for this disorder should be included. We support the opportunity to save more lives and prevent harm to children. LCHADD should not be abandoned at this stage.
UK NSC Health Economic Report	Conclusions on cost saving and result in increased quality of life.	There is considerable financial challenges in the NHS. The cost effectiveness study demonstrates that all 5 conditions are cost saving. Not only will it be cost effective but actually cost saving. We think there would have to be an extremely compelling reason to turn down cost savings when delivering clinical care.
Expanded NBS Study Report to the NSC.	The overall case Para 6 and Para 7 Conclusions	Within the group of “classical” organic acidurias, IVA appears to be exceptional considering its milder neuropathologic implications. The potential to avoid neonatal mortality and to improve neurologic and cognitive outcome under early treatments reinforces IVA to be qualified for newborn screening”. On this basis and with a modified cut off to reduce the number of false positives and improve the PPV percentage (which we understand is quite feasible) IVA should be maintained within the screening panel as early detection appears to offer very significant potential benefit to a proportion of these patients. IVA is included and is valued in other European screening programmes with no country abandoning screening for IVA once introduced.
PANS Comment		The period of the pilot (12 months) was not sufficient in time to resolve all the issues. We, as patient organization representatives, are certainly not insensitive to the anxieties of families. However in terms of the cut offs which we know from

		scientific colleagues can be addressed (and indeed other similar issues that can be reasonably addressed) there will be a process of regular review within the laboratories. This is a standard process of review as dictated by Public Health England. IVA and LCHADD should be implemented along with the NSC recommended 3 and allow any issues to be addressed within the review process **i.e. rather than 'dropping' these 2 disorders and putting children's lives at risk.** The pilot has gone extremely smoothly. The pilot laboratories are doing the screening for IVA and LCHADD. Why would you reasonably remove them? The NSC needs to have confidence in the scientists who confirm the issues can be addressed.
UK NSC Health Economic Report		We understand that the inclusion of IVA and LCHADD alongside other disorders does not actually alter the cost of screening.
		We understand that since the pilot report statistics were prepared for the NSC, true positives of IVA and LCHADD in babies have been identified. This surely supports the criticality of implementing these 2 disorders as part of the newborn screening programme. Why would you drop them when it is proving screening in the pilot laboratories is saving babies lives? Even if IVA does not present neonatally, it will present further down the line. We can be aware of this through newborn screening so that early treatment can be given and not only can the child benefit but it must be economically sensible too.
UK NSC Health Economic Report		Overall the impact of including all five conditions, with a modified cut-off for IVA, rather than only the three proposed by the NSC is likely to result in additional cost savings, significant potential benefit for a proportion of both the IVA and LCHADD patients and little evidence of disbenefit with the generation of only 3 additional false positive results based on the pilot findings.
Birth Prevalence Report of the IMDs	Para 4 Conclusions	Since the introduction of MCADD on to the UK newborn screening programme the number of newborns identified with MCADD has shown to be over 50% more than estimated. This in itself would be a very valid reason to including all 5

		disorders, GA1, HCU, IVA, LCHADD and MSUD to the UK newborn screening programme.
PANS Comment of the position in the Netherlands	International Society for Neonatal Screening (Netherlands)	Neonatal Screening for IVA and LCHADD has been on the Dutch screening panel since 2007. There are 180000 births per year. Each year 2-3 cases of IVA and 2-3 cases of LCHADD are reported. It is clear that screening for these 2 disorders is saving lives. We are aware of cases identified in laboratories in the UK over recent years where the children with IVA and LCHADD have died. Prognosis would have been better if children had been identified through NBS.
PANS Comment of the position in New Zealand	NZ Organization for Rare Disorders	IVA and LCHADD have been part of the New Zealand neonatal screening programme for some years. New Zealand regularly review the disorders on their programme to confirm that screening for disorders have more benefit than harm and remain relevant to the screening programme. IVA and LCHADD screening remains valued and there are no plans to remove these disorders from the NZ screening programme in the foreseeable future.
Omission from the report	Day of screening	No mention has been made in this report in respect of the day of screening. This question does have some relevance to some findings. The NSC has been advising us for several years that they intend re examining the day of screening. We are not aware of any research or study being commissioned. If it has been commissioned it has not been shared with patient groups and stakeholders. We need to point out that it is important that some review is done on the day of screening.

Organisation:	**Leeds Teaching Hospitals Biochemical Genetics Laboratory**		
Name:	Mick Henderson	**Email address:**	xxxxxxxxxxxxxx
Please tick whether you are making this submission as an individual or on behalf of an organisation. **Individual** ☐ **Organisation** ✓			

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.*
Recommendation of the NSC - against	The pilot study findings and the disorders not recommended by the NSC	Whilst we are pleased to see that the NSC is likely to recommend the inclusion of screening for MSUD, homocystinuria and GA1 we would contest the decision to exclude IVA and LCHADD. Our experience of IVA cases through diagnosis strongly suggests that early detection through screening would have improved prognosis. We believe that the milder cases detected in the pilot could be avoided by increasing the laboratory analytical cutoff. We feel that to exclude LHCADD on the basis that insufficient cases were detected in the pilot is not warranted. We would make two points, firstly that the aim of the pilot was to test dysbenefit, i.e. acceptable false positives rather than to test for clinical benefit. The false positive rate from the C16OH was no higher than for the others, there were just cases. Secondly we know from clibnical diagnoses that this condition exists in our population. Our metabolic lab has had four definite and three likely cases in the past fifteen years. Two of these were early deaths, but the others would have benefited from screening

Organisation:	Chairman of the Screening Committee of the German Society for Paediatrics and Adolescent Medicine		
Name:	Prof. Dr. G.F. Hoffmann	**Email address:**	xxxxxxxxxxxxxxx

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Individual ☐ **Organisation** ☒

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.*
	Overall	Excellent report based on a comprehensive analysis of the scientific literature and evidence and careful evaluation of the results
	Overall	Inclusion of MSUD, GA I is coherent and consistent with the German NBS panel and the decision to recommend this disorder to be included for NBS in the UK is highly supported from our own scientific and clinical experience.
	Overall	Homocystinuria is not screened for in Germany mainly for reason of its very low prevalence. Although prevalence is also rather low in the reported study, data are consistent with the decision to continue screening. However, as the prevalence is the lowest for all disorders in the study, continuation of screening is suggested.
	Overall	The study is exceptional in its design and analysis and pathbreaking for NBS in general. However, I express my deep concern that the study may be interrupted too early. As it is stated already in the documents, prevalence values (estimated from the literature as well as empirical data from the study) are still low and to achieve reliable values for the individual disorders them will need a longer study period. I consider this different for the lumped

		evaluation.
	Overall	Information that NBS for all disorders is cost-efficient/ cost-saving is very important also for other NBS programmes
	Overall	A most important information for NBS programmes in general is that overall there was no dysbenefit of screening for all five disorders.
	LCHADD	
Report pages 66 and 79	**Figure 1 for HCU vs. Figure 1 for LCHADD**	Comparing the two figures it is difficult to understand why opposite conclusions were drawn for the two conditions.
	LCHADD	Also NSC argument: one year pilot too short for an evaluation; continuation is recommended.
	LCHADD/MTP	NBS is effective for outcome of LCHADD. Positive NBS result in case of MTP also have a positive effect by early diagnosis despite fatal course.
	IVA	
Report page 58	The patients diagnosed with isovaleric acidaemia were mostly (3 of 4) mild from a biochemical perspective and the remaining patient sadly died. The intervention (emergency regimen only in mild cases) may not have offered significant dysbenefit to the families but the medicalisation of a healthy child is not trivial.	From our experience in Germany severe (classical) cases of isovaleric acidaemia is about equal to mild forms. The outcome in severe cases (~50) is greatly improved with normal middle and long-term development versus death or significant handicap in >90% of patients. The experience from your study in England still rests on very low numbers. , i.e. 4. No doubt medicalization of a healthy child is not trivial, and should be avoided as much as possible. However, the problem of false positive cases is inherent for any screening disorder. It has been shown that negative effects can be well ameliorated if counselling of parents after a false positive result is done in a professional manner (Hewlett, J. & Waisbren, S. E. A review of the psychosocial effects of false-positive results on parents and current communication practices in newborn screening Journal of Inherited Metabolic Disease, 2006, 296). 677-682)
Report page 62	Increasing the cut off value from 1.0 µmol/L to 2.0	We see this to be a strong argument to continue NBS for

	µmol/L would reduce the number of false positives from 14 to 1 and remove two of the three “mild” cases. In the German experience dried blood spot C5 acylcarnitine was >10µ/L in “classic” cases and was 11.9 µmol/L in your single case. It would be reasonable to increase the current cut off to 2 µmol/L to avoid false positive results.	isovaleric acidaemia at least in the forthcoming study period.
Birth prevalence Page 37	As can be seen, the predicted number of cases falls within the estimated number for some conditions (GA-1, IVA) and not others, such as in the case of LCHADD, where the predicted number of cases is higher (three as opposed to one that was an actual screen positive).	As it is written in the text differences between observed and expected values should be interpreted carefully. E.g. given the prevalence rate of 2.94 (table 3.7.b) the binomial probability to find 1 LCHADD in 438000 births is 0.16 (one will find one case every 6.25 years) and to find 3 would be 0.22 (one will find 3 cases every 4.55 years), not a meaningful difference. The observation period seems to be too short to draw solid conclusions.

Organisation:	Royal College of Paediatrics and Child Health		
Name:	Comments provided on behalf of the following: • Dr Jane Hawdon • Dr Oliver Rackham (Consultant)	**Email address:**	xxxxxxxxxxxxxx

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Individual ☐ **Organisation** ☒

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		We agree with the proposal and the review seems to have been thorough and fair.
P25-28	Information leaflet	The “possible” homocystinuria leaflet is very “wordy” for the first thing that parents will see. The abbreviation HCU does not add anything and should not be used in there. There are lots of unnecessary capitals (eg homocystinuria in the middle of sentences, or “specialist metabolic team”).
P29-35	Information leaflet	Again, very “wordy”. Abbreviation doesn’t help. Capitals used inappropriately.
P36	GP letter	Needs to be clearer that this is a “suspected” case. The first sentence talks about a positive test, but needs to say that it is a positive screening test. Will copy go to hospital consultant? – may be under their care for some other reason, or may be admitted. Make it clear that no action is needed by GP.
P37-38	GP letter	Will copy go to hospital consultant? – may be under their care for some other reason, or may be admitted. Make it clear what action is needed by GP; will they be asked to prescribe anything?

Organisation:	Inherited Metabolic Disorders Laboratory, Birmingham Children's Hospital NHS Trust		
Name:	Mary Anne Preece	**Email address:**	xxxxxxxxxxxxxxx

Please tick whether you are making this submission as an individual or on behalf of an organisation.

Individual ☐ **Organisation** ☒

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.*
	Overall comment	We are pleased that the NSC has supported the expanded screening pilot study and in particular that funding has been provided while the results are evaluated and consultation is undertaken.
	Overall comment	In our laboratory the pilot study has proceeded without issue, both from the point of view of the screening assays and the diagnostic protocol.
	Overall comment	We are pleased that the NSC is recommending that screening for GA1, MSUD and HCU (pyridoxine responsive) continues and is rolled out across the country
Report to NSC, P5	Use of pivaloyl antibiotics	These antibiotics are not widely used in this country, but present a problem for NBS because of interference in the screening test for IVA. If screening for this disorder continues, information re potential false positive NBS for IVA should be included in the BNF information for this group of antibiotics.
Report to NSC, P15	Homocystinuria screening algorithm	The use of dried blood spot homocysteine as part of the screening protocol has proved effective. It has enabled a low cut-off for the primary analyte enhancing sensitivity (methionine, 50 µmol/l), whilst maintaining specificity.

Report to NSC, P46	****CORRECTION TO TABLE 5****	Table 5, page 45, IVA false positive patient 2 with C5 of 3.6 µmol/L – mother was taking pivmecillinam, a pivalic acid containing anti-biotic. This was not ascertained at the clinic appointment, which is why we suggest this question is included in the diagnostic protocol.
Report to NSC, P61	Overall case for LCHADD/MTP	It is disappointing that the NSC does not believe there is a case for screening for LCHADD/MTP. The data available is limited. The pilot study aimed to evaluate the logistics and dysbenefits of screening. It did not have the power to determine the outcome of screening. Dysbenefit was not identified. Health economic analysis showed that screening for LCHADD/MTP is potentially cost-saving, and would lead to increased quality of life. This condition is heterogeneous and we have to accept that some cases will die in the neonatal period, and that in most of these cases death is inevitable. In our experience the majority of (historical) surviving non-screened patients with LCHADD/MTP present acutely unwell, sometimes requiring intensive care. This is surely what newborn screening should be trying to prevent. We suggest that screening for this condition continues. Further evaluation could take place after a number of years, or after a certain number of cases have been detected.
Report to NSC, P62	Overall case for IVA	The number of false positives for this condition is clearly of

		concern, however the suggested change of cut-off value for C5 from 1.0 to 2.0 µmol/l would eliminate all but one of the false positive cases. The remaining false positive case was a case of maternal pivmecillinam medication (***omitted in Table 5, page 45, IVA false positive patient 2 with C5 of 3.6 µmol/L***). This could have been ascertained upon first contact made with the family, and although follow-up would still be required, the anxiety level should be much less. We agree with the suggestion that screening for this condition continues with an increased cut off value for C5 of at least 2.0 µmol/l. The first contact with the family could ask about maternal antibiotic usage. Questions regarding anti-biotic usage should be included in the diagnostic protocol. Using this value

Organisation:	Sheffield Teaching Hospitals NHS FT		
Name:	Dr Kathy Jeays-Ward	**Email address:**	xxxxxxxxxxxxxxx

Please tick whether you are making this submission as an individual or on behalf of an organisation.

Individual x☐ Organisation ☐

Section and / or page number	Text or issue to which comments relate	Comment
		nb please note that I was the project manager for part of the Expanded Newborn Screening project
Health economic report conclusions, p10	Whether LCHADD should be screened	As LCHADD screening is predicted to be cost saving for the NHS and has shown no dysbenefit during the ENBS project, can LCHADD screening be continued for the purpose of continued data collection, such that a decision can be made at a later date? Additionally, it may be that in the future, if the day the heel prick test is performed closer to birth (it is currently day 5-8), LCHADD screening will show more obvious benefits (significant patient benefits, as well as further cost savings) as cases are recognised early enough to ensure treatment is effective.
Health economic report conclusions, p10	Whether IVA should be screened	IVA screening is also predicted to be cost saving for the NHS, though has the dysbenefit of medicalising patients who would otherwise not have been detected or treated. Could screening continue for ongoing data collection to clarify the benefits of screening? Raising the screening cut off value for the relevant metabolite (called C5) would decrease the number of false positive screening results. Raising the cut off value would also reduce the number of patients identified with IVA and consequently medicalised; the patients that would not have been identified if the higher cut off value had been used are not receiving ongoing dietarty treatment, though they have received education about their disorder, and provided with an emergency regimen. It remains to be seen whether they will ever display any symptoms of the disorder.

		Several factors are also suspected of causing false positives: maternal antibiotic use, premature births. Ongoing data collection could enable a better-informed screening decision that factors in an altered cut off value, prematurity and antibiotic usage. Additionally, we currently have a funding bid under considering with the Wellcome Trust, which if successful, will allow us to research the complex correlation between genotype (genetics) and phenotype (physical manifestation of the disease) for whichever expanded screening conditions are adopted. If IVA is adopted, correlating genotype and phenotype could enable further cost savings to the NHS through improved clinical definition of patients diagnosed with IVA but who can be shown genetically to be requiring little or no treatment. Without screening for IVA there would not be adequate data available to conduct such a study.
	Screening for HCU, MSUD and LCHADD	I am wholly in support of national screening for these disorders.

Organisation:			
Name:	Catherine Dibden	**Email address:**	xxxxxxxxxxxxxxx

Please tick whether you are making this submission as an individual or on behalf of an organisation.

Individual ☒ **Organisation** ☐

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.*
UK NSC Health Economics report, p7	Table 3 - Costs and effects of screening for each condition compared to no screening	I am encouraged to see that there is a dominating cost benefit to screening for each of the five conditions. In particular I am struck by the considerable cost benefit of screening for LCHADD; only MSUD offers a more significant cost benefit.
UK NSC Health Economics report, p11	Bottom paragraph, beginning “Screening for LCHADD”	I feel strongly that any uncertainty surrounding the nomenclature and classification of LCHADD and its related disorders should not detract from the very real benefits of detecting and treating this group of conditions. I ask you to reconsider including LCHADD in the newborn blood spot screening programme.
Expanded blood spot evaluation UK NSC report**,** p5	Table 2 - Five conditions and countries that offer newborn screening for these conditions	I note that IVA and LCHADD are almost unanimously screened for in every country included in the table. If anything, homocystinuria appears to be the least screened for disorder out of these five conditions.
Expanded blood spot evaluation UK NSC report**,** p60-61	Long chain hydroxyl acyl CoA dehydrogenase/MTP deficiency	It is possible that the small positive case numbers have confounded the conclusions for LCHADD. Would it be possible to re-evaluate the data, combined with additional data from the ongoing pilot extension, before drawing any firm

		conclusions from this?
Expanded blood spot evaluation UK NSC report**,** p61	Isovaleric Acidaemia	I strongly agree with the conclusions of the German study that the treatability of IVA makes it a very worthwhile condition to screen for.
Expanded blood spot evaluation UK NSC report**,** p62	Isovaleric Acidaemia	I support the suggestion to change the cut-off to 2 µmol/L to reduce the number of false positive results, rather than exclude IVA from the screening programme.

Dear Hugh

Thank you for asking for comments on the UK NSC's recommendation to expand newborn blood spot screening. The following comments are based on the opinions of the members of the Clinical Reference Group (CRG) for metabolic disorders. Membership of the CRG include specialist clinical staff, including dieticians and nurses, specialist biochemists, patients and patient representatives.

We fully support the inclusion of homocystinuria, MSUD and GA1. The evidence for screening for these disorders from the evaluation and cost effectiveness study is compelling and additionally there is good international experience that confirms the effectiveness of their inclusion. The clinical benefit from early diagnosis and treatment is well described and in keeping with clinical experience in the UK. Importantly the screening methodology has good sensitivity and specificity.

The issues regarding LCHADD and IVA are somewhat more complex, however, we strongly recommend that both disorders are included in the national expanded screening programme and that their continued inclusion is reviewed after a period of 3 to 5 years. The reasons for our recommendation are as follows:

- The UK NSC has highlighted the number of false positives for IVA screening. However the specificity to detect severe IVA could be improved considerably by increasing the cut off for C5 acyl carnitine from 1 µmol/L to 2.0 µmol/L. In the evaluation study this would have resulted in all but one of the false positive cases being excluded.
- IVA is a treatable condition and there is sufficient clinical experience from those children who have been diagnosed and started treatment in the newborn period to conclude that their outcome with treatment is good. In view of rarity of the severe forms of IVA it is not possible to come to an informed conclusion from such a short period of evaluation regarding clinical benefit. In this context is important to consider the experience of other countries where screening for IVA has been practiced for a number of years. Although not necessarily germane to the UK situation the practice in other developed countries is relevant & the published literature does recommend that IVA is included.
- In view of the above we suggest that it would be appropriate to recommend that IVA screening is included in the programme but with the cut off for a positive test increased to 2 µmol/L.
- LCHAD/MTP deficiency is also an extremely rare disorder and as with IVA it is unreasonable to make a judgement on the clinical benefit of screening from a one year period of evaluation. The severity of LCHAD/MTP deficiency is variable; the outcome for severe disease is often poor even with treatment, however, the clinical experience in the UK and elsewhere for isolated LCHAD deficiency and less severe forms of MTP deficiency is that

outcome is considerably improved with early diagnosis and treatment. Since there was not evidence of dysbenefit and modelling suggesting cost effectiveness, it would seem appropriate to included screening for LHAD/MTP deficiency.

- Newborn screening may in the future be before day 5; this would enable earlier diagnosis and treatment and the international experience is that specificity or sensitivity would not be adversely affected. Since the pilot study has not identified any significant dysbenefit in screening for LCHADD/MTP it would be beneficial to continue to obtain experience with this disorder, particularly with regard to the day of its clinical onset.
- The Newborn Screening and Metabolic Laboratories have reported to us that, from a laboratory point of view, the implementation of the assays went extremely smoothly with little, if any, impact upon the existing laboratory screening programme. They recommend that that both IVA and LCHADD deserve to remain in the repertoire of conditions screened for and that increasing the cut off for IVA, as suggested above, will reduce the number of false positives.
- Finally, the experience of specialist paediatricians and dieticians is that the inclusion of all 5 disorders has not led to a significant increase in work load that will require additional resources.

In conclusion we fully support maintaining homocystinuria, MSUD, and GA1 in the expanded screening programme but also strongly recommend that screening for LCHAD/MTP deficiency and IVA should also be included. A review of the screening programme should then be undertaken after a further 3 to 5 years by which time there will be sufficient data available to make an informed decision as to their continued inclusion.

Professor John Walter MD FRCPCH

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This is a formal response to the consultation on the pilot expanded newborn screening, on behalf of the S.E Thames Regional Newborn Screening service.

We are of the view that all five conditions should remain within the expanded national screening programme.

We believe the National Screening Committee have engaged positively in support of this pilot and should be congratulated for the thought and time that they have afforded to the design and operation of the pilot and the consideration of its findings. In particular they offered financial support to continue screening until 31st March 2014 to allow a considered decision to be reached and this is welcomed.

The recommendation to include MSUD, GA1 and homocystnuria is to be welcomed and supported and the recognition of potential patient benefit is eagerly awaited.

The five conditions selected for study are already widely included within newborn screening programmes in the developed world including Europe with ten countries in Europe screening for ten or more disorders. While not in itself proving evidence of benefit or providing a reason to screen in the UK, this suggests that this is a conservative list and discounting individual disorders from it should be undertaken very cautiously.

All five conditions were considered to be cost saving by a carefully conducted cost effectiveness study. This means that not only will screening for these disorders provide a "cost effective" intervention, it is actually "cost saving". At a time of considerable financial challenge in the NHS there would need to be a very compelling reason to turn down cost savings when delivering clinical care, particularly if these offered potential clinical benefits.

LCHADD It is acknowledged in the summary from the NSC that there was little evidence of dysbenefit from screening for LCHADD. These metabolic disorders are rare and the NSC acknowledged that data relating to benefit was unlikely to be provided by a one year pilot in isolation, as it happens for LCHADD/MTP, all cases identified were mitochondrial trifunctional protein deficiency (MTP) rather than LCHADD. It is generally acknowledged from international experience that there is significant benefit from early detection in true LCHADD deficiency and in a proportion of MTP patients. Without evidence of significant dysbenefit and with the likelihood of cost savings, screening for this disorder should not be abandoned at this stage on the evidence of one year.

IVA Our experience with IVA is broadly in line with international data in that the positive predictive value (PPV%) and ratio of mild:severe cases (3:1) in our study is similar to that in Germany who identified 14 mild cases and 5 severe cases in a recent communication from the Heidelberg centre - this information is included within the study report on page 61. By increasing the C5 screening cut-off from 1.0 µmol/L to 2.0 µmol/L we have the potential to avoid 13 of the 14 false positives experienced during the study and reduce the number of mild cases identified from 3 to 1. This suggested modification to the screening protocol is explained on page 62 of the report and should not reduce the sensitivity of detection for classic cases which the Heidelberg group define as having a C5 of >10 µmol/L. Screening for IVA is valued in other screening programmes and a thorough report of screening outcomes published in 2012

by Grunert *S, Wendelz U, Lindner M, Leichsenring M, Schwab K, Vockley J, Lehnert W and Ensenauer R, 2012. Clinical and neurocognitive outcome in symptomatic isovaleric acidemia. Orphanet Journal of Rare Diseases 2012, 7:9* concluded that ""Within the group of "classical" organic acidurias, IVA appears to be exceptional considering its milder neuropathologic implications. The potential to avoid neonatal mortality and to improve neurologic and cognitive outcome under early treatments reinforces IVA to be qualified for newborn screening". On this basis and with a modified cut-off to reduce the number of false positives and improve the PPV%, IVA should be maintained within the screening panel as early detection appears to offer very significant potential benefit to a proportion of these patients.

While it may not be material in the decision, the inclusion of IVA and LCHADD alongside the other disorders does not really alter the cost of screening from a laboratory perspective as the relevant analytes are already included in the internal standard packages used for the other conditions. With an amended cut-off for IVA the clinical costs associated with including IVA and LCHADD are likely to be very modest, perhaps 5 false positives pa based on the current data.

Overall the impact of including all five conditions, with a modified cut-off for IVA, rather than the three proposed by the NSC is likely to result in additional cost savings, significant potential benefit for a proportion of both the IVA and LCHADD patients and little evidence of dysbenefit with the generation of only 3 additional false positive results based on the pilot findings. The resulting PPV% for all five disorders would be 71%.

Rachel Carling
On behalf of SE Thames Regional Newborn Screening Service

Dr Rachel Carling FRCPath | GSTS Pathology
Director of Service, Biochemical Sciences

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National Screening Committee Expanded Newborn Bloodspot Consultation

Response by PHG Foundation, Cambridge

Hilary Burton (Director) and Sowmiya Moorthie (Project Manager)

Email: xxxxxxxxxxxxxxx

PHG Foundation, March 17, 2014

Introduction

The PHG Foundation (PHGF) is an independent health policy think-tank with a special focus on genomics and other emerging health technologies that can provide more accurate and effective personalised medicine, and their impact upon clinical and public health services. Our overarching mission is to make science work health. Our aims are to influence health and public health systems to make best use of these advances and to promote a social and regulatory environment that is receptive to innovation, without imposing an undue or inequitable public burden.

Background expertise

Our expertise in newborn screening is from the public health perspective. We undertook a systematic review of the 5 conditions that were proposed in preparation for the expanded newborn screening pilot programme under consideration in this consultation[1] and extended and updated the review of prevalence of the conditions in October 2013 as part of the work[2].

We have also contributed over recent years to the development of policies on rare disorders and undertaken policy work on the use of genomic technologies to predict and prevent disease.

More recently we have been involved in screening more generally within the UK, including as a working group member for the current NSC Review. As part of this, we have undertaken a systematic review (not yet published) of international criteria for decision-making on new genetic screening programmes and of the associated ethical, social and legal issues.

Responses to NSC recommendations

[1] Burton H and Moorthie S. Expanded newborn screening. A review of the evidence. PHG Foundation 2010. Download from www.phgfoundation.org

[2] Moorthie S, Cameron L, Sagoo G and Burton H. A systematic review of the birth prevalence of five inherited metabolic disorders.

1 Recommendation to expand the current screening programme to include homocystinuria (HCU), Maple Syrup Urine Disease (MSUD) and Glutaric Aciduria Type 1 (GA1)

We support the recommendation to include MSUD, GA1 and homocystinuria in the newborn blood spot screening programme.

We believe there is evidence that outcomes are better if infants are diagnosed early and treatment commences before symptoms occur. This is also supported by international evidence. The pilot programme showed that screening could be introduced without disruption of current laboratory, clinical diagnostic and treatment systems or community based screening services and without causing anxiety to parents. Suitable laboratory procedures including cut-offs for screening and follow up diagnostic testing were defined and found to be workable.

2 Recommendation not to include Isovaleric acidaemia (IVA)

We do not agree with the recommendation of the NSC not to include IVA.

The Committee considered that early detection by screening was not likely to have conferred benefit for IVA and so did not recommend continuation of screening for this condition. We are concerned that this recommendation was made on the basis of the very small number of cases in this pilot and specifically on the basis of 14 false positives, 3 mild cases and one severely affected baby who died. This decision is not logical and demonstrates a mismatch between the expectations of the NSC and the original purpose of the pilot. Regarding the number and type of diseases diagnosed, the systematic review undertaken by PHG Foundation for the pilot had estimated the numbers of cases that would be diagnosed and the proportion of severe and mild cases. The numbers reported by the pilot are subject to the inherent variation associated with small numbers and so the findings are totally as expected and within the boundaries of random variation.

Regarding positives tests, one of the purposes of the pilot was to develop working cut-off points that would help to diminish the number of false positives. The pilot did indeed achieve this and made recommendations estimated to reduce this number from 14 as found in the pilot to one single false positive.

The pilot was also intended to assess any issues associated with positive case referral and confirmatory testing. Again, it showed that there were no logistical problems in dealing with this number of positive cases.

The preliminary and international evidence had already shown that, on balance, newborn screening is effective and cost-effective. It was not possible for the pilot programme to re-examine this evidence, nor was it the purpose of the pilot to obtain evidence on clinical presentation, response to treatment and outcome. Cases detected through the pilot programme were entirely within the range of expectation of the systematic review, which provided evidence that clinical presentation is most often in the first two weeks (76%), but may also be from 2 weeks to one year (19 %) or even over 1 year. Inevitably the screening pilot entailed very small number of diagnoses and it is illogical to favour the pilot evidence over the more extensive and systematically collected international evidence. The

fact that there was no evidence of significant benefit in the particular pilot cases does not negate the previous wider international evidence.

Finally, the NSC is concerned about medicalization of the three mild cases. The report comments that they may require little medication. However, they may still require support at times of metabolic stress such as surgery or febrile illness and may require low dose carnitine supplementation if the plasma levels are reduced. There was no evidence in the previous systematic review that these patients would be better not to know about a mild diagnosis. Although the pilot report says that this medicalization is not 'insignificant', we would argue that it is one of the inevitable downsides of disease prevention based on risk. It is always necessary to alert patients to potential problems in order that they can avert future harm. In many cases (for example cholesterol testing) individuals undergo tests to find out their level of risk for cardiovascular disease. Those at high risk will inevitably experience inconvenience (e.g. dietary restriction) and even potential harm through preventive treatment, for example with statins. It is the case in risk-based prevention that a number of patients will be made anxious or 'medicalized' in order to prevent disease or severe complications in a few. In the case of IVA, over the whole country, out of 437,187 births, three patients were identified with mild disease and given precautionary advice to avoid potentially catastrophic metabolic crisis. It does not seem to us to be unreasonable medicalization that the newborn screening programme might enable them to do so.

Further, we would also suggest that, as knowledge accrues about the genetic heterogeneity of these conditions, the assembly of such knowledge alongside data on clinical phenotype, natural history and response to treatment will provide valuable clinical evidence on how best to manage the various subsets of these conditions in the future. With such knowledge it may, in the future, be possible to reassure some patients that they have a genetic variation that will not cause further harm. It is not possible to do this at present and, given the rarity of the condition, this position may be some time off. Such knowledge will be essential to ensure future 'personalised' and 'evidence based care' for patients with these rare conditions.

3 Recommendation not to include LCHADD/MTP deficiencies

We do not agree with the recommendation not to include LCHADD/MTP deficiencies.

As for IVA, the NSC decision has been made on a very small number of cases arising in the pilot that are entirely within the range of numbers and presentations that were predicted by the systematic review and background literature. Evidence from the literature showed that a few patients (15%) present in the first month and most within 6 weeks and 6 months of age, with a number of patients dying following these acute presentations. Of the seven cases in the pilot study, there was one who was screen positive, but this case had presented earlier before the screening result was known so did not technically benefit from screening. Two patients died before screening.

The fact that patients identified during the pilot study fell into these particular presentation categories and so did not directly benefit from the screening programme is not a reason to abandon screening for this condition, as it does not negate the international evidence. The literature shows (see p 99 of the 2010 systematic review) that, overall, death and risk of complications is lower in a screened group than

in a clinically detected group. Even for those who still die there was the advantage of early information and the avoidance of unnecessary diagnostic and therapeutic measures together with the availability of information to guide future reproductive choices for their patients.

With regard to test performance for LCHADD, there was one false negative (or missed) case that the pilot programme is confident could be avoided in future by change of cut-off point. There were two false positives, which were resolved in 2 and 4 days respectively.

As for the other conditions, the pilot programme established that testing for LCHADD/MTP could be introduced without disruption to laboratories or clinical services and without causing anxiety to parents.

4 General comments

Overall we would urge the National Screening Committee before it makes its final recommendations to review the purpose of the pilot programmes for expanded newborn screening and to consider the evidence in the light of this purpose. The pilots were not intended to ascertain birth prevalence nor to describe clinical presentation or evaluate clinical outcomes and were not powered to do so. The purpose was to establish whether newborn screening programmes were feasible for these conditions in the UK system without causing undue disquiet and anxiety amongst parents, disruption to services and overburdening the laboratory staff and to establish an effective, efficient and acceptable service. The pilot confirmed that this was the case and, established laboratory systems and cut-offs to refine test performances and ensure optimum sensitivity and specificity. The overall evidence on this service was positive.

We therefore believe and recommend that it is illogical to dismiss two of the conditions on the basis of the precise timing and presentation of the very small number of incident cases during the pilot time frame.

On a wider scale, we would like to reiterate some of our general comments as set out in our May 2010 *Report Chapter 10*.[3]

'An expanded screening program based on pre-established screening technology would create opportunities to significantly improve the quality of life for affected individuals, and reflect a growing institutional and public awareness of the burden of rare diseases. The common problems presented by rare diseases are characterised by inefficiency and waste from misdiagnosis, delay, repeat consultation and inappropriate treatment, problems that could be in many cases alleviated by an expanded screening program. These problems present a chronic challenge to the healthcare system as a whole and an acute disadvantage to individuals, for whom time is of the essence.

The disparity in prognosis between early and late diagnosis is a common concern in rare disease policy and screening for these disorders would indicate a positive trend towards addressing this problem. Given the issue presented by rarity and scale, a full national approach presents the best opportunity for catching cases early and treating them effectively. Early diagnosis also allows for more rapid

[3] Expanded newborn screening programme and EU policy towards rare diseases submitted by GIG (now Genetic Alliance UK) and RDUK. Authors: Alastair Kent, Melissa Hillier and David Brown.

mobilisation and implementation of expertise that may not be immediately available due to the rarity of the condition. Screening will also identify individuals whose condition may not become symptomatic until permanent damage or disability has occurred.

The expansion of the newborn screening programme would be a clear, visible and measurable movement on the part of the UK towards tackling rare diseases as a public health concern in line with their signing of the Council Recommendation on an Action in the Field of Rare Diseases. The five conditions are well below the 5 in 10,000 prevalence threshold for recognition as Rare Diseases'.

Finally, in conjunction with the advances in genomics and research on rare diseases, for example through projects such as the 100,000 genomes project, there is now increasing understanding of the centrality of prospective data collection that would include genotype, clinical and biochemical characteristics, treatment and outcomes. Identifying patients effectively at an early stage and enrolling them in such rare disease cohorts is the only way in which we will learn more about these conditions and their heterogeneity and fine-tune management in order to personalise treatments for individuals. This will be extremely important for clinical care, and we believe that discarding IVA and LCHADD at this stage, without evidence of harm, would be retrogressive.

5 Recommendation

We recommend that the NSC should reconsider its decision to limit expansion of newborn screening and to include all five conditions. This would:

- **Signal its support for UK rare disease strategy by enhancing diagnostic pathways for these rare metabolic disorders**
- **Improve the effectiveness and cost effectiveness of NHS diagnosis and treatment for rare inherited metabolic disorders**
- **Contribute to increased international understanding of these conditions, including genetic heterogeneity and its link to phenotype including clinical presentation, biochemical profile and response to treatment.**

And most importantly:

- **Have a dramatic impact on the lives of a small number of patients and their families by preventing catastrophic consequences of acute metabolic crises, chronic multisystem damage and death.**

To whom it may concern:

I would like to present to you the story of my son xxxxxxx, diagnosed at the age of 7 with HCU. Our family is from xxxxxxxx, in the United States. He was born xxxxxxxxx, at the hospital that I work. He was screened with the newborn metabolic screening test that was available at the time. Knowing the likelihood of any disorder proving positive, I barely paid any mention that his test was negative. Our family is healthy...we had another child without problems. We went on to have a third child, also without problems. It was not until 2 years after the birth if our third child that xxxxxxx failed a kindergarten eye test and we had him seen by an ophthalmologist. Nine months and three sets if glasses later, we recognized the slowly detaching lenses of his left, then right eye. We left the appointment that day worried that xxxxxxxx had Marfan's disease. Of course he couldn't have the other, far rarer disorders that cause that problem. He'd had his newborn screen. Twice. And after doing a great job learning to nurse.
Imagine our surprise when he was diagnosed with classic HCU three weeks later. To explain the crushing pain I felt as a parent, the worry and the fear, is to try and put my heart onto paper. To hear that xxxxxxxxx could have been diagnosed in those first days of life remains devastating. And to know that, had it not been for the test being pulled from the newborn screen for a decade, that he could have been being treated for his disease; that element formed the "what if..," that as a parent, you never can let go of. HCU was not on the newborn screen for that decade because of "low yield". "Low yield" in our family has a name, a face, and a spirit: it's xxxxxxx.

NB: accompanying image has been redacted
xxxxxxxxx, far right, pictured with his sister, xxxxxxxx and younger brother,xxxxxxxxx, Christmas 2013

Shortly after his birth, HCU was added back to Oregon's newborn screen testing. And I wish he'd been born later. I wish he would have been diagnosed as an infant, so we would have been doing for him what he needed. It was far harder to teach a child to take medicine and completely adjust his diet after he had had seven years of life (as a good eater, mind you), to develop a love of all different types of foods: shrimp, ribs, bacon being three that, to this day, 5 years later, he still longs for. I wish he hadn't presented with a level of 396. Normal for non-HCU is 4-12. Target for him, with HCU is 30. I'll forever worry that his normal-for-him-then-diet has put him at long term risk of clots and stroke, and early death.
He has gone on to adjust to his medicine and diet regimen. His eyes are still a problem, and will likely go on to requiring surgical intervention. We have adjusted to the diagnosis as a family. And we've learned that his brother and sister do not have HCU. That relief is tempered only by the likelihood that both of them are carriers for the disorder. They can anticipate for the future accordingly, knowing what they know.
I worry about the families--like ours--out there who have no idea of this disease and it's ramifications. I know the pain of a new metabolic diagnosis. And while I'd never wish another family to have to experience it, to eliminate the in-betweens that we had to suffer, would be to

eliminate so many concerns. Please consider strongly adding in HCU to your newborn screen. Homocystinuria is more common in people of European descent--far more common than the 1:300,000 in the United States that we were quoted when xxxxxxxx was diagnosed. If there are 10 children for every xxxxxxx out there, that's 10 children, many families, that deserve to have that diagnosis as early as they can, to provide the best care for their child. Please do not deny them that because of "low yield", or some other administrative determination. They deserve that, their children deserve that, and it's the best you can do for them.
Thank you for your time and consideration,
Sincerely,
Xxxxx and xxxxxx
xxxxxxx, xxxxxxx, USA