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# Expanded bloodspot screening

In our response to the National Screening Committee consultation on expanded bloodspot screening, we examine their recommendations from a public health perspective. We make the overall recommendation that the NSC should include all five conditions in the decision to expand newborn screening.

## **Recommendation 1 - 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.

## **Recommendation 2 - not to include Isovaleric acidemia (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, three mild cases and one severely affected baby who died. This decision is not logical and demonstrates a mismatch between

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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 two 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.

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The NSC is concerned about medicalisation 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 knowing about a mild diagnosis. Although the pilot report says that this medicalisation 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 'medicalised' 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 medicalisation that the newborn screening programme might enable them to do so.

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 become 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.

### Recommendation 3 - 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 six weeks and six 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 two and four 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.

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### 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<sup>1</sup>.

*“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 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 genome 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.

### 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.

### References

1. 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.
2. Burton H and Moorthie S. Expanded newborn screening. A review of the evidence. PHG Foundation 2010. Download from [www.phgfoundation.org](http://www.phgfoundation.org)
3. Moorthie S, Cameron L, Sagoo G and Burton H. A systematic review of the birth prevalence of five inherited metabolic disorders.



### About the PHG Foundation

The PHG Foundation (PHGF) is an independent health policy think tank whose mission is the responsible and evidence-based application of biomedical science for health. We focus on genetic and genomics advances and their impact upon clinical and public health services. 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 five conditions that were proposed in preparation for the expanded newborn screening pilot programme under consideration in this consultation<sup>2</sup> and extended and updated the review of prevalence of the conditions in October 2013 as part of the work<sup>3</sup>. 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.