

Extended Screening by Tandem Mass Spectrometry

Forward and Meeting Report

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Forward : History and Prospect

History

It is just over 18 years since Dave Millington and his group at Duke University (North Carolina, USA) presented a paper "Tandem mass spectrometry: a new method for acylcarnitine profiling with potential for neonatal screening for inborn errors of metabolism" to the Society for the Study of Inborn Errors of Metabolism meeting in Munich. The resultant publication (*J Inherit Metab Dis* 1990; **13**: 321-324) showed examples from neonates with isovaleric acidaemia, 3-hydroxy-3-methylglutaryl-CoA lyase deficiency, medium-chain acyl-CoA dehydrogenase deficiency, propionic acidaemia and glutaric aciduria type 1. In 1991 Millington attended a meeting of the British Mass Spectrometry Society at the Institute of Child Health, London and discussed his plans for large-scale newborn screening by tandem mass spectrometry (MS-MS) covering phenylketonuria and other amino acid disorders as well as the newly-available range of organic acidaemias and fatty acid oxidation defects. Clearly this was a technique of enormous potential but one which (at that time) was expensive and posed significant technical difficulties. I felt that careful evaluation was required and suggested this as a topic for the newly-launched UK Health Technology Assessment Programme. The suggestion was accepted and eventually two systematic reviews were commissioned, one from a group based at St George's Hospital, London, the other in Sheffield.

These two studies were largely independent and literature-based but early in 1996 Ron Chalmers from the London group and myself visited Millington's Duke University laboratory and also the laboratories of NeoGen Screening Inc, Pittsburgh, USA which had by that time screened samples from over 200,000 neonates using tandem mass spectrometry. It was clear that, though the technology was still evolving, large-scale newborn screening was practicable and produced results largely in line with expectation. In the UK, a group at the Institute of Child Health, London, had analysed over 4,500 samples. A group in Newcastle was well into a retrospective study which eventually covered 100,600 samples (Porfarzam M et al. Neonatal screening for medium-chain acyl-CoA dehydrogenase deficiency. *Lancet* 2001; **358**: 1063-4).

Monographs from both systematic reviews were published in 1997 (*Health Technol Assess* 1(7) and 1(11)). Though differing slightly in detail the two reports came to essentially the same conclusion: a screening programme using the full potential of tandem mass spectrometry to analyse amino acids and acylcarnitines in blood spot samples the method appeared viable but should be carefully monitored in the opening stages.

Report	Pollitt et al <i>Health Technol Assess</i> 1(7)	Seymour et al <i>Health Technol Assess</i> 1(11)
Type of programme	Prospective open "pilot" study plus specific research projects	Prospective open "research" study
Duration	3 years	5 years
Size	>500,000 infants screened in 4 or 5 centres	1,600,000 infants screened in 4 centres
Diseases	Phenylketonuria, medium-chain	Phenylketonuria, medium-chain acyl-

to be covered	acyl-CoA dehydrogenase and other fatty acid oxidation defects, glutaric aciduria type 1, maple syrup urine disease, propionic, methylmalonic and isovaleric acidaemias and other branched chain disorders <i>plus at specific sites (research):</i> tyrosinaemia type 1, urea cycle defects, homocystinurias	CoA dehydrogenase deficiency, glutaric aciduria type 1 <i>plus</i> “many of the other disorders that can be detected by tandem mass spectrometry”
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A further monograph in the Health Technology Assessment series (Pandoor et al, Clinical effectiveness and cost-effectiveness of neonatal screening for inborn errors of metabolism using tandem mass spectrometry: a systematic review. *Health Technol Assess* 2004; **8(12)**) dealt solely with screening by tandem mass-spectrometry, revisiting and updating the areas covered previously. Using TMS to screening for phenylketonuria and MCADD was found to be highly cost-effective but for every other disorder more information on underlying incidence and outcomes, sensitivity and specificity of screening, and the economic impact of the effects of screening on long-term outcomes was required.

The successful completion of the screening phase of the medium-chain acyl-CoA dehydrogenase deficiency (MACDD) pilot study has shown that methodology and instrumentation are now sufficiently robust for large-scale routine use. However, there has been little progress with other disorders which could be incorporated into an MS-MS screening profile and the UK now lags behind many other countries in Europe, Australasia, and elsewhere though there are considerable variations in approach (Pollitt R.J. Introducing new screens. Why are we all doing different things? *J Inherit Metab Dis* 2007; **30**: 243-29; Bodamer OA et al. Expanded newborn screening in Europe *ibid.* 439-44; Therrell BL, Adams J. Newborn screening in North America *ibid.* 447-465, and other papers in that issue). The current position of the UK National Screening Committee (NSC) is that screening for such conditions should not be offered. The National Library for Health website, <http://www.library.nhs.uk/screening/viewResource.aspx?resID=88267>. (accessed 8th October 2007) states that “As part of the pilot project reviewing medium chain acyl CoA dehydrogenase deficiency (MCADD), data are being gathered to help the National Screening Committee explore the most effective and efficient way of making decisions about other rare inherited disorders, such as these amino acid metabolism disorders. The pilot report should be ready in 2006.”

Prospect

The framework developed by the UK NSC for the evaluation of new screening programmes is based on 17 general criteria requiring 87 items of information, many of them quantitative, for their evaluation (NSC Second Report, 2003). There are several factors which make this “Wilson and Jungner with numbers” approach inappropriate when considering MS-MS screening on a disease-by-disease basis as in the Pandoor et al (2004) review.

Availability of quantitative data: The rarity of the individual disorders makes it impossible to collect statistically significant data within a reasonable time-frame. In addition, disease frequency varies greatly in different parts of the UK and will change as a result of population migration and changing reproductive behaviour. In addition, as diagnostic services and treatment methods are continually improving, observational data relating to outcomes soon become obsolete.

Biochemical heterogeneity and clinical outcomes: There is considerable clinical and biochemical heterogeneity within individual disorders which will affect clinical outcomes. For example, given appropriate treatment some individuals with mild variants of propionic acidaemia have an essentially normal quality of life whereas those with severe variants have a very poor outlook. Lumping all cases together under a disease heading may result in individual patients being denied worthwhile treatments.

Underlying assumptions: The Wilson and Jungner principles on which UK policy is founded were drafted primarily with adult disease in mind and largely ignore the family dimensions inherent in newborn screening: the value of genetic information revealed, the importance parents attach to an early diagnosis even though no effective treatment may be available, and the broader impact of childhood disease on other family members

Extending the scope of MS-MS screening is not the same as starting a new programme from scratch. The infrastructure for sample collection, analysis, and reporting are already in place and extending the range of metabolites covered would to some extent replay previous scenarios. Thus screening for phenylketonuria can uncover a number of other rarer diseases (disorders of bipterin metabolism, transferase-deficiency galactosaemia) in a way not envisaged when the programme started in 1969. Additionally, where screening was performed by chromatography (34% of UK babies in 1993) other amino acid disorders such as maple syrup urine disease and pyridoxine non-responsive homocystinuria were diagnosed incidentally. From the discussion at this meeting it is clear that many paediatricians would like to see such disorders reinstated in the screening programme, supplemented by others which have only become available with the development of MS-MS. Most of the additional disorders detectable by extended screening are treated vigorously once they have presented clinically cases once they have been diagnosed. In general they are "if only we had known earlier" diseases in that the earlier in life that the diagnosis is made, the more effective such treatment is. The concept of what is "treatable" needs to be explored and the disparity between clinical practice and screening policy addressed.

It is fairly easy to specify conditions that should not be screened for:

- Conditions with no clinical consequences (eg, histidinaemia, sarcosinaemia) or whose significance is unclear (SCAD deficiency)
- Conditions where specificity is very low. (Specificity = the positive predictive value of the initial screening test + any non-interventional follow-up test)
- Conditions where there is no adequate confirmatory test
- Conditions such as non-ketotic hyperglycinaemia which are genuinely untreatable

It is less easy to deal with conditions of low clinical "penetrance" such as 3-methylcrotonyl-CoA carboxylase deficiency which is found in apparently unaffected adults as well as in a small proportion of infants presenting with Reye syndrome. Such disorders usually require a degree of metabolic stress to elicit symptoms but an acute attack may nevertheless result in permanent neurological damage or prove fatal. Such conditions are probably better regarded as risk factors rather than diseases in themselves: the individuals concerned require appropriate advice, a toned-down version of the MCADD protocol, rather than active treatment.

As a start, considerable progress could be made at minimal expense if:

- attention is limited to metabolites where the initial MS-MS results have a high positive predictive value and presumptive diagnoses are easily confirmed

- the limited sensitivity of MS-MS screening for certain disorders (such as propionic acidaemia, glutaric aciduria type 1) is accepted. Information material for professionals and parents must make this limitation clear.
- the precedent of PKU screening is followed and MS-MS screening is reported to Child Health Records as a bundle rather than by individual conditions. Similarly, the parent and professional information material should refer to additional disorders briefly and in general terms rather than in disease-specific detail (additional information on NHS Direct web site?)
- Existing manufacturer's software is used in preliminary processing of results, limiting the amount of individual attention required
- Analytical quality control to use population distributions, supplemented by results using CDC materials, rather than starting our own independent EQA scheme

For some disorders which come high on clinicians' wish-lists there would need to be specific second-line tests using the initial blood sample in order to ensure acceptable positive-predictive value and this would require additional funding.

There is now a great deal of published data on MS-MS screening programmes abroad. This needs to be interpreted with caution as test performance will be affected by day of life on which the blood is sampled. The way that results are handled and the broader impact of screening are also influenced by the medical and social milieu. Nevertheless there is sufficient information to enable us to set-up practical and robust protocols applicable to the UK.

R J Pollitt, Sheffield Children's Hospital

Extended Screening by Tandem Mass Spectrometry
A Joint MetBioNet/UKNSLN Meeting

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21st September 2007 – EEF, Sheffield

A meeting was arranged to review the case relating to extended screening by tandem mass spectrometry (MS-MS) in the UK. Representatives from screening laboratories and clinical and laboratory IMD services around the country met to discuss ideas and draw on previous experience of the MCADD pilot and progress in International screening programs offering expanded screening.

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The program began with a series of talks reminding everyone of the MCAD pilot, the current international perspective and the case for extended screening in the UK. This was followed by a discussion on how we could approach extended screening and personal views and ideas from each of the centres represented.

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Experiences from the MCADD National Pilot – lessons learnt/issues
Professor Anne Green

Professor Anne Green reminded the group of the study design for the MCADD pilot e.g. a prospective observational multi-centre study, screening for 24 months in 6 UK screening regions. Screening initially began by looking at levels of octanoyl carnitine (C8) and free carnitine (C0) in dried blood spots, followed by repeat assay and a full MS/MS acylcarnitine scan on samples giving abnormal results. The diagnostic algorithm involves a full acylcarnitine profile and measuring C8 in a second blood sample (dried blood spot and plasma), measuring the urinary excretion of hexanoyl glycine, assessing the genotype, and in some cases measuring fatty acid oxidation in cultured skin fibroblast. An agreed clinical and dietary management protocol was also implemented.

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Lessons learnt :

1. Underpinning all of the above required a joint clinical and laboratory approach and this would be important for any future projects. From the onset of any expanded screening pilot it would be recommended to set up a joint steering group to oversee the project.
2. Setting cut offs. Initial cut offs were set for raised a C8 at $>0.8 \mu\text{mol/L}$ and a C0 $<5 \mu\text{mol/L}$. However these changed over time as population data became available (C8 was reduced $>0.5 \mu\text{mol/L}$ and C0 was eventually abandoned). Differences in technology (underderivatised vs derivatised) and age at screening may have affected the cut-off in comparison with other countries.
3. It is important to establish good quality assurance and performance monitoring from the outset
4. During the early stages of any screening pilot attempt to standardise methodology across centres and if possible assay conditions.
5. Maintaining flexibility with regular reviews across centres is important

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Professor Green went on to recapitulate the NSC criteria which require any new test to demonstrate simplicity, safety, precision and validity.

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The success of choosing the agreed cut off was aided by the collection of population data provided by all of the 6 laboratories. Data was presented as median and ranges and from this it was determined that the C8 values did not change with age at

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sampling, and subsequently once the cut off had been changed to 0.5 µmol/L, no further adjustment was needed.

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Other points noted from the MCADD pilot included the simplicity of the test and the fact that no repeat sample was required. In addition the MCADD test was robust, speedy and suitable for large scale use. The collection of the population data demonstrated consistency between and within laboratories.

Discussion then centred on the factors for acceptance of MCADD screening by the NSC. These need to be reviewed when considering conditions that could be future candidates for extended screening. Ideally any condition should meet the following criteria:

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1. An important health problem
2. The epidemiology should be well known and the clinical prevalence should be higher than the epidemiological prevalence
3. The natural history should be known
4. The condition should have a recognised latent stage (this is especially important for extended screening in the UK where samples are obtained at 5 days of life).
5. There should be effective treatment available following early detection

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For the screening programme to be successful there must be adequate resources for diagnosis, treatment and management.

The benefits of early detection must outweigh any harm. It is important that parents have the appropriate information and most important that the parents support the screening programme.

In summary, the MCADD pilot satisfied the criteria, with a high positive predictive value, low false negative rate and clear health benefits from early diagnosis. The well-developed QA scheme offered additional analytical reassurance.

There are still some ongoing issues with the MCADD pilot, the algorithm and the use of C8/C10 ratios for carrier detection are still being investigated. From the study it is clear that this takes time, co-operation, collaboration and a means of sharing experience is important.

Further discussion followed Anne's talk, Dr Jim Bonham suggested establishing a data review panel to oversee any extended screening pilot and this gained support from the group. The need to collect analytical results as population data was highlighted by Professor Green, it was accepted that this was a lot of work but necessary as a valuable control measure.

Comments from the group:

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Autonomy of the laboratory was raised and can screening laboratories decide what to screen for as a group rather than depend on the NSC – Dr John Walter

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Strict Wilson and Junger criteria would be difficult to apply to extended screening for rare disorders - Professor Rodney Pollitt ¶

Funding issues, the MCADD pilot was only funded for two years initially and future funding was not guaranteed at the outset – however it would be difficult to stop screening once it had begun – Dr Guy Besley

The current international perspective Professor Rodney Pollitt

International comparisons and how to make progress in the UK, was the theme of the second talk given by Professor Rodney Pollitt. He presented a table detailing the screening tests in use in various countries, and highlighted that while many countries are carrying out extended screening none are screening for the same panel of disorders. Indeed, from an international perspective NBS policies vary not only with the country but sometimes with the region within that country. These discrepancies may in part be attributable to the difficulty in formulating newborn screening policy in terms of the classical Wilson and Jungner criteria. We were reminded that we tended to be conservative in our approach when compared with other developed and some developing countries in relation to the adoption of newborn screening programs. The UK has a relatively late sampling age and this may reduce the clinical validity of screening for some conditions.

Professor Pollitt went on to discuss the issues of screening specificity, highlighting that other conditions may be picked up when screening for the disease selected e.g. PKU screening will always pick up bipterin defects. In the USA such incidentally-detected disorders are classed as 'secondary targets' and all are reported. In Germany any disorder not on the official list of the federal Ministry for Health and Social security is to be ignored and the relevant data destroyed – a policy that has been over-ruled by some of the state *landtagen*.

Professor Pollitt suggested that we should take the secondary detection of galactosaemia and bipterin defects whilst screening for PKU as precedents and view the additional conditions that might be detected by MS-MS as a bonus from MCADD and PKU screening - **not** as a series of new screening programmes. This would allow a careful UK-wide expansion of the range of metabolites covered:

- Low key
- Minimise cost
- Minimise additional burden on clinical services

Learning from the experiences of the MCADD pilot, we should take this forward collectively and monitor the results carefully.

Comments from the group:

We should look at data from overseas and may not need a pilot study – Dr John Walter

Because of the time scale of taking the blood spot we may need to follow America and have a two tier screen, e.g. one NBS at 24hrs after birth and one later – Dr Guy Besley

Even if we keep with the same NBS time as now, this will bring the diagnosis earlier and will have an effect on clinical outcome – Dr John Walter

The case for extended screening in the UK Dr Mick Henderson

Dr Mick Henderson began his discussion by reviewing the background for extended screening and discussed some of the additional screens already carried out in Yorkshire. He went on to discuss future candidate disorders and suggested devising a priority list.

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¶ We were reminded that we tended to be conservative in our approach when compared with other developed and some developing countries in relation to the adoption of newborn screening programs. This discrepancy may in part be attributable to the difficulty in formulating policy. The National Screening committee in 2004 (Pandor et al) requested a need for more data, but this is unachievable for many of the inherited metabolic diseases.¶
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Dr Henderson reminded us of the current situation in the UK in which screening for five disorders is being carried out or implementation is already planned. These include:

1. PKU
2. CHT
3. CF
4. MCAD
5. Sickle cell disease

In some parts of Yorkshire an additional 3 screens are carried out: tyrosinaemia type 1, homocystinuria and MSUD. Tyrosinaemia type 1 is screened for by measuring tyrosine in the first instance and then succinylacetone as a second tier test on the same bloodspot; homocystinuria by measuring methionine; MSUD by detection of an increased leucine.

The positive predictive value for many of the conditions we want to detect will not be known until we actually start screening and collect the data. We will need to be cautious in extrapolating from the experience of other countries due to the differences in collection time. Thus cut-off values and screening efficacy are likely to be quite different for us. Dr Henderson also reminded us that it is important to take into account the population variations in the UK and the effect this has on the incidence of some disorders.

Dr Henderson advised that, when determining the disorders we should screen for, we have to take into account the current technology and this would limit extended screening by MS-MS currently to

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1. Amino acid disorders
2. Fatty acid oxidation disorders
3. Organic acidaemias

The amino acid disorders we could screen for using the current technology include:

1. MSUD by leucine
2. Urea Cycle defects by citrulline
3. Homocystinuria by methionine, with the risk of missing pyridoxine responsive patients.
4. Tyrosinaemia type 1 by tyrosine and succinylacetone

The fatty acid oxidation defects include:

1. GA1 and GA2 by glutaryl carnitine (C5-DC)
2. LCHAD and trifunctional protein by C16:05
3. VLCAD by C14:1

Of the organic acid disorders

1. Isovaleric aciduria by Isovaleryl carnitine (C5)
2. Propionic acidaemia and MMA by propionyl carnitine (C3) (we need to be aware of the high false positive rate using C3).

It was agreed that we would not decide on the panel today but a subgroup would offer advice on potential candidate disorders to consider.

Discussion followed and a potential strategy was developed:

1. Discuss and agree on a list of candidate disorders
2. Agree a short list with the strongest case
3. Acknowledge other categories for expanded screening (non IEM)

How could it begin in the UK – Introduction and Discussion Dr Jim Bonham

Dr Bonham began the discussion with acknowledgement that there is no hub of resistance to extended screening in the UK and that we should use MCADD as an example of success. We need to approach scientific, medical and patient groups for support and need to look carefully at the growing number of international programmes.

We need to agree a panel of disorders; individual disorders are too rare to be piloted on a regional basis, and we need to have a unified response.

Dr Bonham explained that we should be conservative rather than ambitious, the resources need to be modest and met locally and the disease burden addressed should be relatively limited. It is important that we initiate this activity as a pilot scheme on the same basis as MCADD indeed we should view this as a national extension of the existing MCADD pilot.

From this meeting we should demonstrate a single voice, we should produce a meeting report with clear clinical and dietetic input. We should feed this into Carol's Dezateaux's meeting planned for January 2008. Professor Green will feedback to the programme centre and we will need to seek comment and endorsement from GenCAG, the BIMDG, UKSLN, MetBioNet and JCMG.

Discussions with commissioners should occur at an early stage and we should attempt to gain support from CLIMB and GIG. We should also seek support and involvement from industry and from political allies as they arise.

The key messages we need to agree is that expanded screening is:

1. Clinically useful
2. Widely available internationally
3. Safe
4. Requires marginal resources
5. Popular with patients/parents
6. Politically acceptable

The main next step is to agree a panel. This process should be clinically led and scientifically acceptable, the conditions selected need to be treatable and dietetic input is essential.

Views/experiences from around the country

Manchester- Dr Guy Besley and Dr John Walter

Dr Guy Besley explained the view from the Manchester laboratory, that newborn screening for PKU was historically carried out using paper chromatography and they subsequently continued to look at the amino acid disorders when switching to ~~MS~~ **MS**. Dr Besley was against carving the country up and felt it was important to avoid a postcode lottery and subsequently supports a role out of a panel of disorders throughout the country.

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Dr John Walter stated that clinically the conditions screened for must be treatable, the list he suggested and reasons included:

1. GA1 - must be high on the agenda as it is treatable and would be unethical not to screen for it.
2. Homocystinuria is also very treatable and previously patients picked up on screening have done well.
3. Tyrosinaemia type 1, even if it involves a 2nd tier test.
4. MSUD, this is slightly less clear, would be treatable if diagnosis made prior to neonatal encephalopathy
5. VLCADD, LCHADD and LCAD, less clear and a concern over carriers
6. PA, MMA and IVA (although problems with false positive C3's for PA and MMA).

Birmingham – Mary Anne Preece

Mary Anne Preece gave the view from Birmingham which screen the West Midlands region and have approximately 80 additional inborn error diagnoses per year in their diagnostic service. Mary Anne focussed on the disorders which are relatively common in their population, and of which there have been on average 1 or more diagnoses per year over the last 5 years. She considered whether patients were diagnosed in the neonatal period (<10 days), during childhood, or after 14 years of age.

Tyrosine is measured as part of the PKU screen. In all patients with tyrosine >400 μ mol/l a galactosaemia screen, and a tyrosinaemia screen are carried out. The majority of cases of galactosaemia presented clinically at around the time the results from the newborn screen were available,, however it was felt that this is a useful test and speeds up diagnosis and treatment.

Considering the other disorders that have a relatively high incidence in the region and which could be detected by amino acid or acyl carnitine analysis, she made the following comments.

- Tyrosinaemia type 1 is not reliably detected by tyrosine measurement. The PBG synthase screen is a reliable test, but there are many patients who have normal tyrosine results at screening. There is currently a research project looking at the methodologies available for screening for in Birmingham. From the Birmingham experience 5 infants were diagnosed following newborn screening and 3 infants presented clinically between 10 days and 7 years.
- Fatty acid oxidation defects 4 patients presented greater than 14 years with undefined defects with raised C8 (may have been picked up by MCADD screening), and 3 patients in childhood also undefined defects with raised C4.
- OTC, several patients were picked up after the screening period, however although they may be picked up by screening they are difficult to manage.
- MMA – most patients were diagnosed after 10 days however this would include the B12 responsive and Cbl defects which may not be picked up by screening.

- NKH had equal numbers 3/3 before and after 10 days but once again these are not very treatable.
- Most of the propionic acidaemia patients were detected clinically before 10 days (5/6).
- All tyrosinaemia type III patients were detectable by screening.
- VLCAD's were all picked up after the neonatal period but the age of onset of symptoms is very variable with some being asymptomatic until later in life.
- All GA1 patients (5) were picked up 10 days to 7 years and there is strong evidence to treat early however Mary Anne raised the question, can we reliably diagnose GA1? (referring to non-excretors and use of non derivitised assay)
- Carnitine transporter patients – of those who had C0 measured at screening the results were between 3 and 5 μ M
- Citrin deficiency – 3 patients in the last few years – do we need to screen to look at the incidence/natural history (research)

Other points raised include:

LSDs – highest incidence in WM region are MPS4A, Niemann Pick C, MLD – no ERT currently available, but may become so. Note that by the time these, non-treatable, disorders are diagnosed, there is often an asymptomatic sibling. NBS would offer the opportunity for ante-natal diagnosis.

There is growing pressure to screen for MPS1 and Pompe disease as these are treatable – Dr Guy Besley.

GOSH – Dr Maureen Cleary and Steve Krywachwych

Dr Maureen Cleary gave a list of disorders that would be potential candidates for expanded NBS, these are listed below and follow the same theme as previous speakers. Steve Krywachwych highlighted some potential laboratory issues.

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| 1. | Tyrosinaemia | treatable and no illness in first week |
| 2. | GA1 | treatable and no illness in first week |
| 3. | MSUD | treatable but may present in first week |
| 4. | UCD | treatable but often very ill in first week |
| 5. | Homocystinuria | treatable and strong candidate |
| 6. | FAO defects | technically may be difficult |
| 7. | Biotinidase | treatable and strong candidate ? <u>MS-MS</u> method |
| 8. | LSD's | strong political and parental pressure |
| 9. | Citrin def | research only |
| 10. | IVA | treatable and strong candidate |

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Other conditions may be good candidates but no strong supporting evidence was presented, however may be good to diagnose early from a clinical course, including MMA.

Steve Krywachwych gave an insight from the laboratory perspective agreeing with previous comments, clear cut offs, modest costs, unified approach etc. He also highlighted other issues such as the cost implications for producing parent leaflets, teaching midwives etc.

Comments from the group

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GA1 is a strong candidate but concern over missing patients with low free carnitine – Dr Simon Olpin will investigate patients previously diagnosed as GA1 and will advise

which patients the other centres should go back and review the free carnitines in the new born blood spots.

Dietary management of GA1 was a concern and there is little UK experience of treating it in the neonatal period; part of the consideration in choosing which conditions should be screened for is whether dietary management available, this is the same for IVA – Marjorie Dixon

A metabolic practicing group should go to the DoH with therapeutic guidelines – Dr Mick Henderson

Guys – Fiona Carragher

Fiona gave a view from the SE Thames region from an analytical perspective and highlighted some of the potential pitfalls.

Biotinidase deficiency using end point MS-MS would require an additional blood spot.

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Tyrosinaemia type I using succinyl acetone, however this is potentially a difficult assay and would require a 2nd tier tests.

Homocystinuria measuring total homocysteine using a reduction step but again to achieve this a second spot is required.

Galactosaemia, galactose 1-phosphate using a direct injection and negative ionisation. The same spot could be used but as discussed earlier the clinical presentation is early.

Other conditions were discussed and similar support was given by Fiona as the previous speakers.

Guys went on to suggest an acute metabolic workup for sick neonates, as a type of targeted screening.

Worries about sensitivity of MS/MS and whether to use derivatised or underderivatised were raised by Charles Turner.

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Sheffield – Dr Mark Sharrad

Sheffield effectively screens for galactosaemia on the basis of an elevated phenylalanine. Almost all galactosaemia patients in this region have been identified in this way.

Other tests not mentioned previously that may be considered for expanded screen may include:

Beta ketothiolase deficiency – similar in clinical course to MCADD, with good outcome although possible concerns that patients picked up by screening may not ever present clinically.

Further Discussions

Dr Paul Griffiths raised some concerns over the communication links to child health systems, and highlighted the fact the IT system is in desperate need for external investment. This will become ever more important as screening is extended.

Dr Jim Bonham highlighted the need for training for midwives and investment in information leaflets for parents.

Melanie Downing suggested that to simplify things we should group expanded metabolic screen as a single test for reporting, thus concentrating on the simplicity of feedback to parents.

Other issues raised:

The time to run the assay may require a second MS/MS (an additional 3 mins per test) would result in the tandem time being run beyond the maximum. – Steve Krywachych

Suggest establishment of fact finding missions, and link with other people in different countries already carrying out extended screening and in the UK – Nigel Manning

Worries about the availability of local funds were raised. – Morteza Pourfarzam

Next steps

1. Agree notes from this meeting and include in a wider report which can be used to:
 - a. Help inform the meeting planned by Carol Dezateaux in January 2008
 - b. Offer feed back to parent groups and seek their support to stimulate debate
 - c. Inform local commissioners
 - d. Form a basis for dialogue with the National Screening Committee
2. Form a multi-disciplinary panel of people to consider the most appropriate tests and to determine the candidate disorders included. The panel are:

Dr John Walter
Dr Mark Sharrard
Dr Maureen Cleary
Dr Anupam Chakrapani
Dr Mary Anne Preece
Dr Mick Henderson
Dr Fiona Carragher
Melanie Downing
Marjorie Dixon
Fiona White.

3. Develop an agreed panel of tests and associated disorders to consider for extended screening
4. Invite comments, further discussion and endorsement for the candidate disorders from the wider membership of BIMDG, MetBioNet, UKNSLN and other relevant bodies.

Appendix 1: A limited panel of disorders which were considered as candidates for inclusion as part of a pilot scheme for extended screening by the group outlined above.

Clinical agreement as a priority and possible on the primary screen at marginal cost

Maple Syrup Urine Disease
Glutaric aciduria type 1
Isovaleric acidaemia

Clinical agreement as a priority but requiring secondary testing or an alternative approach

Tyrosinemia I
Homocystinuria

Additional possibilities meriting further discussion or consideration

Citrullinaemia (1 and hence 2)
Argininosuccinic aciduria
Long chain hydroxy acyl CoA dehydrogenase deficiency
Methymalonic acidaemia and propioninc acidaemia (using second tier test)
Beta-ketothiolase deficiency (if appropriate second tier test developed)

Conclusion

It will be wise to restrict any pilot to a very limited range if this is to be achievable. The list will be submitted for consultation to BIMDG, MetBioNet and UKNSLN.

Comment to be returned by the end of January 2008. Following this consultation period the multi-disciplinary panel will make a detailed assessment addressing conformity with the current and evolving NSC criteria for screening selection. This list will be presented at the meeting to be arranged by Carol Dezateaux in Spring 2008.