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Birth prevalence of five inherited metabolic disorders

A systematic review

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Executive summary

Inherited Metabolic Diseases

Inherited metabolic diseases are monogenic diseases resulting from deficient activity in a single enzyme in a pathway of intermediary metabolism, usually due to mutations in a single gene. In patients with an inherited metabolic disorder (IMD) the accumulation of toxic metabolites following acute metabolic decompensation or their chronically increased levels can lead directly to irreversible neurological damage or death. These adverse outcomes can often be avoided or markedly reduced by the early recognition and treatment of patients whilst they are asymptomatic or at an early stage in their disease. Until recently the problem has been how to identify these rare disorders in a population of normal children or those with non-specific but common symptoms. Clinical opinion is that the outcome for most inherited metabolic disorders is improved by early detection. For some classes of disorder the advent of tandem mass spectrometry (MS/MS) is allowing clinicians to overcome these diagnostic difficulties and solve this important problem.

Background

As a prelude to the clinical phase of a research project to evaluate screening for five additional diseases (maple syrup urine disease, homocystinuria, glutaric aciduria, isovaleric aciduria and long-chain hydroxyacyl-CoA dehydrogenase deficiency) using MS/MS in 500,000 newborns, the PHG Foundation was asked to conduct a systematic review of the available evidence for expanded newborn screening. In particular there was a need for an updated literature review, as the last Health Technology Assessment (HTA) report, published in 2004, only included data up to 2002. The PHG Foundation report, published in 2010 had a wide scope, which, in addition to assessing the birth prevalence of the disorders, also examined aspects such as test performance, clinical validity, clinical utility and cost-effectiveness. This work involved reviewing the evidence in the literature against the National Screening Committee Criteria to identify gaps in knowledge that could be filled by a pilot research programme.

This current systematic review is aimed at providing updated information on the birth prevalence of the five target disorders. Whilst building on the work of the 2010 report, a slightly different approach has therefore been taken. As the focus is limited to estimating the birth prevalence of the target disorders, we have widened the inclusion criteria to include studies other than those based on MS/MS screening programmes alone. This has identified studies covering different methods of detecting cases: recent studies describing detection through the use of MS/MS and, in the case of homocystinuria and MSUD, detection using older methods such as the bacterial inhibition assay (BIA). Data on clinically detected cases was also collected in order to gather some information on the symptomatic incidence of these conditions. However, it is recognised that there are biases in each study method. For this reason birth prevalence has been calculated separately for these three different groups: cases detected through screening with MS/MS; cases detected clinically and cases detected through other screening methods.

Findings

The current review identified a total of 99 studies that were able to provide information on the prevalence of one or more of the target disorders. The vast majority of studies were of screening programmes with some reporting on clinically detected cases. Data on the MS/MS screen-detected prevalence of the conditions were available from both established and pilot MS/MS screening programmes across the world. In comparison to the 2010 review, additional 62 data sources were identified. These comprised studies published prior to 2002 (n=38), studies published since the initial review in 2010 (n=17), grey literature (n=3) and additional data identified through contacting newborn screening laboratories (n=4).

Conclusions

The birth prevalence for the five target conditions ranged from 0.49 -1.04/100,000 live births. Across all conditions, apart from homocystinuria, prevalence estimates based on screen-detected cases are much higher than those based on clinical detection. Extrapolating findings in other Western populations suggest that for these target conditions we would expect approximately 27 screen-detected cases in England and Wales per year. However, this may range from as few as 20 cases to as many as 37 cases in total. Although the estimated prevalences are higher in comparison to the calculations made in 2010, they are likely to reflect a more accurate assessment of the true prevalence, as they are based on a larger number of studies.

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 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.

1 Introduction

In 2010 PHG Foundation undertook an evidence-based synthesis to support proposals for a pilot project evaluating expanded newborn screening using Tandem Mass Spectrometry (MS/MS) in England. The findings and recommendations of the resultant PHG Foundation report: E*xpanded newborn screening: A review of the evidence*[1] was presented to the UK National Screening Committee (NSC). The report concluded that there was evidence to support expanding the existing newborn screening programme within the UK; however, there were some gaps in knowledge which could be answered through a large scale pilot study.

The clinical phase of the pilot programme began in July 2012 and has now been completed. A final report of the pilot programme and a health economic evaluation prepared by The School of Health and Related Research (ScHARR) to sit alongside the overall study report will be presented to the National Screening Committee for their consideration. The PHG Foundation has been asked to provide an updated review focussing more specifically on the birth prevalence of the five conditions included in the pilot study.

1.1 Aim

To undertake a systematic review to establish the reported birth prevalence of the five conditions which are part of the pilot study. To identify key individuals in the UK and abroad who may be able to provide data from unpublished sources.

1.2 Scope

To review the birth prevalence of five candidate disorders:

1. Maple Syrup Urine Disease (MSUD)
2. Homocystinuria (HCY)
3. Glutaric Aciduria Type I (GA-1)
4. Isovaleric Acidaemia (IVA)
5. Long-chain hydroxyacyl-CoA dehydrogenase deficiency; includes trifunctional protein deficiency (LCHADD/MTP)

This updated systematic review, whilst building on the work of the 2010 report, has taken a different approach to reflect the specific need for up-to-date birth prevalence data for the five conditions. In order to provide the best estimates possible, it was decided that no date limits would be set on the search for publications. This would allow the identification of studies covering different methods of detecting cases, such as recent studies describing detection through the use of MS/MS and, in the case of homocystinuria and MSUD, detection using methods such as the bacterial inhibition assay (BIA). In addition, it would also allow identification of studies that are based on clinical diagnosis.

1.3 Objectives

To undertake a systematic review covering the following main aspects:

1. To provide an assessment of the epidemiology of each disorder in the UK, including estimates of birth prevalence and the likely number of cases, using suitable population denominators
2. To provide a timely report to the pilot project's management committee in order to inform the health economic evaluation and the final report of the pilot project.

1.4 Method of operation

The project team at the PHG Foundation was led by Dr. Hilary Burton (Consultant in Public Health and Director) and supported by a team from the Foundation (Dr Sowmiya Moorthie, Ms Louise Cameron and Dr Gurdeep Sagoo). Expert guidance was provided by Professor Jim Bonham, Clinical Director, Sheffield Children's NHS Foundation Trust and Expanded Newborn Screening Project Lead.

2 Methods

2.1 Search strategy

Similar to the previous report, a two-stage strategy was used to identify published studies for this review[1]. The first stage identified all articles relating to screening programmes in all of the electronic resources listed in Box 1. The second stage involved searching for articles related to epidemiology and screening for the five chosen diseases in PubMed (MEDLINE). The searches were conducted in May 2013, with no date or language restrictions. The search terms are presented in Appendix 1.

Reference lists of identified articles and international HTA reports were scrutinised to identify other articles that may have been missed. A number of neonatal screening laboratories worldwide were contacted in order to obtain additional information, specifically data that had not been published (see Appendix 2 for the neonatal laboratory questionnaire). Data in the grey literature was identified by conducting a search for published reports from newborn screening laboratories.

Literature searching was conducted by two reviewers (Sowmiya Moorthie and Louise Cameron) and the initial screen for eligibility of titles and abstracts conducted by a single reviewer (Sowmiya Moorthie). Full texts were sought where confirmation was needed regarding an article's suitability.

2.2 Review inclusion and exclusion criteria

As the focus here was on estimating the birth prevalence of the target disorders, we widened the inclusion criteria to include studies other than those based on MS/MS screening alone. Along with studies reporting results based on MS/MS screening, we also included studies reporting on screening by other methods (such as Bacterial Inhibition Assay) as well as those that ascertained cases by clinical diagnosis. The criteria for including studies in the review are listed below.

Box 1

- PubMed (MEDLINE)
- EMBASE
- CINAHL
- CRD Databases (NHS DARE, EED, and HTA)
- Web of Knowledge
- Cochrane Library

- Inclusion criteria:

  Target population: neonates or newborn infants [AND][1]

  Target IMDs: Homocystinuria, IVA, GA-1, MSUD, LCHADD (studies investigating other IMDs must have data on at least one of the five targets) [AND]

  Outcomes: Incidence and/or birth prevalence [AND]

  Study designs: Primarily randomised controlled trials and cohort studies, case-control, other non-randomised evaluations of treatment effectiveness, cross-sectional epidemiological studies

[1]For studies reporting on clinically detected cases, those studies that did not give a denominator relating to birth cohort were excluded.

- Exclusion criteria:

  Non-human studies [OR]

  Studies which provided only a calculated estimate or a modelled calculation of IMD prevalence

  Studies were excluded if they did not contain appropriate prevalence data; for example, review papers or studies of high-risk population without appropriate denominators.

2.3 Data extraction strategy

An electronic, pre-piloted extraction form was used by independent reviewers (Sowmiya Moorthie and Louise Cameron) to extract data. Disagreements were resolved in conference or by a third reviewer (Gurdeep Sagoo). Where there were multiple publications of the same study, we extracted data from each publication and identified the most complete and up-to-date data. The data were analysed following resolutions of overlaps in the extracted data and exclusion of studies if they did not present any cases.

2.4 Statistical analysis

For each study, live birth prevalence was calculated for the five conditions as the total number of cases per 100,000 live births. This was calculated directly from data when the appropriate number of cases and denominator was given. The definition of a case from screening studies was all cases that were true positives, as well as those that had been classified as false negatives and had been subsequently confirmed as disease positive. The denominator was the total population screened or, in the case of clinically detected cases, the number of births during the period of the study or the number of births in the corresponding unscreened population.

Due to the variation in both study size and study characteristics it was decided that calculating a weighted average (via the random-effects meta-analysis) was the best approach to obtain prevalence estimates. A random effects meta-analysis assumes that the true effect size varies across studies. As mentioned above, there was considerable variation between the studies in a number of factors, including sample size, timings, age at screening, cut-offs *etc*. The true effect size is therefore likely to vary across studies.

Studies without any cases were excluded from this analysis because birth prevalence cannot be calculated for a study with zero events, and hence does not provide data to the final prevalence estimate. These zero event studies could have contributed data to a birth prevalence estimate calculated by pooling the data together. As a sensitivity analysis, a comparison of pooled averages was calculated with these studies included and excluded which showed that their exclusion did not have a major influence.

For all meta-analyses the calculated live birth prevalences, were transformed to the logit of these proportions to improve their statistical properties and were back transformed and expressed as prevalence per 100,000 births. Meta-analyses were conducted separately for each sub-group of study type i.e. prevalence based on MS/MS screening; prevalence based on screening by other methods and prevalence based on clinical detection. For each category; a subset of data identified as from Western populations were also analysed separately with the aim of providing comparable data for the UK. "Western populations"' were defined as those from Europe, North America, Australia and New Zealand. Statistical analyses were performed using Stata® statistical software package, version 11 (StataCorp LP, College Station, TX).

3 Results

3.1 Summary of volume and type of studies

Figure 1 illustrates the yield of studies. A total of 504 studies were examined for potential inclusion. Laboratories carrying out newborn screening using MS/MS were identified and contacted with a request for data and a standard questionnaire (Appendix 2) was sent if they were willing to provide data. Of the eleven laboratories that were contacted, four submitted data. A search was also conducted to identify grey-literature providing reports of screening programmes from international laboratories.

A total of 99 studies met the inclusion criteria. 87 of these were identified via the literature search. A further 12 studies were identified through hand-searching which included laboratory data received from four laboratories: New South Wales (Australia), New Zealand, Netherlands and Singapore; and through reports of screening programmes from Germany, USA and Spain. The majority of identified reports were related to either MS/MS screening programmes or screening by other methods.

Data on the MS/MS screen-detected prevalence of the conditions were available from both established and pilot MS/MS screening programmes across the world. Table 3.1 shows the volume of peer-reviewed studies reporting on experiences in screening using MS/MS including one or all of the target conditions. This review has identified an additional 55 peer-reviewed studies worldwide with published data in comparison with the previous review. In addition to older studies (pre-2002) we were able to identify new reports from countries such as Poland, Austria, Spain and Denmark, as well as from a number of countries in the Middle East and South East Asia. This reflects an expansion of MS/MS newborn screening programmes in countries worldwide in the three years since the previous review. We were also able to include unpublished data from laboratories such as those in the Netherlands and Singapore. Table 3.2 gives a summary of the number of data points included in the analysis for each condition, after resolution of overlaps in between the studies.

Figure 1 Flow chart for the yield of all identified articles

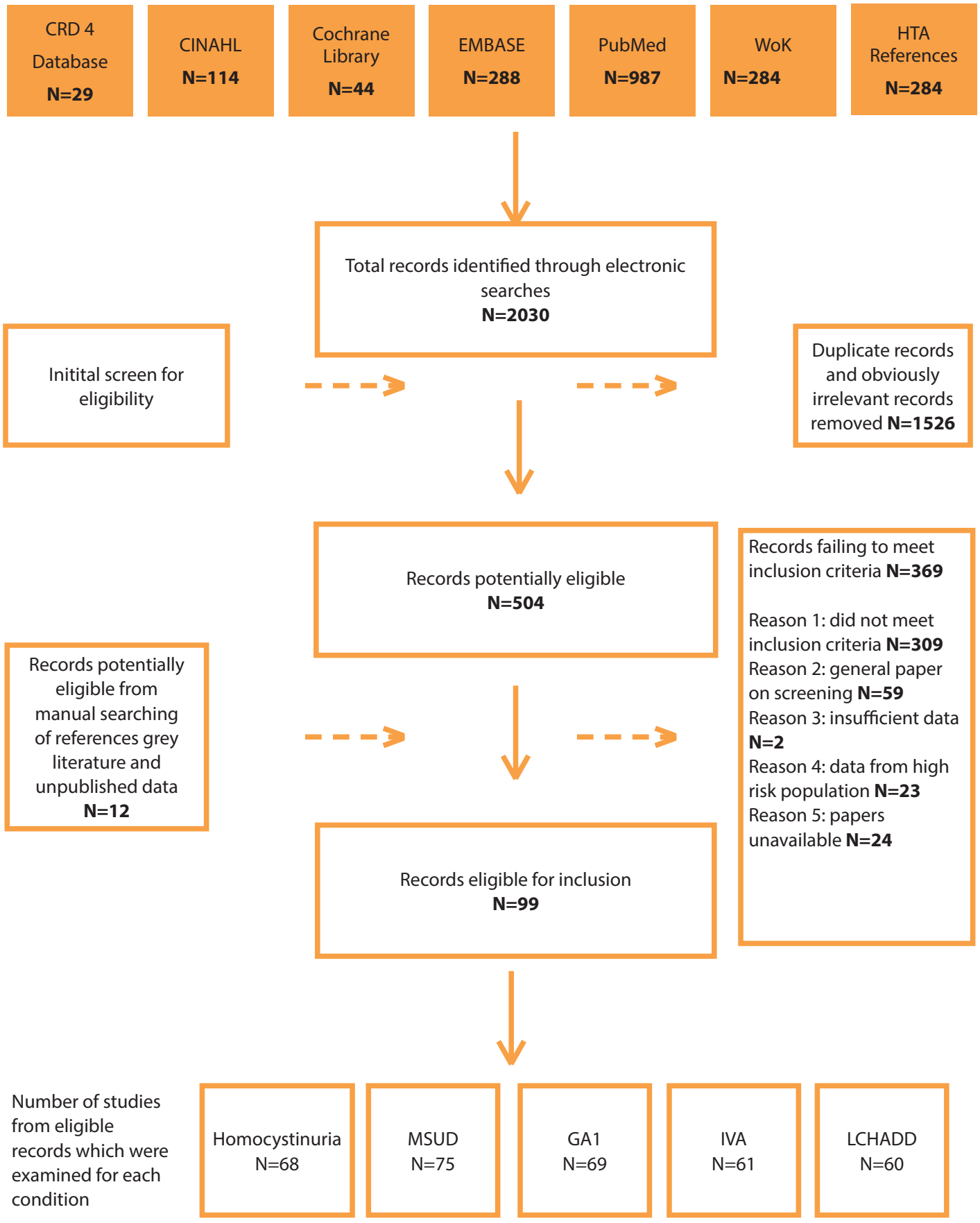

Table 3.1 Volume of peer-reviewed publications on MS/MS screening including target IMDs

Study Author	Country	HCY	MSUD	GA1	IVA	LCADD
			Europe			
Kasper *et al* [2]	Austria	0	1	1	1	1
Lund *et al* [3]	Denmark	0	1	1	0	1
Burgard *et al* [4]	EU Countries	1	1	1	1	1
Ensenauer *et al* [5]	Germany, Munich	0	0	0	1	0
Hoffmann *et al* [6]	Germany, Bavaria & Baden-Wurttemberg	0	0	1	1	0
Kolker *et al* [7]	Germany, Baden-Wurttemberg Bavaria, Lower Saxony	0	0	1	0	0
Lindner *et al* [8]	Germany, Baden-Wurttemberg	1	1	1	1	1
Lindner *et al* [9]	Germany, South Western	1	1	1	1	1
Roscher *et al* [10]	Germany, Bavaria	1	1	1	1	1
Sander *et al* [11,12]	Germany, Hanover	1	1	1	1	1
Schulze *et al* [13]	Germany, Baden-Wurttemberg	1	1	1	1	1
Loukas *et al* [14]	Greece	1	1	1	1	1
Antonozzi et al [15]	Italy	1	1	0	0	0
La Marca *et al* [16]	Italy	1	1	1	1	1
Sykut-Cegielska *et al* [17]	Poland	0	0	0	0	1
Vilarinho *et al* [18]	Portugal	1	1	1	1	1
Quental *et al* [19]	Portugal	0	1	0	0	0
Couce-Pico *et al* [20,21]	Spain, Galicia	1	1	1	1	1
Juan-Fita *et al* [22]	Spain, Murcia	1	1	1	1	1
Paz Valinas *et al* [23]	Spain, Gallego	1	1	1	1	1

Study Author	Country	HCY	MSUD	GA1	IVA	LCADD
North America						
Chace *et al* [22]	Pennsylvania & North Carolina	1	1	1	1	1
Naylor *et al* [25]	Pennsylvania & North Carolina	1	0	0	1	0
Marsden *et al* [26,27]	Massachusetts	1	1	1	1	1
Comeau *et al* [28]	New England	1	1	1	0	0
Zytkovicz *et al* [29]	New England	1	1	1	1	1
Muenzar *et al* [30]	North Carolina	1	1	1	1	1
Frazier *et al* [31]	North Carolina	1	1	1	1	1
Tiwana *et al* [32]	Texas	1	1	1	1	1
Watson *et al* [33]	USA	1	1	0	0	0
Australasia						
Wilcken *et al* [34]	Australia	1	1	1	1	0
Wilcken *et al* [35,36]	New South Wales	1	1	1	1	1
Wiley *et al* [37,38]	New South Wales	1	1	1	1	1
Wilson *et al* [39]	New South Wales	1	1	1	1	1
Boneh *et al* [40]	Australia	0	0	1	0	0
Southeast Asia						
Yang *et al* [41]	China	0	0	1	0	0
Sahai *et al* [42]	India	1	1	1	1	1
Yamaguchi *et al* [43]	Japan	1	1	1	1	0
Kuhara *et al* [44]	Japan	1	1	1	1	0
Shigematsu *et al* [45]	Japan	1	1	1	1	1
Aoki *et al* [46]	Japan	1	1	0	0	0
Yoon *et al* [47]	Korea	1	1	1	1	1
Abdul Rahman *et al* [48]	Malaysia	0	1	0	0	0

Study Author	Country	HCY	MSUD	GA1	IVA	LCADD
Lin *et al* [49]	Taiwan	1	1	1	1	1
Niu *et al* [50]	Taiwan	1	1	1	1	0
Hsieh *et al* [51]	Taiwan	0	0	1	0	0
Huang *et al* [52]	Taiwan	0	1	1	0	0
Hwu *et al* [53]	Taiwan	1	0	0	0	0
Middle East						
Abdel- Hamid *et al* [54]	Kuwait	0	1	0	0	1
Khneisser *et al* [55]	Lebanon	1	1	1	1	1
Lindner *et al* [56]	Qatar	1	1	1	1	1
Gan-Schrier *et al* [57]	Qatar	1	0	0	0	0
Rashed *et al* [58]	Saudi Arabia	0	1	1	1	0
South America						
Abdenur *et al* [59]	Argentina	1	1	1	1	1
Torres-Sepulveda *et al* [60]	Mexico	1	1	1	1	1

Table 3.2 Summary of number and types of studies contributing to the final analysis

Condition	Study Type		
	Screening by MS/MS	Screening by other methods	Clinical detection
Homocystinuria	14	14	5
MSUD	22	10	8
GA-1	26	-	10
IVA	17	-	5
LCHADD	16	-	5

A number of countries have long-running established screening programmes, which have screened a large number of births for the target disorders. Examples include Germany where MS/MS has been occurring since 2001. We were able to gather data from Germany's national screening reports for the years 2004-2010[61]; the inclusion of these reports provided data on over 4 million births. Screening for the target conditions has been occurring in New South Wales, Australia since 1998, and we were able to obtain data covering the period 1998-2012[62], where over 1.4 million births were screened. Other large data sets include those from Denmark[63], which covered approximately 500,000 births over a nine year period and different centres in the USA[24;28;32;64] which, although providing data over shorter time periods have screened a large number of births.

Reports from historical screening programmes using methods such as bacterial inhibition assay were also available for MSUD and homocystinuria. Although the volume of information was much less when compared to MS/MS screening reports, some reports such as those by Yap & Naughten[65] and Aoki[46] provide experience of established long-running programmes in Ireland and Japan respectively, covering a large number of births.

A smaller number of studies provided data on clinically detected cases. Data were available from studies that were investigating unscreened populations during the same period as a screening programme[3;6;19;34;39] or from those looking at retrospective data over a particular time period[6;7;66-68.]

3.2 Homocystinuria

The final prevalence figure for homocystinuria was based on 33 data points: 14 data points related to MS/MS screening, 14 to screening by other methods and 5 to clinical detection. Tables 3.2a-c provide summary data from these studies by mode of detection. In comparison to the 2010 review, an additional 8 studies were included in the screen-detected prevalence calculation here. Sources of additional data include laboratory data from Spain[69], Singapore[70] and the Netherlands[71]; older studies which had not been included in the 2010 report due to date restriction (*e.g.* Chace *et al.*[24]); and newly identified studies (*e.g.* Burgard *et al.*[4], Tiwana *et al.*[32], Khneisser *et al.*[55] and Gan-Schreier *et al.*[57]).

Table 3.2a Homocystinuria prevalence in MS/MS screened cohorts

Study	Location	Period	Results			
			Total screened (n)	Number of cases (n)	Birth prevalence One in	Per 100,000
Vilarinho *et al.* (2010)	Portugal	2005-2009	316,243	1	316,243	0.32
Loeber *et al.* (2013)	Netherlands	2009	186,128	2	93,064	1.07
AECNE (Spanish NBS association) (2012)[a]	Spain	2001-2011	808,149	8	101,019	0.99
Burgard *et al.* (2012)	Hungary	2008-2009	60,429	1	60,429	1.65
Wiley *et al.* (2013) [b]	Australia, New South Wales and Australian Capital Territory	Apr 1998-Dec 2012	1,430,227	5	286,045	0.35
Comeau *et al.* (2004)	USA, New England	Jan 1999-Jan 2003	472,255	1	472,255	0.21
Chace *et al.* (2002)	USA, Pennsylvania and North Carolina	Not presented	1,100,000	1	1,100,000	0.09
Frazier *et al.* (2006)	USA, North Carolina	1999-2005	749,695	2	374,848	0.27
Tiwana *et al.* (2012)	USA, Texas	2007	400,000	3	133,333	0.75
Loeber *et al.* (2013)[c]	Netherlands	2009	186,128	1	186,128	0.54
Lim *et al.* (2013)[d]	Singapore	Mar 2002-Feb 2004	42,264	1	42,264	2.37
Khneisser *et al.* (2008)	Lebanon	Nov 2006-Aug 2008	22,000	1	22,000	4.55
Lindner *et al.* (2007)	Qatar	Dec 2003-Jul 2006	25,214	2	12,607	7.93
Gan-Schrier *et al.* (2010)	Qatar	Jul 2006-Jun 2009	46,406	14	3,315	30.17
Torres-Sepulveda *et al.* (2008)	Mexico	Mar 2002-Feb 2004	42,264	1	42,264	2.37

a Data collated by AECNE (Asociación Española de Cribado Neonatal) Presented at XVIII Reunion de los Centros de Cribado Neonatal Bilbao 2012
b Data from New South Wales screening programme, Australia (unpublished)
c Data from Netherlands screening programme (unpublished)
d Data from Singapore screening programme (unpublished)

Table 3.2b Homocystinuria prevalence in cohorts screened by alternate techniques

Study	Location	Period	Results			
			Total screened (n)	Number of cases (n)	Birth prevalence One in	Per 100,000
Yap & Naughten (1998)	Ireland	1971-1996	15,800,000	25	632,000	0.16
Whiteman *et al.* (1979)	UK, London area	May 1970-Dec 1977	670,674	3	223,558	0.45
Komrower *et al.* (1979)	UK, Manchester	1968-1978	506,821	6	84,470	1.18
Mudd *et al.* (1995)	Scotland	Not presented	1,012,500	1	1,012,500	0.10
Bickel (1987)	Germany - Heidelberg (Baden-Wurttemberg)	1969-1984	940,369	3	313,456	0.32
Bickel (1987)	Germany, Federal Republic of Germany	1969-1984	5,180,071	43	120,467	0.83
Naughten *et al.* (1998)	Austria	Not presented	500,000	1	500,000	0.20
Scriver *et al.* (1985)	France	Not presented	274,000	1	274,000	0.36
Antonozzi *et al.* (1980)	Italy	1978-1980	116,000	2	58,000	1.72
Mudd *et al.* (1995)	New Zealand	Not presented	957,834	2	478,917	0.21
Wilcken *et al.* (1980)	Australia, New South Wales	Not presented	1,000,000	1	1,000,000	0.10
Peterschmitt *et al.* (1999)	USA, New England	Oct 1966-Dec 1998	3,300,000	16	206,250	0.48
Hwu *et al.* (2003)	Taiwan	1984-2000	4,015,939	16	250,996	0.40
Aoki *et al.* (2003)	Japan	1977-1994	23,579,319	22	1,071,787	0.09

Table 3.2c Homocystinuria prevalence based on clinical detection

Study	Location	Period	Results			
			Total screened (n)	Number of cases (n)	Birth prevalence One in	Per 100,000
Applegarth *et al*. (2000)	Canada, British Columbia	1969-1996	1,142,912	6	190,485	0.52
Wilcken & Turner (1978)	Australia, New South Wales	1960-69	820,797	14	58,628	1.72
Wilcken *et al*. (2009)	Australia	1994-2002	1,551,200	2	775,600	0.13
Wilcken *et al*. (2003)	Australia, New South Wales	Apr 1974-Mar 1994	1,754,000	13	134,923	0.74
Moammar *et al*. (2010)	Saudi Arabia	Jan 1983-Dec 2008	165,530	4	41,383	2.42

Table 3.2d summarises the estimated prevalence for homocystinuria based on mode of case detection. A higher prevalence estimate for Western populations was obtained when the calculations were based on reports of clinically detected cases as opposed to those identified by screening. This probably reflects the fact that screening programmes do not identify the milder pyridoxine-responsive patients, who do not show markedly elevated levels of methionine (screen detection is based on identifying elevated levels of methionine). Also of note is the disparity between the estimated worldwide prevalence [1.10; 95% CIs 0.35 to 3.44] and the prevalence in Western populations [0.49; 95% CIs 0.29 to 0.83] when only considering MS/MS based reports. Although the confidence intervals overlap, studies from non-Western populations generally show a higher prevalence. This is particularly noticeable for the study in Qatar by Gan-Schreier *et al*. 2010[57], which showed a high prevalence in this population. A previous study conducted in Qatar by Lindner et al.[56] also showed a high prevalence; however, it was not as extreme. There are suggestions that homocystinuria is particularly prevalent in the Qatari population due to a founder effect and consanguinity[72].

Table 3.2d Estimated prevalence of homocystinuria in Worldwide and in Western populations

Method of detection	Worldwide	Western
Screening by MS/MS	1.10 (0.35-3.44)	0.49 (0.29-0.83)
Screening by other methods	0.34 (0.19-0.59)	0.39 (0.22- 0.69)
Clinical detection	0.82 (0.39-1.73)	0.64 (0.28-1.46)

3.3 Maple Syrup Urine Disease (MSUD)

The final prevalence estimates for MSUD were based on a total of 40 data points; 22 relating to MS/MS based screening programmes (see Table 3.3a); 10 relating to screening by other methods (see Table 3.3b), and 8 reporting on clinical detection (see Table 3.3c). In comparison to the 2010 review, an additional 14 studies were included in the MS/MS screen-detected prevalence calculation here. Sources of additional data include laboratory data from Germany (Nennstiel-Ratzel *et al.*[61]), Spain[69], New Zealand[73] and Singapore[70] older studies which had not been included in the 2010 report due to date restriction (*e.g.* Roscher *et al.*[10], Chace *et al.*[24], Abdenur *et al.* [59] and Rashed *et al.*[58]); and newly identified studies (Lindner *et al.*[56], Kasper *et al.*[2], Lund *et al.*[3], Quental *et al.*[19], Tiwana *et al.*[32] and Niu *et al.*[50])

The largest single data set for MS/MS screening was from the German laboratory reports and represented data on over 4.5 million newborns screened (Nennstiel-Ratzel *et al.*[61]). Other large studies included laboratory data from Australia (Wiley *et al.* [62]), US (Chace *et al.*[24]) and Taiwan (Niu *et al.*[50]) There were a number of smaller studies from non-Western populations, with one study from Kuwait (Abdel-Hamid *et al.*[54]) showing a particularly high prevalence figure. This is likely to have been affected by the fact that it was a very small study (1,158 births in a tertiary centre) and in a population where consanguinity may contribute to the incidence of the disease.

Table 3.3d provides a summary of the estimated prevalence of MSUD based on different modes of case detection. The mean prevalence as detected by MS/MS was higher for worldwide populations [1.19; 95% CIs 0.77 to 1.84] as opposed to Western populations [0.71; 95% CIs 0.53 to 0.95]. Although the confidence intervals overlap, it is likely that the higher prevalence observed in some of the non-Western setting studies (*e.g.* Abdel-Hamid *et al.*[54], Abdenur *et al.*[59] and Abdul-Rahman *et al.*[48]) are contributing to the higher observed worldwide prevalence. The estimated prevalence in Western populations based on screening by other methods was similar to that calculated based on MS/MS screening only, whereas a lower prevalence was calculated when based on those studies reporting on clinically detected cases.

Table 3.3a MSUD prevalence in MS/MS screened cohorts

Study	Location	Period	Results			
			Total screened (n)	Number of cases (n)	Birth prevalence One in	Per 100,000
Roscher *et al.* (2001)	Germany-Bavaria	Jan 1999-Jul 2001	307,676	2	153,838	0.65
Lindner *et al.* (2011)	Germany - South Western - Baden-Wuttemberg	Jan 1999-Apr 2005	1,084,195	7	154,885	0.65
Nennstiel-Ratzel *et al.* (2010)[a]	Germany	2004-2010	4,611,782	26	177,376	0.56
Kasper *et al.* (2010)	Austria	Apr 2002-Dec 2009	622,489	2	311,245	0.32
Lund *et al.* (2012)	Denmark, Faroe Islands, Greenland	2002-2011	504,049	1	504,049	0.20
Quental *et al.* (2010)	Portugal	2005-2009	434,000	5	86,800	1.15
AECNE (2012)[b]	Spain	2001-2011	808,149	11	73,468	1.36
Wiley *et al.* (2013)[c]	New South Wales & ACT, Australia	Apr 1998-Dec 2013	1,430,227	12	119,186	0.84
Wilson *et al* (2007)	New Zealand	2004-2006	175,000	1	175,000	0.57
Webster *et al.* (2013)[d]	New Zealand	Dec 2006-Dec 2011	315,000	1	315,000	0.32
Chace *et al* (2002)	USA - Pennsylvania and North Carolina	Not presented	1,100,000	12	91,667	1.09
Comeau *et al* (2004)	USA, New England	Jan 1999-Jan 2003	472,254	2	236,127	0.42
Frazier *et al* (2006)	USA, North Carolina	1999-2005	749,695	1	749,695	0.13
Tiwana *et al* (2012)	USA, Texas	2007	400,000	1	400,000	0.25
Lim *et al.* (2013)[e]	Singapore	2006-2013	135,000	1	135,000	0.74

Table 3.3a continued MSUD prevalence in MS/MS screened cohorts

Study	Location	Period	Results			
			Total screened (n)	Number of cases (n)	Birth prevalence One in	Per 100,000
Niu *et al*. (2010)	Taiwan	Mar 2000-Jun 2009	1,321,123	13	101,625	0.98
Yoon *et al*. (2003)	Korea	Apr 2001-Mar 2004	79,179	2	39,590	2.53
Abdul Rahman *et al*. (2007)	Malaysia	2006-2008	13,793	2	6,897	14.50
Abdenur *et al*. (2000)	Argentina	1996-1999	9,320	1	9,320	10.73
Lindner *et al*. (2007)	Qatar	Dec 2003-Jul 2006	25,214	2	12,607	7.93
Rashed *et al*. (1999)	Saudi Arabia	1995-1998	27,624	2	13,812	7.24

a National Screening reports Germany 2004-2007; 2008; 2009; 2010
b Data collated by AECNE (Asociación Española de Cribado Neonatal) Presented at XVIII Reunion de los Centros de Cribado Neonatal Bilbao 2012
c Data from New South Wales screening programme, Australia (unpublished)
d Data from New Zealand screening programme (unpublished)
e Data from Singapore screening programme (unpublished

Table 3.3b MSUD prevalence in cohorts screened by alternate techniques

Study	Location	Period	Results			
			Total screened (n)	Number of cases (n)	Birth prevalence	
					One in	Per 100,000
Bickel (1987)	Germany - Heidelberg (Baden-Wurttemberg)	1969-1984	940,369	7	134,338	0.74
Bickel (1987)	Germany - Federal Republic of Germany	1969-1984	5,063,298	25	202,532	0.49
Bachmann & Columbo (1982)	Switzerland	1965-1980	1,111,251	8	138,906	0.72
Scriver (1985)	Austria	N/A	823,000	1	823,000	0.12
Naylor & Guthrie (1978)	Belgium	1964-1976	168,630	1	168,630	0.59
Antonozzi *et al.* (1980)	Italy	1978-1980	116,000	3	38,667	2.59
Naylor & Guthrie (1978)	Western Australia	1964-1976	74,652	1	74,652	1.34
Naylor & Guthrie (1978)	USA	1964-1976	1,450,068	14	103,576	0.97
Naylor & Guthrie (1978)	Japan	1964-1975	104,574	1	104,574	0.96
Aoki (2003)	Japan	1977-1994	23,579,319	36	654,981	0.15

Table 3.3c MSUD prevalence based on clinical detection

Study	Location	Period	Results			
			Total screened (n)	Number of cases (n)	Birth prevalence One in	Per 100,000
Wilson *et al.* (2007)	New Zealand	2004-2006	175,000	1	175,000	0.57
Applegarth *et al.* (2000)	Canada, British Columbia	1969-1996	1,142,912	2	571,456	0.17
Wilcken *et al.* (2009)	Australia	1994-2002	1,551,200	4	387,800	0.26
Wilcken *et al.* (2003)	Australia, New South Wales	Apr 1974-Mar 1994	1,754,000	12	146,167	0.68
Hoffmann *et al.* (2004)	Germany	1999-2000	844,575	2	422,288	0.24
Quental *et al.* (2010)	Portugal	1977–2009	4,084,525	31	131,759	0.76
Lund *et al.* (2012)	Denmark	1992-2002	266,465	2	133,233	0.75
Moammar *et al.* (2010)	Saudi Arabia	Jan 1983-Dec 2008	165,530	48	3,449	29.00

Table 3.2d Estimated prevalence of MSUD Worldwide and in Western populations

Method of detection	Worldwide	Western
Screening by MS/MS	1.19 (0.77-1.84)	0.71 (0.53- 0.95)
Screening by other methods	0.61 (0.32-1.17)	0.75 (0.50-1.14)
Clinical detection	0.74 (0.14-3.99)	0.51 (0.33-0.79)

3.4 Glutaric Acidaemia 1 (GA-1)

As screening for GA-1 was not possible prior to MS/MS, identified studies relate to either detection by MS/MS screening or clinical detection. The final prevalence estimates for GA-1 were based on studies reporting on MS/MS based screening programmes - 26 studies (see Table 3.4a) and studies reporting on clinical detection - 10 studies (see Table.3.4b). In comparison to the 2010 review, an additional 19 studies were included in the screen-detected prevalence calculation here. Sources of additional data include laboratory data, older studies which had not been included in the 2010 report due to date restriction and newly identified studies. The additional reports ranged in size from over one million in the USA[24] and Taiwan[50] to smaller studies such as those from Argentina[59] and Lebanon[55].

Table 3.4c provides a summary of the estimated prevalence of GA-1 based on the mode of detection. The screen-detected prevalence of GA-1 in Western populations is estimated to be 1.04; 95% CIs 0.89 to1.23. This may be an underestimate as screening may not be able to identify those patients classified as low excretors, as they tend to have normal concentrations of glutarylcarnitines. The screen-detected prevalence is much higher than the prevalence based on clinical detection for Western populations [0.25; 95% CIs 0.16 to 0.40]. Under-ascertainment by clinical diagnosis is likely, due to the heterogeneous clinical presentation of GA-1. Kolker *et al*[74] in their guidelines for diagnosis and management, state that "*The only effective way to identify patients with a low a priori risk is via newborn screening.*"

Table 3.4a GA-1 prevalence in MS/MS screened cohorts

Study	Location	Period	Results			
			Total screened (n)	Number of cases (n)	Birth prevalence One in	Per 100,000
Kolker *et al.* (2007)	Germany (Baden-Wurttemberg, Bavaria, Lower Saxony)	1999-2005	3,807,600	38	100,200	1.00
Nennstiel-Ratzel *et al.* (2010)[a]	Germany	2006-2010	3,404,987	23	148,043	0.68
Kasper *et al.* (2010)	Austria	Apr 2002-Dec 2009	622,489	9	69,165	1.45
Loeber *et al.* (2013)[b]	Netherlands	2009	186,128	1	186,128	0.54
Lund *et al.*	Denmark, Faroe Islands, Greenland	2002-2011	504,049	7	72,007	1.39
AECNE[c]	Spain	2001-2011	808,149	9	89,794	1.11
Vilarinho *et al.* (2010)	Portugal	2005-2009	316,243	6	52,707	1.90
La Marca *et al.* (2008)	Italy	2002-2008	160,000	1	160,000	0.63
Boneh *et al.* (2008)	Australia (Victoria)	Oct 2001–Sep 2007	391,651	6	65,275	1.53
Wiley *et al.* (1999)	New South Wales, Australia	1997-1998	137,120	1	137,120	0.73
Wiley *et al.* (2013)[d]	New South Wales & ACT, Australia	Apr 1998-Dec 2013	1,346,999	15	89,800	1.11
Webster *et al.* (2013)[e]	New Zealand	Dec 2006-Dec 2011	315,000	3	105,000	0.95
Chace *et al.* (2002)	USA - Pennsylvania and North Carolina	Not presented	1,100,000	13	84,615	1.18
Comeau *et al.* (2004)	USA, NENSP	Jan 1999-Jan 2003	472,254	2	236,127	0.42
Frazier *et al.* (2006)	USA, North Carolina	1999-2005	749,695	5	149,939	0.67
Tiwana *et al.* (2012)	USA, Texas	2007	400,000	7	57,143	1.75

Table 3.4a continued GA-1 prevalence in MS/MS screened cohorts

Study	Location	Period	Results			
			Total screened (n)	Number of cases (n)	Birth prevalence One in	Per 100,000
Sahai *et al.* (2011)	India (Andra Pradesh)	2006-2008	4,896	1	4,896	20.42
Niu *et al.* (2010)	Taiwan	Mar 2000- Jun 2009	1,321,123	13	101,625	0.98
Yang *et al.* (2011)	China	Jan 2008-Dec 2010	129,415	2	64,708	1.55
Yoon *et al.* (2003)	Korea	Apr 2001-Mar 2004	79,179	2	39,590	2.53
Lim *et al.* (2013)[f]	Singapore	2006-2013	135,000	3	45,000	2.22
Yamaguchi *et al.* (2007)	Japan	1997-2007	606,380	3	202,127	0.49
Abdenur *et al.* (2000)	Argentina	1996-1999	9,320	1	9,320	10.73
Khneisser *et al.* (2008)	Lebanon	Nov 2006-Aug 2008	22,000	1	22,000	4.55
Abdel-Hamid *et al.* (2007)	Kuwait	May 2004-Mar 2006	1,158	1	1,158	86.36
Rashed *et al.* (1999)	Saudi Arabia	Jun 1995-1998	27,624	2	13,812	7.24

a Data collected by DGNS (German Association for Newborn Screening) National Screening reports Germany 2004-2007; 2008; 2009; 2010
b Data from Netherlands screening programme (unpublished)
c Data collated by AECNE (Asociación Española de Cribado Neonatal) Presented at XVIII Reunion de los Centros de Cribado Neonatal Bilbao 2012
d Data from New South Wales screening programme, Australia (unpublished)
e Data from New Zealand screening programme (unpublished)
f Data from Singapore screening programme (unpublished)

Table 3.4b GA-1 prevalence based on clinical detection

Study	Location	Period	Results			
			Total screened (n)	Number of cases (n)	Birth prevalence One in	Per 100,000
Wilson *et al.* (2007)	New Zealand	2004-2006	175,000	1	175,000	0.57
Applegarth *et al.* (2000)	Canada, British Columbia	1979-1996	785,400	3	261,800	0.38
Wilcken *et al.* (2009)	Australia	1994-2002	1,551,200	6	258,533	0.39
Wilcken *et al.* (2003)	Australia, New South Wales	April 1974-March 1994	1,754,000	2	877,000	0.11
Hoffmann *et al.* (2004)	Germany	1999-2000	844,575	3	281,525	0.36
Kolker *et al.* (2007)	Germany (South Western)	1975-1991	611,400	1	611,400	0.16
Kolker *et al.* (2007)	Germany (South Western)	1991-1999	187,200	1	187,200	0.53
Lund *et al.* (2012)	Denmark, Faroe Islands, Greenland	1992-2002	251,468	1	251,468	0.40
Kyllerman *et al.* (1994)	Sweden and Norway	1977-2004	10,000,000	12	833,333	0.12
Moammar *et al.* (2010)	Saudi Arabia	Jan 1983- Dec 2008	165,530	3	55,177	1.81

Table 3.4c Estimated prevalence of GA-1 Worldwide and in Western populations

Method of detection	Worldwide	Western
Screening by MS/MS	1.37 (1.04-1.80)	1.04 (0.89-1.23)
Clinical detection	0.33 (0.18-0.62)	0.25 (0.16-0.40)

3.5 Isovaleric Acidaemia (IVA)

The prevalence estimates for IVA were based on studies reporting on MS/MS based screening programmes (17 studies) and those reporting on clinical detection (5 studies) (Tables 3.5a & b). In comparison to the 2010 review, an additional 5 studies were included in the screen-detected prevalence calculation here. Sources of additional data include laboratory data; older studies which had not been included in the 2010 report due to date restriction, and newly identified studies.

The largest contributing datasets were from the Germany[61] with over 4 million screened, and the New South Wales screening programme in Australia contributing data from over 1.4 million screened[62]. Other larger studies included those from the US24 and Taiwan[50]. Smaller studies included those from Korea[75], Lebanon[55] and India[42]. Table 3.5a provides summary data from these studies. An interesting point to note is that one study from New Zealand identified five screen positive cases of IVA; however, four of these were subsequently classified as benign variants. It was decided to not include these four cases as true-positives.

Five studies were examined for prevalence detected by clinical diagnosis, most being from Western populations: Canada[66], Australia[34;36] and Germany[6] and one smaller study from Saudi Arabia[68] which showed a markedly higher prevalence in comparison with the Western studies.

Table 3.5c provides a summary of the estimated prevalence of IVA based on the mode of detection. Similar to GA-1 the estimated prevalence of IVA for Western populations based on screen-detected cases [0.81; 95% CIs 0.56 to 1.17] was higher than that based on clinical detection [0.19; 95% CIs 0.10 to 0.36]. IVA has a spectrum of clinical phenotypes, which is likely to influence ascertainment through clinical diagnosis. Again, worldwide prevalence estimates were much higher than those for Western populations; this is likely to be as a result of the higher prevalence observed in particular non-Western populations such as those from the Middle-East, Malaysia and India. It is also interesting to note that the prevalence in German populations is higher in comparison with the reported prevalence in other European countries. Newborn screening does lead to the identification of individuals who are positive on screening but are later shown to have a mutation that is defined as a benign variant[76]. Most reports do not provide enough information to ascertain whether these benign variants were included or excluded from the case definition.

Table 3.5a IVA prevalence detected in MS/MS screened cohorts

Study	Location	Period	Results			
			Total screened (n)	Number of cases (n)	Birth prevalence One in	Per 100,000
Lindner *et al.* (2011)	Germany, Heidelberg	Jan 1999-Apr2005	1,084,195	15	72,280	1.38
Ensenauer *et al.* (2011)	Germany, Munich	Jan1999-Jun 2008	1,612,105	24	67,171	1.49
Nennstiel-Ratzel *et al.* (2010)[a]	Germany - minus Heidelberg and Munich lab data	2004-2010	4,014,848	42	95,592	1.05
Kasper *et al.* (2010)	Austria	Apr 2002-Dec 2009	622,489	1	622,489	0.16
Loeber *et al.* (2013)[b]	Netherlands	2009	186,128	3	62,043	1.61
AECNE [c]	Spain	2001-2011	808,149	1	808,149	0.12
Vilarinho *et al.* (2010)	Portugal	2005-2009	316,243	3	105,414	0.95
La Marca *et al.* (2008)	Italy	2002-2008	160,000	1	160,000	0.63
Wiley *et al.* (2013)[d]	New South Wales & ACT, Australia	Apr 1998-Dec 2013	1,430,227	4	357,557	0.28
Webster *et al.* (2013)[e]	New Zealand	Dec 2006-Dec 2011	315,000	1[ϕ]	315,000	0.32
Chace *et al.* (2002)	USA – Pennsylvania and North Carolina	Not presented	1,100,000	4	275,000	0.36
Frazier *et al.* (2006)	USA, North Carolina	1999-2005	749,695	7	107,099	0.93
Sahai *et al.* (2011)	India (Andra Pradesh)	2006-2008	4,896	1	4,896	20.42
Niu *et al.* (2010)	Taiwan	Mar 2000-Jun 2009	1,321,123	2	660,562	0.15
Yoon *et al.* (2003)	Korea	Apr 2001-Mar 2004	79,179	3	26,393	3.79
Khneisser *et al.* (2008)	Lebanon	Nov 2006-Aug 2008	22,000	1	22,000	4.55
Rashed *et al.* (1999)	Saudi Arabia	June 1995-1998	27,624	2	13,812	7.24

ϕ 4 benign variants were also detected

a Data collected by DGNS (German Association for Newborn Screening) National Screening reports Germany 2004-2007; 2008; 2009; 2010

b Data from Netherlands screening programme (unpublished)

c Data collated by AECNE (Asociación Española de Cribado Neonatal) Presented at XVIII Reunion de los Centros de Cribado Neonatal Bilbao 2012

d Data from New South Wales screening programme, Australia (unpublished)

e Data from New Zealand screening programme (unpublished)

Table 3.5b IVA prevalence based on clinical detection

Study	Location	Period	Results			
			Total screened (n)	Number of cases (n)	Birth prevalence One in	Per 100,000
Applegarth *et al*. (2000)	Canada, British Columbia	1979-1996	785,400	2	392,700	0.25
Wilcken *et al*. (2009)	Australia	1994-2002	1,551,200	2	775,600	0.13
Wilcken *et al*. (2003)	Australia, New South Wales	April 1974-March 1994	1,754,000	3	584,667	0.17
Hoffmann *et al*. (2004)	Germany	1999-2000	844,575	2	422,288	0.24
Moammar *et al*. (2010)	Saudi Arabia	Jan 1983-Dec 2008	165,530	6	27,588	3.62

Table 3.5c Estimated prevalence of IVA Worldwide and in Western populations

Method of detection	Worldwide	Western
Screening by MS/MS	0.99 (0.65-1.52)	0.81 (0.56-1.17)
Clinical detection	0.36 (0.08-1.61)	0.19 (0.10-0.36)

3.6 Long-chain 3-hydroxyacyl CoA dehydrogenase deficiency (LCHADD) / MTP

The prevalence estimates for LCHADD/MTP are based on studies reporting on MS/MS based screening programmes (16 studies) and those reporting on clinical detection (5 studies). In comparison to the 2010 review, an additional 11 studies were included in the screen-detected prevalence calculation here. Sources of additional data include laboratory data from Germany, Netherlands and Spain, older studies which had not been included in the 2010 report due to date restriction, and newly identified studies. Tables 3.6a & b provide a summary data from the studies included in the analysis.

The larger of these studies comprised the data from German laboratories[61] and from the New South Wales screening programme[62], Australia, with over 4 million and 1 million screened respectively. Other large studies included further German data from Sander *et al*.[12] and US data from Chace *et al.*[24] Studies with small numbers screened were included from Korea[75] and Kuwait[54], and these showed markedly higher prevalence figures from the larger, Western studies, which is reflected in the difference between worldwide and Western prevalences.

Table 3.6c provides a summary of the estimated prevalence of LCHADD based on the mode of detection. The estimated prevalence based on MS/MS screening for Western populations is 0.67; 95% [CIs 0.49 to 0.91]. An important note here is that MS/MS based screening identifies those with isolated LCHADD as well as those with other MTP deficiencies. Most reports from screening programmes did not provide sufficient detail regarding their case definition of LCHADD; hence it is unclear if the reported cases were restricted to isolated LCHADD only or included other MTP deficiencies as well. Only two studies differentiated between LCHADD and MTP deficiencies in their reporting: Sander *et al*.[12] and Loukas *et al*.[14]. The Sander *et al* study identified seven cases of isolated LCHADD and three with other MTP deficiencies following screening of 1.2 million babies. Loukas *et al* did not identify any cases. In the absence of more detailed information, it is assumed that the calculated prevalence estimates include the full spectrum of MTP deficiencies; however, this may be an under-estimate.

Five studies (four of which were from Western populations) were used to calculate prevalence based on clinical detection. The estimated prevalence of 0.46 [95% CIs 0.21 to 1.02] for Western populations is smaller in comparison to screen-detected prevalence. However, the disparity is not as large as seen for the other conditions examined as part of this review.

Table 3.6a LCHADD/MTP prevalence detected in MS/MS screened cohorts

Study	Location	Period	Results			
			Total screened (n)	Number of cases (n)	Birth prevalence One in	Per 100,000
Sykut-Cegielska *et al.* (2011)	Poland	2001-2009	658,492	11*	59,863	1.67
Roscher *et al.* (2001)	Germany, Munich	Jan 1999-Jul 2001	307,676	1	307,676	0.33
Sander *et al.* (2005)	Germany, Hannover	1999-2005	1,200,000	11	109,091	0.92
Lindner *et al.* (2011)	Germany, Heidelberg	Jan 1999-Apr 2005	1,084,195	6	180,699	0.55
Nennstiel-Ratzel *et al.* (2010)[a]	Germany	2004-2010	4,238,335	26	163,013	0.61
Kasper *et al.* (2010)	Austria	Apr 2002-Dec 2009	622,489	9	69,165	1.45
Lund *et al.* (2012)	Denmark, Faroe Islands, Greenland	2002-2011	504,049	3	168,016	0.60
Loeber *et al.* (2013)[b]	Netherlands	2009	186,128	1	186,128	0.54
Vilarinho *et al.* (2010)	Portugal	2005-2009	316,243	3	105,414	0.95
AECNE (2012)[c]	Spain	2001-2011	808,149	4	202,037	0.49
Burgard *et al.* (2012)	Hungary	2008-2009	22,661	1	22,661	4.41
Wiley *et al.* (2013)[d]	Australia, New South Wales and Australian Capital Territory	Apr 1998-Dec 2013	1,065,713	2	532,857	0.19
Chace *et al.* (2002)	USA, Pennsylvania and North Carolina	Not presented	1,100,000	2	550,000	0.18
Frazier *et al.* (2006)	USA, North Carolina	1999-2005	749,695	3	249,898	0.40
Yoon *et al.* (2003)	Korea	Apr 2001-Mar 2004	79,179	3	26,393	3.79
Abdel-Hamid *et al.* (2007)	Kuwait	May 2004-Mar 2006	1,158	3	386	259.07

a Data collected by DGNS (German Association for Newborn Screening) National Screening reports Germany 2004-2007; 2008; 2009; 2010
b Data from Netherlands screening programme (unpublished)
c Data collated by AECNE (Asociación Española de Cribado Neonatal) Presented at XVIII Reunion de los Centros de Cribado Neonatal Bilbao 2012
d Data from New South Wales screening programme, Australia (unpublished)
*This includes 5 cases that were detected by chance as they had abnormal Phe levels.

Table 3.6b LCHADD prevalence based on clinical detection

Study	Location	Period	Results			
			Total screened (n)	Number of cases (n)	Birth prevalence One in	Per 100,000
Sykut-Cegielska *et al.* (2011)	Poland	2001-2009	3,348,000	29	115,448	0.87
Wilcken *et al.* (2009)	Australia	1994-2002	1,551,200	3	517,067	0.19
Wilcken *et al.* (2003)	Australia, New South Wales	Apr 1974-Mar 1994	1,754,000	5	350,800	0.29
Lund *et al.* (2012)	Denmark, Faroe Islands, Greenland	1992-2002	266,465	2	133,233	0.75
Moammar *et al.* (2010)	Saudi Arabia	Jan 1983- Dec 2008	165,530	1	165,530	0.60

Table 3.6c Estimated prevalence of LCHADD Worldwide and in Western populations

Method of detection	Worldwide	Western
Screening by MS/MS	1.02 (0.52-2.02)	0.67 (0.49-0.91)
Clinical detection	0.48 (0.24-0.96)	0.46 (0.21-1.02)

3.7 Estimated birth prevalence in England and Wales

The estimated numbers of cases based on 729,624 births in England and Wales (number of births from Office for National Statistics for 2012) is shown in Table 3.7a. These were calculated by applying the estimated prevalence rate in Western populations from MS/MS screening studies to the number of births in England and Wales. When looking across all conditions the expected number of cases per year in England and Wales is between 20 and 37.

As a comparison, also included is the estimated number of cases for 438,000 births (the number screened in the clinical phase of the pilot) as well as the actual screen-positives obtained (Table 3.7b). This was calculated again by applying the prevalence in Western populations to the number of births screened (438,000).

Table 3.7a: Summary overall birth prevalence data

Condition	Prevalence in Western populations per 100,000	Estimated number of cases in England and Wales per 729,674
Homocystinuria	0.49 [0.29, 0.83]	3.60 [2.15, 6.03]
MSUD	0.71 [0.53, 0.95]	5.19 [3.90, 6.90]
GA-1	1.04 [0.89, 1.23]	7.62 [6.48, 8.96]
IVA	0.81 [0.56, 1.17]	5.88 [4.06, 8.51]
LCHADD	0.67 [0.49, 0.91]	4.90 [3.60, 6.68]
Overall		27.18 [20.18, 37.08]

Table 3.7b: Comparison of overall birth prevalence data with results from the UK pilot programme

Condition	Prevalence in Western populations per 100,000	Estimated number of cases in England and Wales per 438,000	Actual number of cases
Homocystinuria	0.49 [0.29, 0.83]	2.16 [1.29, 3.62]	1
MSUD	0.71 [0.53, 0.95]	3.11 [2.34, 4.14]	2
GA-1	1.04 [0.89, 1.23]	4.57 [3.89, 5.38]	4
IVA	0.81 [0.56, 1.17]	3.53 [2.44, 5.11]	4
LCHADD	0.67 [0.49, 0.91]	2.94 [2.16, 4.01]	1

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). 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, and this can be seen in annual reports from Germany composed by the Deutschen Gesellenschaft fur Neugeborenenscreening (DGNS)[61]. Here we can see that between the years 2004-2010, the number of cases each year of the target disorders varied. For example, the number of cases of MSUD varied between two cases in one year and six in another, and the number of cases of LCHADD between four and two cases. Although test algorithms are likely to have some influence on these figures, it also reflects the rare nature of these disorders.

Furthermore, although we are basing the prevalence estimates on 'Western' populations; it is possible that there are differences in the prevalence between Western populations. The prevalence of LCHADD/MTP in Germany, Austria and Poland was higher than that from studies in Australia and the USA. Another reason is that these 'Western' populations also contain different sub-populations that may be at higher or lower risk of these conditions which, in turn, influence the aggregated number of events observed across the entire population.

4 Conclusions

This review has produced estimates of prevalence for the five target conditions based on different modes of detection. The birth prevalence for the five target conditions is very small. Across all conditions, apart from homocystinuria, prevalence estimates based on screen-detected cases are higher than those based on clinical detection. An additional point of note is that higher prevalence estimates have been obtained for all conditions in comparison to the previous review conducted in 2010. This is likely to be in part, due to differences in data analysis between the two reviews. Prevalence estimates for the 2010 review were based on MS/MS screening studies published between January 2002 and June 2009. As a result, studies reporting on MS/MS screening programmes published prior to 2002 were not included in the prevalence analysis. The current study includes data from studies published prior to 2002 as well as additional data from published and unpublished sources. The higher prevalence estimates are also likely to be due to improved ascertainment of cases, especially as screening programmes have become established. This is also reflected by the fact that, on the whole, prevalence estimates based on screen-detected cases are much higher than those based on clinical detection.

As can be evidenced, there was variation in the international prevalence of the selected diseases. A number of factors are likely to contribute to this, including the mode of case ascertainment as well as population specific factors such as consanguinity.

In most instances case ascertainment has been either through clinical detection or screening programmes. There are inherent biases in both these methods. The target disorders all have heterogeneous clinical presentation. Reports based on clinical detection are likely to miss a number of cases, either due to 'fulminant death' without diagnosis or through under-reporting. This is also likely when screening programmes are in place, if infants are missed by the programme. In addition, different standards applied to diagnosis in different settings and over different time periods are likely to affect case ascertainment.

Screening programmes are able to identify more cases due to a more active mode of identifying 'affected' individuals. For most of the target conditions, screening has only been possible since the advent of MS/MS. Screening for homocystinuria and MSUD using techniques such as the bacterial inhibition assay had been established in some countries (*e.g.* Japan and Ireland) for a number of years. For both these conditions, MS/MS does not lead to markedly increased ascertainment over traditional screening techniques. There were still differences in reported birth prevalence of the target conditions between centres. These could be due to differences between and within screening programmes over time, in the age at screening and choice of population cut-offs.

In carrying out our analysis for this review, we did not differentiate studies on factors such as age at screening and cut-offs used for metabolites. This was because our primary interest was in examining prevalence as opposed to test performance; however, test performance can have some influence. It is possible that cut-offs are aimed at certain variants of disease, but studies often do not provide enough detailed information on confirmed cases. In addition, identification of patients missed by screening relies on clinical detection and reports from screening programmes were often of insufficient follow-up time to assess this fully.

It was notable that there were differences in estimated prevalences for Worldwide and Western populations. In general, the estimates made for Worldwide populations were larger than that for Western populations only. This was in part influenced by studies from the Middle East, India and Malaysia which showed much higher prevalences. Although the prevalence estimates from these are likely to have been biased, as many were small studies in tertiary centres, it is also possible that these areas have a higher burden of inherited metabolic diseases, as these are also regions with increased rates of consanguinity.

Extrapolating findings in other Western populations suggest that for these target conditions we would expect approximately 27 new cases in England and Wales per year. However, this may range from as few as 20 cases to as many as 37 cases in total. Comparison of these estimated numbers with data from the clinical phase of the pilot programme suggest that they are comparable. Although the estimated prevalences are higher in comparison to the calculations made in 2010, they are likely to reflect a more accurate assessment of the true prevalence, as they are based on a larger number of screening population studies.

5 References

1. Burton H and Moorthie S. Expanded newborn screening: A review of the evidence. PHG Foundation (2010) ISBN 978-1-907198-03-8.

2. Kasper DC, Ratschmann R, Metz TF, Mechtler TP, Moslinger D, Konstantopoulou V *et al*. The National Austrian Newborn Screening Program - Eight years experience with mass spectrometry. Past, present, and future goals. *Wiener Klinische Wochenschrift* 2010; 122(21-22):607-613.

3. Lund AM, Hougaard DM, Simonsen H, Andresen BS, Christensen M, Duno M *et al*. Biochemical screening of 504,049 newborns in Denmark, the Faroe Islands and Greenland - Experience and development of a routine program for expanded newborn screening. *Molecular Genetics and Metabolism* 2012; 107(3):281-293.

4. Burgard P, Cornel M, Di Flippo F, Haege G, Hoffmann G, Lindner M *et al*. Report on the practices of newborn screening for rare disorders implemented in Member States of the European Union, Candidate, Potential Candidate and EFTA Countries 2012 . http://ec.europa.eu/eahc/documents/news/Report_NBS_Current_Practices_20120108_FINAL.pdf. Date accessed 10.07.13.

5. Ensenauer R, Fingerhut R, Maier EM, Polanetz R, Olgemoller B, Roschinger W *et al*. Newborn Screening for Isovaleric Acidemia Using Tandem Mass Spectrometry: Data from 1.6 Million Newborns. *Clin Chem* 2011; 57(4):623-626.

6. Hoffmann GF, von KR, Klose D, Lindner M, Schulze A, Muntau AC *et al*. Frequencies of inherited organic acidurias and disorders of mitochondrial fatty acid transport and oxidation in Germany. *Eur J Pediatr* 2004; 163(2):76-80.

7. Kolker S, Garbade SF, Boy N, Maier EM, Meissner T, Muhlhausen C *et al*. Decline of acute encephalopathic crises in children with glutaryl-CoA dehydrogenase deficiency identified by newborn screening in Germany. *Pediatr Res* 2007; 62(3):357-363.

8. Lindner M, Hoffmann GF. Congenital disorders of intermediate metabolism - Neonate screening and rational diagnostic work-up of clinical problems [German] Angeborene storungen des intermediarstoffwechsels: Neugeborenenscreening und rationale diagnostik bei klinischen problemstellungen. *Klinikarzt* 2005; 34(3):50-54.

9. Lindner M, Gramer G, Haege G, Fang-Hoffmann J, Schwab KO, Tacke U *et al*. Efficacy and outcome of expanded newborn screening for metabolic diseases - Report of 10 years from South-West Germany. *Orphanet Journal of Rare Diseases* 2011; 6.

10. Roscher AA, Fingerhut R, Liebl B, Olgemoller B. Erweiterung des neugeborenen-screening durch tandemmassenspektrometrie, Monatsschrift Kinderheilkunde 2001; 149: 1297-1303.

11. Sander J, Janzen N, Sander S, Melchiors U, Steuerwald U. Neonatal screening for inborn errors of metabolism using tandem mass spectrometry [German] Tandemmassen-spektrometrie: Beitrag zum Neugeborenenscreening auf angeborene strorungen des stoffwechsels. *Monatsschrift fur Kinderheilkunde* 2000; 148(8):771-777.

12. Sander J, Sander S, Steuerwald U, Janzen N, Peter M, Wanders RJ *et al*. Neonatal screening for defects of the mitochondrial trifunctional protein. *Mol Genet Metab* 2005; 85(2):108-114.

13. Schulze A, Lindner M, Kohlmuller D, Olgemoller K, Mayatepek E, Hoffmann GF. Expanded newborn screening for inborn errors of metabolism by electrospray ionization-tandem mass spectrometry: results, outcome, and implications. *Pediatrics* 2003; 111(6 Pt 1):1399-1406.

14. Loukas YL, Soumelas GS, Dotsikas Y, Georgiou V, Molou E, Thodi G *et al*. Expanded newborn screening in Greece: 30 months of experience. *J Inherit Metab Dis* 2010; 33(Suppl 3):341-348.

15. Antonozzi I, Dominici R, Andreoli M, Monaco F. Neonatal screening in Italy for congenital hypothyroidism and metabolic disorders: hyperphenylalaninemia, maple syrup urine disease and homocystinuria. *J Endocrinol Invest* 1980; 3(4):357-363.

16. la Marca G, Malvagia S, Casetta B, Pasquini E, Donati MA, Zammarchi E. Progress in expanded newborn screening for metabolic conditions by LC-MS/MS in Tuscany: Update on methods to reduce false tests. *J Inherit Metab Dis* 2008; 31(Suppl 2):395-404.

17. Sykut-Cegielska J, Gradowska W, Piekutowska-Abramczuk D, Andresen BS, Olsen RK, Oltarzewski M *et al*. Urgent metabolic service improves survival in long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency detected by symptomatic identification and pilot newborn screening. *J Inherit Metab Dis* 2011; 34(1):185-195.

18. Vilarinho. Four years of expanded newborn screening in Portugal with tandem mass spectrometry. *J Inherit Metab Dis* 2010; 33(Suppl 3):133-138.

19. Quental S, Vilarinho L, Martins E, Teles EL, Rodrigues E, Diogo L *et al*. Incidence of maple syrup urine disease in Portugal. *Mol Genet Metab* 2010; 100(4):385-387.

20. Couce Pico ML, Castineiras Ramos DE, Boveda Fontan MD, Iglesias Rodriguez AJ, Cocho de Juan JA, Fraga Bermudez JM. [Advances in the diagnosis and treatment of maple syrup urine disease: experience in Galicia (Spain)]. *An Pediatr* (Barc) 2007; 67(4):337-343.

21. Couce ML, Castineiras DE, Boveda MD, Bana A, Cocho JA, Iglesias AJ *et al*. Evaluation and long-term follow-up of infants with inborn errors of metabolism identified in an expanded screening programme. *Mol Genet Metab* 2011; 104(4):470-475.

22. Juan-Fita MJ, Egea-Mellado JM, Gonzalez-Gallego I, Moya-Quiles MR, Fernandez-Sanchez A. Expanded newborn screening in the Region of Murcia, Spain. Three-years experience. *Medicina Clinica* 2012; 139(13):566-571.

23. Paz Valinas L AMG. [Clinical effectiveness of neonatal screening for inborn errors of metabolism using tandem mass spectrometry. Systematic Review]. *Systematic review* 2007.

24. Chace DH, Kalas TA, Naylor EW. The application of tandem mass spectrometry to neonatal screening for inherited disorders of intermediary metabolism. *Annual Review of Genomics and Human Genetics* 2002; 3:17-45.

25. Naylor EW, Chace DH. Automated tandem mass spectrometry for mass newborn screening for disorders in fatty acid, organic acid, and amino acid metabolism. *J Child Neurol* 1999; 14 Suppl 1:S4-S8.

26. Marsden D, Zytkovicz TH, Larson C, Shih VE, Grady GF. Prevalence of fatty acid oxidation disorders and organic acidemias in New England newborns screened by tandem mass spectrometry. *J Inherit.Metab Dis* 23[Suppl 1], 15.

27. Marsden D. Expanded newborn screening by tandem mass spectrometry: the Massachusetts and New England experience. *Southeast Asian J Trop Med Public Health* 2003; 34(Suppl 3):111-114.

28. Comeau AM, Larson C, Eaton RB. Integration of new genetic diseases into statewide newborn screening: New England experience. *American Journal of Medical Genetics Part C-Seminars in Medical Genetics* 2004; 125C(1):35-41.

29. Zytkovicz TH, Fitzgerald EF, Marsden D, Larson CA, Shih VE, Johnson DM *et al*. Tandem mass spectrometric analysis for amino, organic, and fatty acid disorders in newborn dried blood spots: a two-year summary from the New England Newborn Screening Program. *Clin Chem* 2001; 47(11):1945-1955.

30. Muenzer J, Frazler DM, Wweavil SD *et al*. Incidence of metabolic disorders detected by newborn screening in North Carolina using tandem mass spectrometry. *Am J Human Genet Suppl* 2, 36.

31. Frazier D, Millington D, McCandless S, Koeberl D, Weavil S, Chaing S *et al*. The tandem mass spectrometry

newborn screening experience in North Carolina: 1997-2005. *Journal of Inherited Metabolic Disease* 2006; 29(1):76-85.

32. Tiwana SK, Rascati KL, Park H. Cost-effectiveness of expanded newborn screening in Texas (Provisional abstract). *Value in Health* 2012; 15:613-621.

33. Watson MS. Current status of newborn screening: decision-making about the conditions to include in screening programs. *Ment Retard Dev Disabil Res Rev* 2006; 12(4):230-235.

34. Wilcken B, Haas M, Joy P, Wiley V, Bowling F, Carpenter K *et al*. Expanded newborn screening: outcome in screened and unscreened patients at age 6 years. *Pediatrics* 2009; 124(2):e241-e248.

35. Wilcken B, Smith A, Brown DA. Urine screening for aminoacidopathies: is it beneficial? Results of a long-term follow-up of cases detected bny screening one millon babies. *J Pediatr* 1980; 97(3):492-497.

36. Wilcken B, Wiley V, Hammond J, Carpenter K. Screening Newborns for Inborn Errors of Metabolism by Tandem Mass Spectrometry. *N Engl J Med* 2003; 348(23):2304-2312.

37. Wiley V, Carpenter K, Wilcken B. Newborn screening with tandem mass spectrometry: 12 months' experience in NSW Australia. *Acta Paediatrica* 1999; 88:48-51.

38. Wiley V, Carpenter K, Bayliss U, Wilcken B. Newborn screening--is it really that simple? *Southeast Asian J Trop Med Public Health* 2003; 34 Suppl 3:107-10.:107-110.

39. Wilson C, Kerruish NJ, Wilcken B, Wiltshire E, Webster D. The failure to diagnose inborn errors of metabolism in New Zealand: the case for expanded newborn screening. *N Z Med J* 2007; 120(1262):1-11.

40. Boneh A, Beauchamp M, Humphrey M, Watkins J, Peters H, Yaplito-Lee J. Newborn screening for glutaric aciduria type I in Victoria: treatment and outcome. *Mol Genet Metab* 2008; 94(3):287-291.

41. Yang L, Yin H, Yang R, Huang X. Diagnosis, treatment and outcome of glutaric aciduria type I in Zhejiang Province, China. *Medical Science Monitor* 2011; 17(7):H55-H59.

42. Sahai I, Zytkowicz T, Rao KS, Lakshmi KA, Eaton RB, Akella RR. Neonatal screening for inborn errors of metabolism using tandem mass spectrometry: experience of the pilot study in Andhra Pradesh, India. *Indian J Pediatr* 2011; 78(8):953-960.

43. Yamaguchi S. Newborn screening in Japan: restructuring for the new era. *Ann Acad Med Singapore* 2008; 37(12 Suppl):13-15.

44. Kuhara T. Diagnosis of inborn errors of metabolism using filter paper urine, urease treatment, isotope dilution and gas chromatography-mass spectrometry. *Journal of Chromatography B* 2001; 758(1):3-25.

45. Shigematsu Y, Hirano S, Hata I, Tanaka Y, Sudo M, Sakura N *et al*. Newborn mass screening and selective screening using electrospray tandem mass spectrometry in Japan. *Journal of Chromatography B-Analytical Technologies in the Biomedical and Life Sciences* 2002; 776(1):39-48.

46. Aoki K. Long term follow-up of patients with inborn errors of metabolism detected by the newborn screening program in Japan. *Southeast Asian J Trop Med Public Health* 2003; 34 Suppl 3:19-23.

47. Yoon HR, Lee KR, Kim H, Kang S, Ha Y, Lee DH. Tandem mass spectrometric analysis for disorders in amino, organic and fatty acid metabolism: two year experience in South Korea. *Southeast Asian J Trop Med Public Health* 2003; 34 Suppl 3:115-20.

48. Abdul Rahman S, Mohd YZ, Yew SC, Omar A, Othman NA, Shaharudin AS. Pilot project on neonatal screening of inborn errors of metabolism (IEM) using tandem mass spectrometry in Malaysia. *Journal of Inherited Metabolic Disease* 2007; 30:4.

49. Lin WD, Wu JY, Lai CC, Tsai FJ, Tsai CH, Lin SP *et al*. A pilot study of neonatal screening by electrospray ionization tandem mass spectrometry in Taiwan. *Acta Paediatr Taiwan* 2001; 42(4):224-230.

50. Niu DM, Chien YH, Chiang CC, Ho HC, Hwu WL, Kao SM *et al*. Nationwide survey of extended newborn

screening by tandem mass spectrometry in Taiwan. *J Inherit Metab Dis* 2010; 33(Suppl 2):S295-S305.

51. Hsieh CT, Hwu WL, Huang YT, Huang AC, Wang SF, Hu MH *et al*. Early detection of glutaric aciduria type I by newborn screening in Taiwan. *J Formos Med Assoc* 2008; 107(2):139-144.

52. Huang HP, Chu KL, Chien YH, Wei ML, Wu ST, Wang SF *et al*. Tandem mass neonatal screening in Taiwan--report from one center. *J Formos Med Assoc* 2006; 105(11):882-886.

53. Hwu WL, Huang AC, Chen JS, Hsiao KJ, Tsai WY. Neonatal screening and monitoring system in Taiwan. *The Southeast Asian journal of tropical medicine and public health* 2003; 34 Suppl 3:91-93.

54. Abdel-Hamid M, Tisocki K, Sharaf L, Ramadan D. Development, validation and application of tandem mass spectrometry for screening of inborn metabolic disorders in Kuwaiti infants. *Medical Principles and Practice* 2007; 16(3):215-221.

55. Khneisser I, Adib SM, Megarbane A, Lukacs Z. International cooperation in the expansion of a newborn screening programme in Lebanon: a possible model for other programmes. *J Inherit Metab Dis* 2008; 31(Suppl 2):S441-S446.

56. Lindner M, Abdoh G, Fang-Hoffmann J, Shabeck N, Al Sayrafi M, Al Janahi M *et al*. Implementation of extended neonatal screening and a metabolic unit in the State of Qatar: developing and optimizing strategies in cooperation with the Neonatal Screening Center in Heidelberg. *J INherit Metab Dis* 2007; 30(4):522-529.

57. Gan-Schreier H, Kebbewar M, Fang-Hoffmann J, Wilrich J, Abdoh G, Ben-Omran T *et al*. Newborn population screening for classic homocystinuria by determination of total homocysteine from Guthrie cards. *Journal of Pediatrics* 2010; 156(3):427-433.

58. Rashed MS, Rahbeeni Z, Ozand PT. Application of electrospray tandem mass spectrometry to neonatal screening. *Seminars in Perinatology* 1999; 23(2):183-193.

59. Abdenur JE, Chamoles NA, Schenone AB, Guinle AE, Fusta M, Gagglioli D. Supplemental newborn screening of amino acids (AA) and acylcarnitines (AC) by electrospray tandem mass spectrometry (ESI-MS/MS): experiences in Argentina. *J Inherit. Metab Dis* 23[Suppl 1], 13.

60. Torres-Sepulveda MD, Martinez-de Villarreal LE, Esmer C, Gonzalez-Alanis R, Ruiz-Herrera C, Sanchez-Pena A *et al*. Expanded newborn screening using tandem mass spectrometry: Two years' experience in Nuevo Leon, Mexico. *Salud Publica de Mexico* 2008; 50(3):200-206.

61. Nennstiel-Ratzel U *et al*. Deutsche Gesellschaft fur neugeborenenscreening E.V. National Screening Report Germany: years 2004-1007; 2008; 2009; 2010. Retrieved from http://www.screening-dgns.de/ Date accessed 10.07.13.

62. Wiley *et al*. 2013 Data from New South Wales screening programme, Australia (unpublished).

63. Lund AM, Hougaard DM, Simonsen H, Andresen BS, Christensen M, Duno M *et al*. Biochemical screening of 504,049 newborns in Denmark, the Faroe Islands and Greenland - Experience and development of a routine program for expanded newborn screening. *Molecular Genetics and Metabolism* 2012; 107(3):281-293.

64. Frazier D, Millington D, McCandless S, Koeberl D, Weavil S, Chaing S *et al*. The tandem mass spectrometry newborn screening experience in North Carolina: 1997-2005. *Journal of Inherited Metabolic Disease* 2006; 29(1):76-85.

65. Yap S, Naughten E. Homocystinuria due to cystathionine beta-synthase deficiency in Ireland: 25 years' experience of a newborn screened and treated population with reference to clinical outcome and biochemical control. *J Inherit Metab Dis* 1998; 21(7):738-747.

66. Applegarth DA, Toone JR, Lowry RB. Incidence of inborn errors of metabolism in British Columbia, 1969-1996. *Pediatrics* 2000; 105(1):e10.

67. Kyllerman M. Dystonia and dyskinesia in glutaric aciduria type I: clinical heterogeneity and therapeutic considerations Mov.Disord. 1994; 9(1):22-30.

68. Moammar H, Cheriyan G, Mathew R, Al-Sannaa N. Incidence and patterns of inborn errors of metabolism in the Eastern Province of Saudi Arabia, 1983-2008. *Ann Saudi Med* 2010; 30(4):271-277.

69. AECNE, Asociación Española de Cribado Neonatal Presented at XVIII Reunion de los Centros de Cribado Neonatal Bilbao SM2, Programas de cribado neonatal en España (2001-2011) Retrieved from http:aecne.es/datos2.htm. Date accessed 10/07/13.

70. Lim J *et al*. Data from Singapore screening programme 2006-2013 (unpublished data).

71. Loeber G *et al*. Data from netherlands screening programme 2009 (unpublished data).

72. El-Said MF, Badii R, Bessisso MS, Shahbek N, El-Ali MG, El-Marikhie M *et al*. A common mutation in the CBS gene explains a high incidence of homocystinuria in the Qatari population. *Hum Mutat* 2006; 27(7):719.

73. Webster *et al*. Data from New Zealand screening programme 2006-2011 (unpublished raw data).

74. Kolker S, Christensen E, Leonard JV, Greenberg CR, Boneh A, Burlina AB *et al*. Diagnosis and management of glutaric aciduria type I--revised recommendations. *J Inherit Metab Dis* 2011; 34(3):677-694.

75. Yoon H-R, Lee KR, Kang S, Lee DH, Yoo H-W, Min W-K *et al*. Screening of newborns and high-risk group of children for inborn metabolic disorders using tandem mass spectrometry in South Korea: A three-year report *Clinica Chimica Acta* 2005; 354(1-2):167-180.

76. Ensenauer R, Vockley J, Willard JM, Huey JC, Sass JO, Edland SD *et al*. A common mutation is associated with a mild, potentially asymptomatic phenotype in patients with isovaleric acidemia diagnosed by newborn screening. *American Journal of Human Genetics* 2004; 75(6):1136-1142.

Appendix 1 Search strategies used in major electronic bibliographic databases

Stage 1 Identification of all articles relevant to the evaluation of MS/MS screening programmes. Search dates: 20th- 23rd May 2013

CINAHL database

#1 Exp health screening/

#2 Exp infant, newborn/
#3 1 AND 2
#4 Neonat* ADJ2 screen*
#5 Newborn* ADJ2 screen*
#6 3 OR 4 OR 5
#7 Exp metabolism, inborn errors/
#8 Inborn ADJ2 error*
#9 7 OR 8
#10 6 AND 9
#11 Spectrum analysis/
#12 Mass ADJ2 spect*
#13 MS ADJ2 spect*
#14 Tandem ADJ2 mass
#15 11 OR 12 OR 13 OR 14
#16 10 AND 15

CRD database

CRD database search (NHS DARE, EED, HTA) via website http://www.crd.york.ac.uk/crdweb/

((neonat* AND screen*) OR (newborn AND screen*)) AND ((mass AND spect*) OR (ms AND spect*) OR (tandem AND spect*))

Web of knowledge Search Terms

Topic=(mass OR MS OR tandem) AND Topic=(spect*)
Timespan=All Years.
Databases SCI-EXPANDED, SSCI, A&HCI, CPCI-S.

Cochrane library

#1 Neonatal screening
#2 Neonat* near/1 screen
#3 Newborn* near/1 screen*
#4(#1 OR #2 OR #3)

EMBASE

http://www.library.nhs.uk/booksandjournals/Default.aspx

1 Exp newborn screening/
2 Neonat* ADJ2 screen*
3 Newborn* ADJ2 screen*
4 Exp mass screening/
5 Exp newborn/
6 #4 AND #5
7 #1 OR #2 OR #3 OR #6
8 Exp inborn-error-of-metabolism
9 Inborn ADJ2 error ADJ2 metabolism
10 #8 OR #9
11 #7 AND #10
12 Exp mass spectrometry/
13 Mass ADJ2 spect*
14 MS ADJ2 spect*
15 Tandem ADJ2 mass
16 #12 OR #13 OR #14 OR #15
17 #11 AND #16

Medline via Pubmed

1. Neonatal screening
2. Neonat* screen*
3. Newborn* screen*
4. Mass screening
5. Infant, newborn
6. #4 AND #5
7. #1 OR #2 or #3 OR #6
8. Metabolism, inborn errors
9. Inborn error*
10. #8 OR #9
11. #7 AND #10
12. Spectrum analysis, mass
13. Mass spect*
14. MS spect*
15. Tandem mass
16. #12 OR #13 OR #14 OR #15
17. #11 and #16

Stage 2 Search terms used to identify articles relating to epidemiology and screening for the five chosen diseases in PubMed (MEDLINE)

Glutaric Acidaemia

1. Glutaryl CoA
2. Glutaryl aciduria
3. GCDH
4. GA 1
5. Glutaric aciduria
6. Glutaric acidemia
7. Glutaric acidaemia
8. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7

Homocystinuria

1. Homocystinuria
2. Hypermethioninaemia
3. Hypermethioninemia
4. (Cystathionine OR cbs) AND deficien*
5. #1 OR #2 OR #3 OR #4

Isovaleric Acidaemia

1. Isovaleric acidaemia
2. Isovaleric academia
3. Isovaleric aciduria
4. Ivd deficien*
5. Isovaleric acid AND dehydrogenase deficien*
6. Isovaleryl AND dehydrogenase deficien*
7. Isovalericacidemia
8. Isovalericacidaemia
9. #1 OR #2 OR #3 OR#4 OR #5 OR #6 OR #7 OR #8

Maple syrup urine disease

1. Maple syrup urine disease
2. MSUD
3. Branched chain ketoaciduria
4. Keto acid decarboxylase deficien*
5. #1 OR #2 OR #3 OR #4

Long chain hydroxacyl-CoA Dehydrogenase deficiency

1. Trifunctional protein deficien*
2. 3-hydroxyacyl coa dehydrogenase
3. Multienzyme complexes
4. Long chain AND dehydrogenase deficien*
5. LCHAD
6. HADHdeficien*
7. Hydroxacyl AND dehydrogenase
8. long chain
9. #7 AND #8
10. Hydroxydicarboxylicaciduria
11. Hydroxydicarboxylic aciiduroa
12. #1 OR #2 OR #3 OR # OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11

Epidemiology terms

1. Epidemiology
2. Morbidity
3. Mortality
4. Survival analysis
5. Disease
6. Disease progression
7. Natural history
8. Epidemiolog*
9. Genetic heterogeneity
10. Incidence
11. Prevalence
12. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #9 OR #10 OR #11

Screening terms

1. Neonatal screening
2. Neonat* screen*
3. Newborn* screen*
4. Mass screening
5. Infant, newborn
6. Genetic screening
7. #4 AND#5 and #6
8. #1 OR #2 OR#3 OR #7
9. Metabolism, inborn errors*
10. Inborn error*
11. #9 or #10
12. #8 and #11

Appendix 2 Neonatal Laboratory Questionnaire

Neonatal Laboratory Questionnaire

Background

We are currently carrying out a systematic review to identify and collate studies describing the prevalence of five inherited metabolic disorders (MSUD, LCHADD, GA1, Homocystinuria and Isovaleric acidaemia), and to summarize the findings of these studies. We are contacting you in order to identify grey literature that will inform the study objectives.

Please return your completed questionnaire:

Dr. Sowmiya Moorthie
PHG Foundation
2 Worts Causeway, Cambridge CB1 8RN
United Kingdom
Email: sowmiya.moorthie@phgfoundation.org

Part 1: Laboratory details

Country	

Type of screening programme

	Tick
Primary research	
A pilot project	
An existing screening programme	

Please let us know the time period the data you are providing us is for:

Part 2: Assay details – initial sample, screening test, confirmatory tests

Initial patient sample (tick)

Heel-prick blood	
Capillary blood	
Plasma	
Serum	
Urine	

	Screening assay	Confirmatory (reference) assay
Guthrie (bacterial inhibition assay)		
Chromatography		
DELFIA		
Mass Spectrometry (MS-MS)		
Enzymology		
DNA-based		
Radio-immunoassay		
Other (describe)		

Timing of screening test (age in days)

Please let us know if the above is based on collected data or actual screening protocol

How is prematurity dealt with? *e.g.* was time of screening adjusted for prematurity?

Details of any preliminary screening questions – if used

Part 3: Screening details

Disorders screened for

Number of disorders		
	Please tick if these disorders are screened for	Please indicate for how long screening has been occurring
Glutaric aciduria type 1 (GA1)		
Homocystinuria		
Isovaleric acidaemia (IVA)		
Maple Syrup Urine Disease		
Long-chain hydroxyacyl-CoA dehydrogenase deficiency (LHCADD; including trifunctional protein deficiency)		

The population screened

Definition of eligible population for screening

Size of eligible population

Neonatal laboratory questionnaire continued

Coverage – proportion of population actually screened

Ethnicity – Please provide details of the ethnicity of your population

Screening test and diagnostic confirmation

Briefly provide details of the methodology used for screening (e.g. MS/MS *etc*.).

Describe process for confirmation of **screen-detected positive** assay results for each of the relevant conditions

Describe process for confirmation of **clinical diagnosis** in confirmed screen-positive assay results for each of the relevant conditions

How were population cut-offs determined?

What were the cut-offs (please provide details for each of the conditions).

Please give us information on how you define false-negative results and if/how you obtain this information.

Part 4: Programme performance

1. Screening test phase

PROVIDE ROC CURVES IF AVAILABLE

Please complete the table(s) for each of the conditions

Condition 1: Glutaric aciduria type 1 (GA1)

	Disease positive (Number and %)	Disease negative (Number and %)	Disease that would have remained latent
Screening test positive			
Screening test negative			
		Total screened	

Please report the following:

Sensitivity	
False negative rate	
Specificity	
False positive rate	
Positive predictive value	
Negative predictive value	
Number and/or % unusable results	
Number and/or % borderline results	
Number and/or % uncertain results	

Condition 2: Homocystinuria

	Disease positive (Number and %)	Disease negative (Number and %)	Disease that would have remained latent
Screening test positive			
Screening test negative			
		Total screened	

Please report the following:

Sensitivity	
False negative rate	
Specificity	
False positive rate	
Positive predictive value	
Negative predictive value	
Number and/or % unusable results	
Number and/or % borderline results	
Number and/or % uncertain results	

Condition 3: Isovaleric acidaemia (IVA)

	Disease positive (Number and %)	Disease negative (Number and %)	Disease that would have remained latent
Screening test positive			
Screening test negative			
		Total screened	

Please report the following:

Sensitivity	
False negative rate	
Specificity	
False positive rate	
Positive predictive value	
Negative predictive value	
Number and/or % unusable results	
Number and/or % borderline results	
Number and/or % uncertain results	

Condition 4: Maple Syrup Urine Disease

	Disease positive (Number and %)	Disease negative (Number and %)	Disease that would have remained latent
Screening test positive			
Screening test negative			
		Total screened	

Please report the following:

Sensitivity	
False negative rate	
Specificity	
False positive rate	
Positive predictive value	

Negative predictive value	
Number and/or % unusable results	
Number and/or % borderline results	
Number and/or % uncertain results	

Condition 5: Long-chain hydroxyacyl-CoA dehydrogenase deficiency (LHCADD; including trifunctional protein deficiency)

	Disease positive (Number and %)	Disease negative (Number and %)	Disease that would have remained latent
Screening test positive			
Screening test negative			
		Total screened	

Please report the following:

Sensitivity	
False negative rate	
Specificity	
False positive rate	
Positive predictive value	
Negative predictive value	
Number and/or % unusable results	
Number and/or % borderline results	
Number and/or % uncertain results	

Please let us know if you have previously published these results and you have details of the publication(s) they appear in.

Are you aware of any published or unpublished data on the birth incidence/prevalence of the five inborn errors under consideration in your population prior to establishment of the screening programme

Any other information

Thank you for taking the time to complete this questionnaire and help us with our review. We will acknowledge your contribution to this work. We are planning to publish our findings in a peer-reviewed publication. Please also let us know if it is NOT acceptable to use the data you have provided in any peer-reviewed publication.