The University Of Sheffield.

EXPANDED NEWBORN SCREENING FOR INBORN ERRORS OF THE METABOLISM

HEALTH ECONOMICS

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INTRODUCTION

The newborn bloodspot screening programme in England currently tests babies for five disorders; phenylketonuria, congenital hypothyroidism, sickle cell disorders, cystic fibrosis and MCADD. The NHS NIHR programme has funded a pilot to evaluate expansion of the programme to include screening for five further conditions, maple syrup urine disease (MSUD) , homocystinuria (HCY), isovaleric acidaemia (IVA), glutaric aciduria type 1 (GA1) and long chain hydroxy acyl CoA dehydrogenase deficiency (LCHADD). The expanded newborn screening pilot involves six screening centres in England (Leeds, Manchester, Sheffield, Birmingham, Guy's St Thomas and Great Ormond Street) and the populations they serve and is co-ordinated by the South Yorkshire Collaboration for Leadership in Applied Health Research and Care (SY-CLARHC).

In parallel with the pilot evaluation the School of Health and Related Research (ScHARR) was commissioned to undertake an analysis of the economic impact of expanding the screening programme. This short report outlines the methods and summarises the key findings of this economic evaluation.

METHODS

Overview

The economic evaluation aims to include the potential lifelong impacts of screening, this necessitates a model based approach. The economic model is based upon data obtained from the expanded screening pilot, a systematic review of published and unpublished screening programme data, other published literature and expert judgement obtained from professionals involved in the screening pilot. A decision tree model, see Figure 1, is used to compare screening options.

The economic assessment includes direct health and social care costs and benefits and both are discounted at 1.5% as per current NICE guidelines. An indicative cost effectiveness acceptability threshold of £25,000 per QALY is used to calculate net benefits, it should be noted that NICE currently allows consideration of a higher threshold when assessing very rare and ultra-rare conditions though whether this is appropriate in the mass screening setting is open to debate.

Detailed descriptions of the economic models, parameter values and uncertainty ranges for each of the five inborn errors of the metabolism are presented in the Appendices

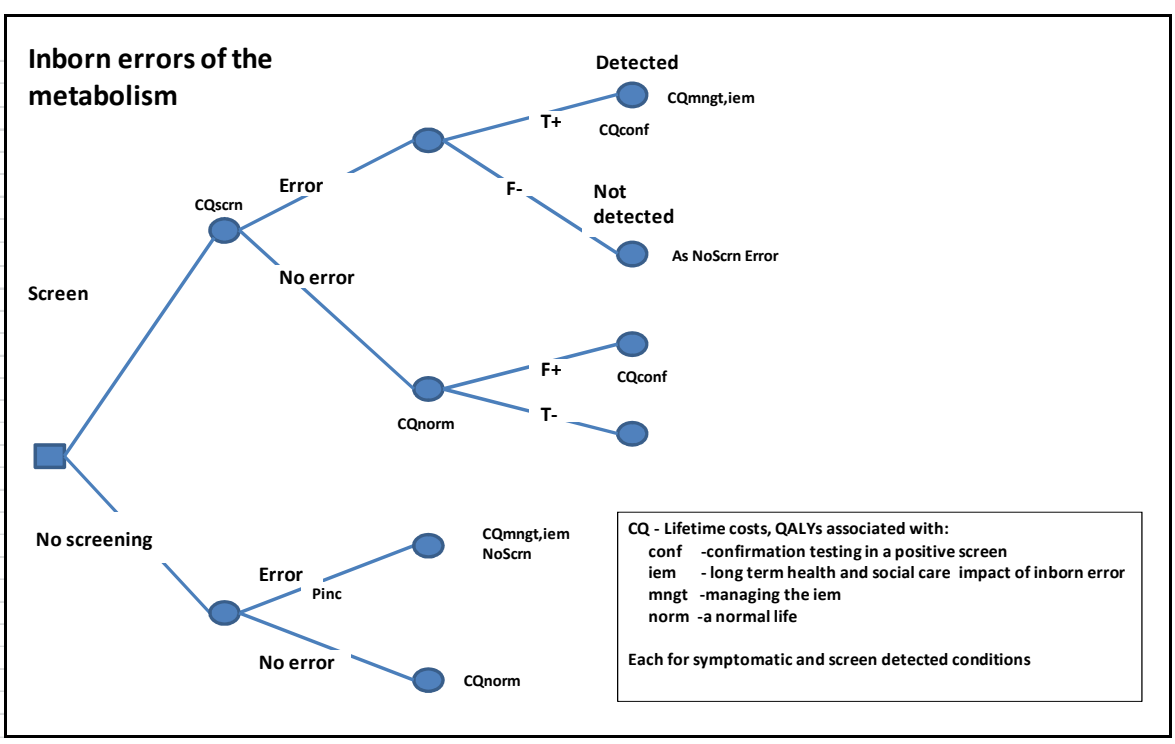
Prevalence of the inborn errors

In 2010 the PHG Foundation published a systematic review of the evidence relating to the inborn errors being considered.(Burton and Moorthie 2010) One of the original authors has updated this review with a specific focus on recent data respecting the birth prevalence of the conditions with and without MSMS screening.(Moorthie et al. 2013)

All the conditions under consideration are rare, understanding and awareness of the conditions is increasing rapidly and screening for the conditions is becoming more widely implemented. This situation together with the lack of contemporaneous comparative trials means that it is very difficult to interpret the evidence base regarding birth prevalence. Two specific biases that have opposing

effects are particular issues. Firstly high rates of early mortality, non-specific symptoms and lack of awareness of the condition, particularly in the older case series, means that the pre-screening evidence is likely to underestimate true prevalence. Secondly some of the conditions have a spectrum of severity, sometimes associated with particular variants of disease, this means that screening may have the potential to identify individuals for treatment that may otherwise have remained asymptomatic.

Figure 1: Decision model structure



In order to predict the economic, and indeed the clinical, impact of screening it is important to be able to estimate the birth prevalence of the disease and how this might change when moving from a system that relies primarily on clinical or symptomatic detection to mass screening detection.

A fixed effect logit model is used within a Bayesian meta-analysis to synthesise evidence on prevalence of disease. Studies reporting incidence in a 'western' population without screening and with MSMS screening are selected. For conditions where there is a marked difference in prevalence between the screened and clinically detected situations a lognormal bias adjustment is included within the model that has the effect of lifting the estimated 'real' clinical incidence.

Screening test characteristics

The sensitivity and specificity of the MSMS device in the mass screening setting is estimated from the data extracted in the PHG systematic review update. A logit model is used within a Bayesian synthesis to estimate these independently.

The screening programme and management of the condition

Marginal cost and resource estimates of expanding the MSMS screening system are taken from the screening extension pilot. These include all elements of the process from the midwife taking the bloodspot sample and providing information to parents, identification of positive screen results and subsequent confirmatory testing and initial consultations, advice and diet management for the period of the pilot follow-up.

Longer term management of the condition is taken from the expansion study protocol, diet management advice provided on the Expanded Newborn Screening website (http://www.expandedscreening.org), expert dietician input and published management guidelines where these exist.

Unit costs for resources are taken from routine data sources including primarily the PSSRU Unit Costs of Health and Social Care 2012.(Curtis 2012) Prices for prescription nutritional supplements and food stuffs are taken from the BNF.

The main impact on parents experience of sample collection is on the provision and interpretation of information regarding inborn errors of the metabolism. No quality of life impact is assumed for this part of the system.

Health and social care impact of the inborn errors of the metabolism

Survival

Published case series have been used to estimate survival with and without mass screening, where these are available. Survival in pre-symptomatically diagnosed cases is used as a proxy for screened survival where this is the best available evidence and expert judgement has been used to supplement published evidence. Background all-cause mortality is taken from the ONS.

Morbidity

Systematic searches were undertaken for quality of life, cost studies and disease natural history in the five conditions being studied. No studies directly assessing the quality of life impact of the conditions was identified. Published evidence and expert judgement concerning the short and long term health impacts and health and social care consequences was used to estimate the lifetime impact of the conditions.

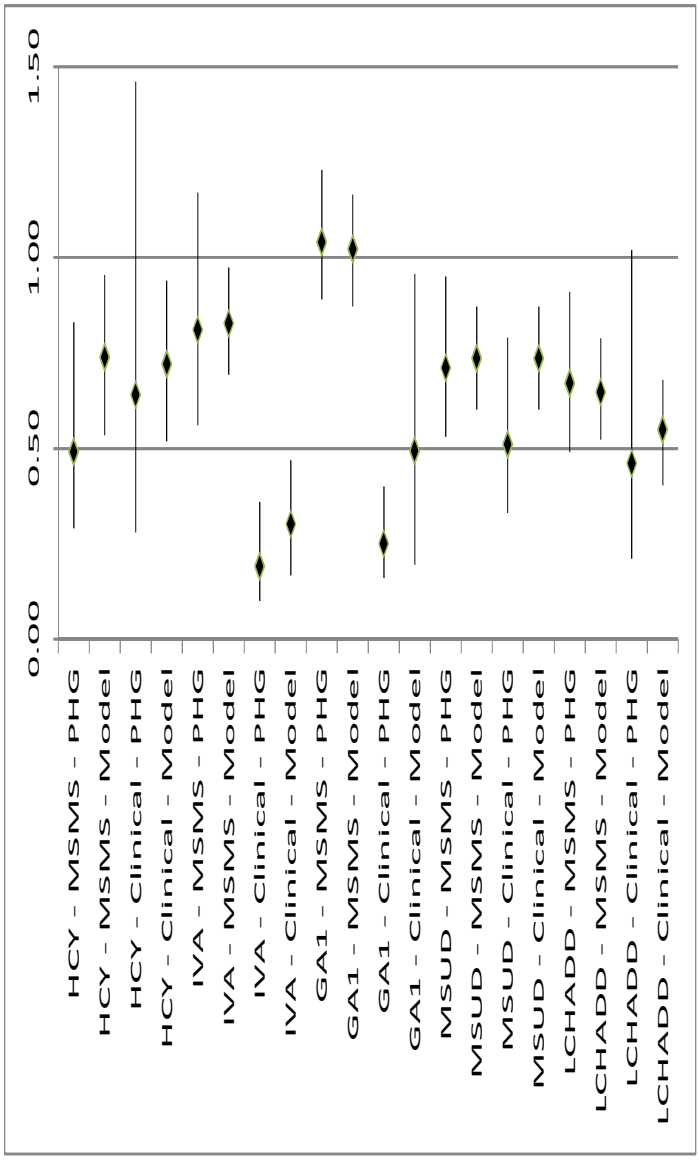
RESULTS

Prevalence of the five inborn errors of the metabolism.

Figure 2 presents the prevalence estimates for the five inborn errors of the metabolism. For each condition four prevalence estimates are provided. For example for MSUD we have:

- MSUD–MSMS - Model: Bayesian synthesis of MSMS data use in economic modelling
- MSUD–MSMS – PHG: PHG meta-analysis result for MSMS in the Western population
- MSUD – Clinical - Model: Bayesian synthesis of the unscreened data with bias adjustment for use in economic modelling
- MSUD – Clinical - PHG: PHG meta-analysis result for an unscreened population.

Figure 2: Birth prevalence per 100,000 births MSUD, LCHADD, IVA, HCY and GA1.



From Figure 2 we can see that for all conditions except HCY the MSMS prevalence is higher than the clinical prevalence. For HCY the clinical prevalence is much more uncertain than the screened prevalence and whilst the lower 95% limits are equivalent the upper limit is almost double the upper limit in the screened population. For MSUD, HCY and LCHADD the model estimates the birth prevalence to be virtually equivalent in the screened and unscreened populations. For IVA and GA1 the raw data synthesis suggests that the screened prevalence is much higher than the clinical prevalence. This is in line with published accounts by Kolker(Kolker et al. 2007b) and Ensenauer(Ensenauer et al. 2004) for GA1 and IVA respectively.

MSMS sensitivity and specificity

Table 1 presents the sensitivity and specificity estimates of MSMS for the five conditions derived from the Bayesian synthesis of screening studies in a western population.

Table 1: MSMS sensitivity and specificity

	Sensitivity		Specificity	
	Mean	95% CI	Mean	95% CI
MSUD	88.47%	(16.55% ,100%)	99.99%	(99.97% ,100%)
HCY	93.26%	(48.9% ,99.98%)	99.95%	(99.75% ,100%)
IVA	93.80%	(56.46% ,99.96%)	99.99%	(99.94% ,100%)
GA1	90.72%	(35.46% ,99.97%)	99.99%	(99.94% ,100%)
LCHADD	89.35%	(38.34% ,99.89%)	100.00%	(99.98% ,100%)

Cases detected

Table 2 presents estimates of the number of cases that may be expected to arise with MSMS screening for a 5 year England and Wales birth population, together with projections of the number of these cases that might be considered overdetected cases. Overdetected cases here are defined as patients that would be identified by screening but might otherwise have been asymptomatic without screen.

Economic outcomes

Table 3 presents the estimated costs and quality of life effects of screening for each of the conditions compared to no screening. It can be seen that screening for all conditions is predicted to be cost saving and more effective when compared to not screening for each condition, that is screening for each condition dominates no screening.

Figure 3 presents the cost effectiveness planes for each of the five conditions, with the £25,000 per QALY threshold superimposed. This figure again demonstrates that each of the conditions is expected to be cost saving and more effective than not screening. However we can see that all conditions, with the possible exception of LCHADD have some probability of having a cost effective greater than £25,000 per QALY.

Table 2 Estimated prevalence and projected overdetection with screening

5 year birth population 3,648,370

	Incidence			Projected overdetection		
	Mean	95%CI		Mean	95%CI	
MSUD[a]	26.82	21.97	31.81	-	-	-
HCY	26.93	19.48	34.81	0.67	0.00	1.39
IVA	30.14	25.27	35.51	19.15	10.92	26.34
GA1	37.27	31.81	42.51	20.27	9.76	29.40
LCHADD	23.60	19.10	28.78	3.61	0.00	11.35

a) Projected MSUD overdetection is subject to some methodological uncertainty, this is discussed further in the Appendix.

Table 3: Costs and effects of screening for each condition compared to no screening

	No screening		Screening		Marginal compared to no screening			
	Cost	QALYs	Cost	QALYs	Cost	QALY	INB[#]	Cost effectiveness
MSUD	£ 7.58	41.7934	£ 7.30	41.79347	-£ 0.28	0.000069	£ 2.00	Dominating
HCY	£ 6.31	41.79146	£ 2.98	41.79156	-£ 3.33	0.000105	£ 5.94	Dominating
IVA	£ 1.31	41.79356	£ 1.20	41.79358	-£ 0.10	0.000014	£ 0.46	Dominating
GA1	£ 2.87	41.79344	£ 2.72	41.79356	-£ 0.15	0.000120	£ 3.14	Dominating
LCHADD	£ 3.94	41.79347	£ 1.54	41.79358	-£ 2.40	0.000114	£ 5.25	Dominating

- INB: Incremental net benefit calculated at a threshold of £25,000 per QALY

Table 4 presents an analysis of uncertainty by means of an expected value of perfect information analysis for the 5 conditions. The per birth analysis is multiplied by the expected number of births in England and Wales over a five year period to give a meaningful estimate of value of information for the healthcare system as a whole.

Table 4: Expected value of perfect information for a 5 year England and Wales birth population

Birth pop 3,648,370

	MSUD	HCY	IVA	GA1	LCHADD
CiemNoScrn	£0	£0	£0	£0	£0
CmngtNoScrn	£0	£0	£0	£0	£0
QiemNoScrn	£0	£0	£3	£0	£0
CiemScrn	£206	£0	£0	£0	£0
CmngtScrn	£1,229	£0	£13	£0	£0
QiemScrn	£0	£0	£17,483	£0	£0
Cscrn	£0	£0	£0	£0	£0
Psens	£3,469	£336	£1,421	£202	£21
Pspec	£0	£1,753	£48,069	£7,769	£0
PincScrn	£0	£0	£0	£0	£0
PincNat	£0	£0	£162,786	£3,078	£0
Pab	£0	£0	£0	£34	£0

Figure 3: Cost effectiveness planes for MSUD, HCY, IVA, GA1 & LCHADD screening each compared to no screening.

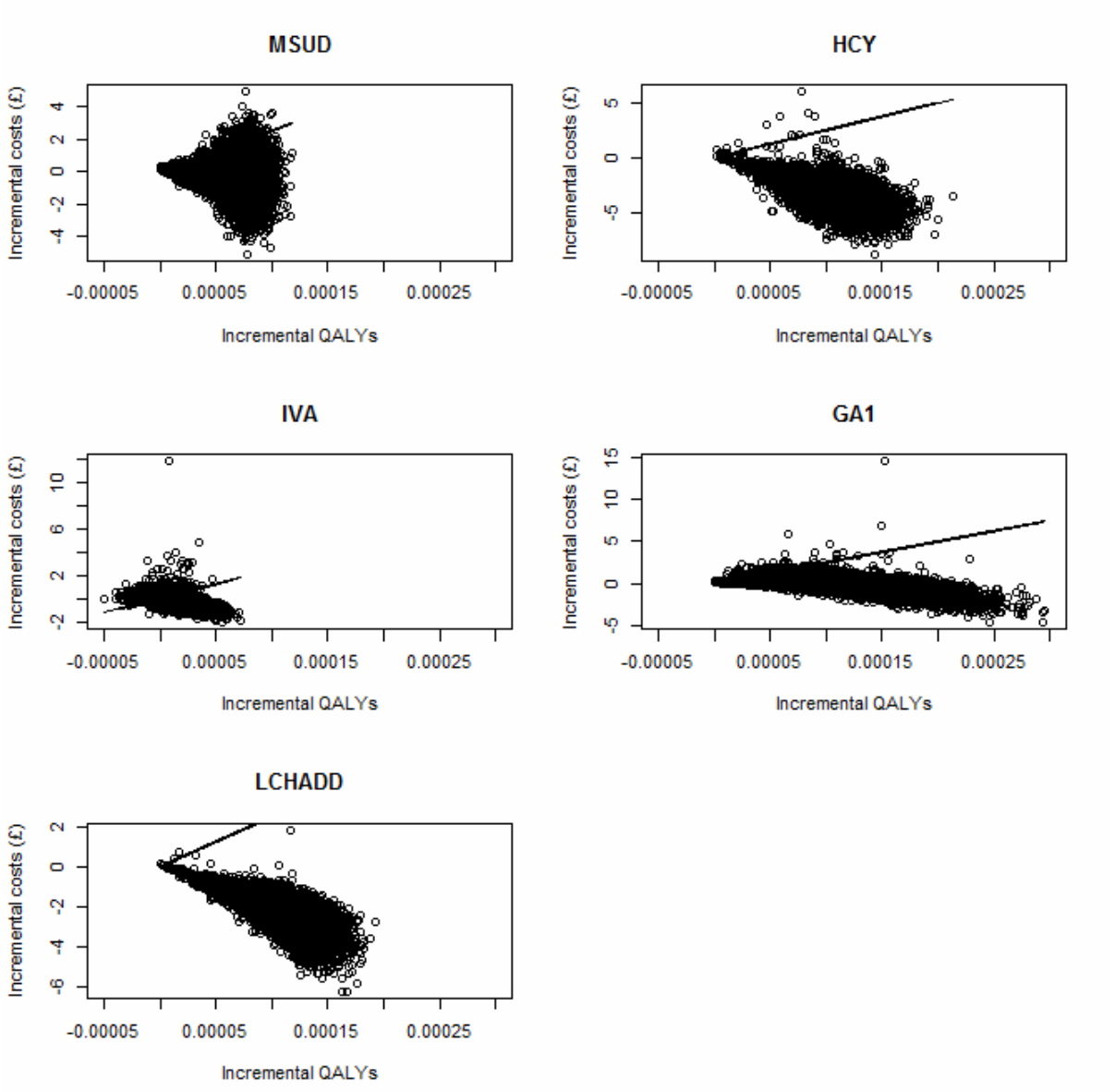
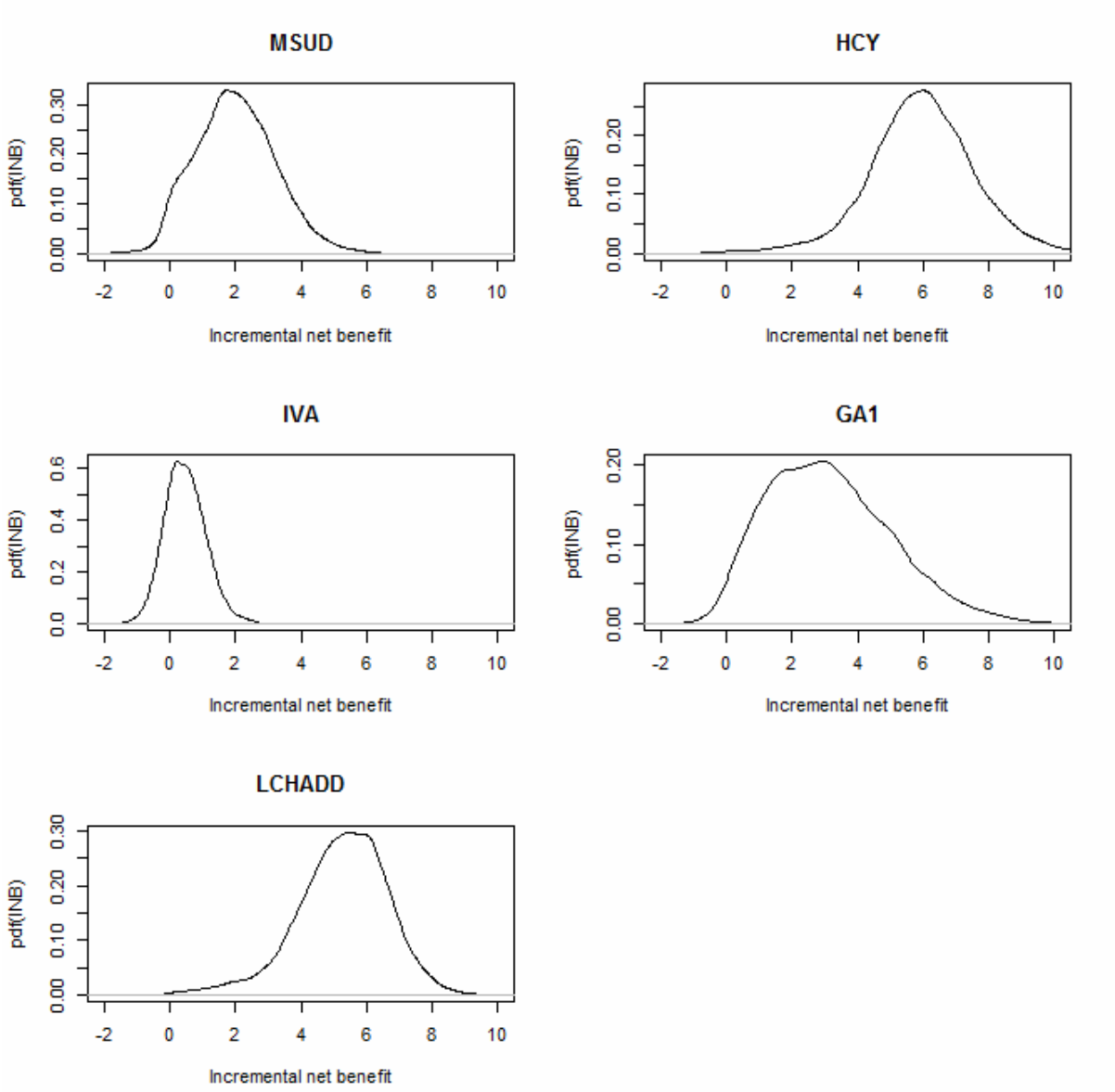


Figure 4: Incremental net benefit distributions for each condition versus no screening



CONCLUSIONS

Screening for MSUD, HCY, IVA, GA1 and LCHADD are each estimated to be potentially cost saving and result in increased quality of life compared to no screening.

The key uncertainties for MSUD screening are firstly the health and social care costs associated with the long term impact of the condition, particularly for screen detected cases (CiemScrn), secondly the long term costs of managing the condition in the screen detected survivors (CmngtScrn) and thirdly the sensitivity of the test. For MSUD it has not been possible to estimate the degree of potential over-detection from screening due to ambiguities in the evidence base regarding prevalence in the clinical and screened populations. This may be worthy over further investigation.

For HCY the key uncertainties are associated with the test characteristics of MSMS, particularly the specificity but also to a lesser extent the sensitivity.

For IVA the key uncertainties impacting on the economics of screening are associated with the true clinical birth prevalence of symptomatic disease, the specificity and to a lesser extent the sensitivity of the test and the long term quality of life impact from being screen detected. The high overdetection estimated for IVA is most probably related to the prevalence of the 932C->T mutation, individuals with which are likely to remain asymptomatic without screening. The model includes management costs for this subgroup in the form of regular clinical appointments, however it is assumed that these individuals are correctly identified and that there are no long term dietary costs. It has further been assumed that there is no adverse quality of life impact to these individuals from being subject to clinical management.

It is estimated that GA1 is similarly subject to some potential overdetection. However , in this case dietary management is short lived, thus whilst appointments and monitoring are estimated to continue over life the potential cost impact of overdetection is such that screening is still estimated to be cost saving. This does not however, take into account any potential adverse quality f life impacts from clinical management.

Screening for LCHADD is estimated to dominate no screening. This conclusion however is subject to provisos relating to the difficulties in nomenclature, specifically relating to uncertainties surrounding definitions, treatments and outcomes between LCHADD and the spectrum of conditions described as MTP that make parameterisation of the economic model difficult and subject to greater uncertainty than is captured within the economic results.

APPENDIX 1 CALCULATING THE COSTS OF MANAGING THE FIVE INBORN ERRORS OF THE METABOLISM: GENERIC ISSUES

COSTS OF MANAGING THE CONDITIONS

The management costs of the inborn errors consist of the cost of diagnosis, the cost of regular appointments and the cost of dietetic and other supplements. In order to estimate resource use the Expanded Screening Pilot study protocol, the technical resources section of the NHS NIHR Expanded Newborn Screening Programme website (http://www.expandedscreening.org), the pilot study case reports and expert elicitation were used. Staff costs shown in Table A1.1 were taken from the PSSRU,(Curtis 2012) supplement costs were estimated from the BNF, blood tests costs were estimated from the Sheffield Children's NHS foundation trust's clinical chemistry and Sheffield diagnostic genetic service user's handbook for metabolic investigations, other appointment costs were estimated from National Schedule of Reference Costs 2011-12. Blood test costs are shown in Table A1.2, tests are only included once even if they are used in more than one IEM.

Table A1.1 Staff costs used in the economic analysis

Resource	Cost	Source
Consultant (medical) (per hour)	£157	Curtis 2012: Unit costs of health and social care 2012
Nurse specialist (Band 6) (per hour)	£49	Curtis 2012: Unit costs of health and social care 2012
Dietician (per hour)	£34	Curtis 2012: Unit costs of health and social care 2012

Table A1.2 Blood test costs used in the economic analysis

Blood test	Blood test assumed	Cost	Source
IVA			
Plasma quantitative amino acids	Amino acids: Full quantitation	£80	Metabolic handbook
Urinary/organic acids	Organic acid (GCMS) including extraction, assay and identification	£89	Metabolic handbook
Blood plasma acyl carnatine	Carnitine (Total and free)	£87	Metabolic handbook
DNA IVA		£200	Assumption
FBC	Routine chemistry	£12	Metabolic handbook
Ca, Pi, LFT	Routine chemistry	£12	Metabolic handbook
Plasma amino acids & ammonia	Amino acids: Full quantitation	£80	Metabolic handbook
Free carnitine & acyl carnitine	Carnitine (Total and free)	£87	Metabolic handbook
Micronutrients	Routine chemistry	£12	Metabolic handbook

GA1			
DNA analysis (GA1)		£200	Assumption
Plasma amino acids including tryptophan	Amino acids: Full quantitation	£80	Metabolic handbook
HCU			
Total homocysteine	Total homocysteine	£35	Metabolic handbook
Folate	Routine chemistry	£12	Metabolic handbook
B12	Routine chemistry	£12	Metabolic handbook

Calculation of dietary supplements

A number of simplifications were used to estimate the overall dietary supplement requirements. For most of the diet supplements there is a considerable variation between individual patients. For the purpose of this analysis average age/weight specific dietary requirements are used to estimate total needs.

Table A1.3 Average age specific body weights used in the analysis

Age	Weight (Kg)	Age	Weight (Kg)
0	7.6	7 yr	26
2 months	4.77	8 yr	29.7
6 months	7.69	9 yr	33.5
10 months	9	10 yr	38.3
1 yr	11.5	11 yr	44
2 yr	14.1	12 yr	49.5
3 yr	16.5	13 yr	56.2
4 yr	18.1	14 yr	59.8
5 yr	20.4	15 yr	61.4
6 yr	23.2	16 yr	65

DISCOUNTING

All costs and health benefits are discounted at 1.5% per annum form birth.

NORMAL LIFE EXPECTANCY AND HEALTH RELATED QUALITY OF LIFE

Age specific all-cause mortality is taken from ONS Interim Life Tables, England & Wales 2008-2010. Age specific health related quality of life is taken from Kind using the EQ-5D instrument.(Kind et al. 1999) When discounted this gives an overall quality adjusted life valuation of 41.8 (40.1, 43.4) QALYs.

Model parameter:

Qnorm - 41.8 (40.1, 43.4)

OPERATING COSTS FOR THE EXPANDED SCREENING PROGRAMME

It is assumed that all capital and equipment costs of operating the newborn screening programme for inborn errors of the metabolism are already recouped and that there are therefore no marginal costs associated with expanding the programme to include the additional five conditions.

It is further assumed that there is no additional impact to the midwifery service, as an individual discussion for each condition would not be expected. Costs subsequent to receipt of a positive screen test result, including costs of confirmation are captured within the specific condition analyses. The programme costs therefore include the preparation and distribution of pre-screening information, lab screening costs, maintaining the website and cost of making the referral, these model estimates are based upon current payments to the labs and are:

£0.50/baby tested for labs

£0.09 per baby screened for dietetic input

Model parameter:

Cscrn - £0.59/5 = £0.118

For example assuming 700k births the annual operating costs would be: £350k + £63k = £413k pa.

APPENDIX 2 - HOMOCYSTINURIA

OVERVIEW

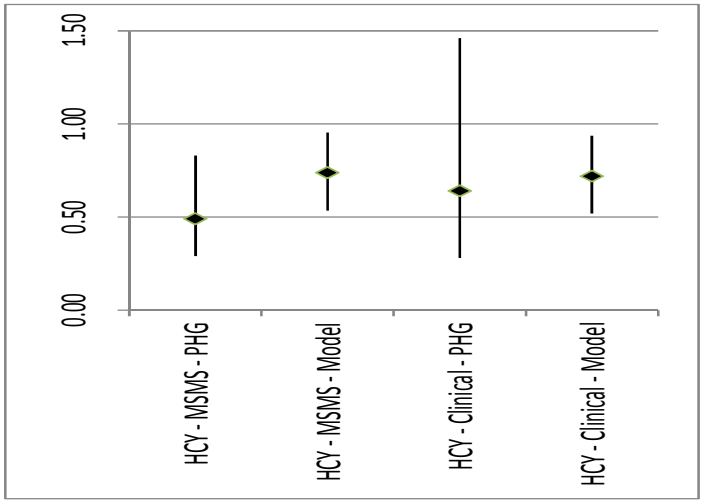
This appendix includes a description of the derivation of input parameters for the economic evaluation of HCY.

It is assumed that MSMS screening is only capable of detecting classical pyridoxine non-responsive homocystinurea, unless specified otherwise the abbreviation used throughout this report HCY refers specifically to the potentially screen detectable subgroup.

PREVALENCE

The birth prevalence estimates of homocystinuria are presented in Figure A2.1. The prevalence estimates presented in the PHG report do not distinguish between pyridoxine responsive and non-responsive cases. As noted in the PHG report this potentially gives rise to the higher prevalence incidence estimates in the clinically detected group (HCY – Clinical – PHG). In order to estimate the clinical prevalence rate of pyridoxine non-responsive cases (HCY – Clinical – Model) it is assumed that between 0-5% (expert judgement) of birth prevalent cases would remain asymptomatic without screening.

Figure A2.1 Birth prevalence of homocystinuria per 100,000 births



Model parameters:

PincScrn **-**Birth prevalence with screening 0.74 (0.53, 0.95)

PincNat **-** Birth prevalence without screening 0.72 (0.52, 0.94)

TEST CHARACTERISTICS

The sensitivity and specificity of the MSMS device in the mass screening setting is estimated from the data extracted in the PHG systematic review update. A logit model is used within a Bayesian synthesis to estimate these independently.

Model parameters:

PSens - Sensitivity for homocystinurea is estimated at 0.9326 (0.4890, 0.9998)

PSpec - Specificity for homocystinurea is estimated at 0.9995 (0.9975, 1.0)

DIAGNOSIS AND MANAGEMENT OF HCY

The next three tables list the resources used in the management of HCY in terms of staff time, blood tests taken and supplements prescribed. They are split into diagnosis costs in Table A2.1, regular appointments in Table A2.2 and supplements prescribed in Table A2.3 .

Table A2.1 HCY diagnosis costs

Cost of 1st appointment	
Staff	60 mins Consultant paediatrician 60 mins Specialist nurse 60 mins Dietician
Bloods	Plasma quantitative amino acids Total homocysteine
Other	Carnitine 100mg per day (7 days)
Cost of 2nd appointment (Diagnosis confirmed)	30 mins Consultant paediatrician 30 mins Specialist nurse 30 mins Dietician
Cost of 2nd appointment (False positive)	Same as above

Table A2.2 HCY appointments

Age	**Staff**	**Blood**	**Other**
1st Year (excluding diagnosis appointments)	30 mins Consultant paediatrician x5 30 mins Specialist nurse x5 30 mins Dietician x5 30 mins Dietician x14 (additional apps)	Plasma quantitative amino acids x27 Total homocysteine x27 B12 Folate	Baseline ophthalmology
2nd Year	30 mins Consultant paediatrician x4 30 mins Specialist nurse x4 60 mins Dietician x4	Plasma quantitative amino acids x6 Total homocysteine x6 B12	Ophthalmology
3rd Year	30 mins Consultant paediatrician x3	Plasma quantitative	Ophthalmology

	30 mins Specialist nurse x3 30 mins Dietician x3	amino acids x4 Total homocysteine x4 B12	
4 + (per year)	30 mins Consultant paediatrician x2 30 mins Specialist nurse x2 30 mins Dietician x2	Plasma quantitative amino acids x4 Total homocysteine x4 B12	Ophthalmology Psychometric assessment (at ages4 and 10) Dexa Scan (yearly from 16)

Table A2.3 HCY supplements

Age	Product
1st Year	HCU anamix to give 75ml per day Pyridoxine 50mg per day Folate acid 5mg per day
2nd Year to 5th Year	HCU gel, 1 24g sachet per day, (10g)
6th Year to 10th Year	HCU cooler, 1 130ml sachet per day, (15g)
12 Years +	HCU express 20, 1 34g sachet per day , (20g)

Table A2.4 presents the annual costs for the diagnosis and management of HCY in the screened population. Under no screening it is assumed that diagnosis costs occur in the year of symptomatic presentation(Taylor et al. 1998) but are the same as for screen diagnosis, similarly it is assumed management costs (not including health and social care costs of sequelae) once diagnosed are similar. Dietary management is assumed to be lifelong.

The annual costs of diagnosis and management projected over a full life course are presented in Figure A2.2.

Model parameters:

Cconf – Confirmation cost in false positives for HCY £475 (£428, £521)

CmngtNoScrn – Discounted lifetime cost of management of HCY without screening

£172,197 (£127,031, £229,408)

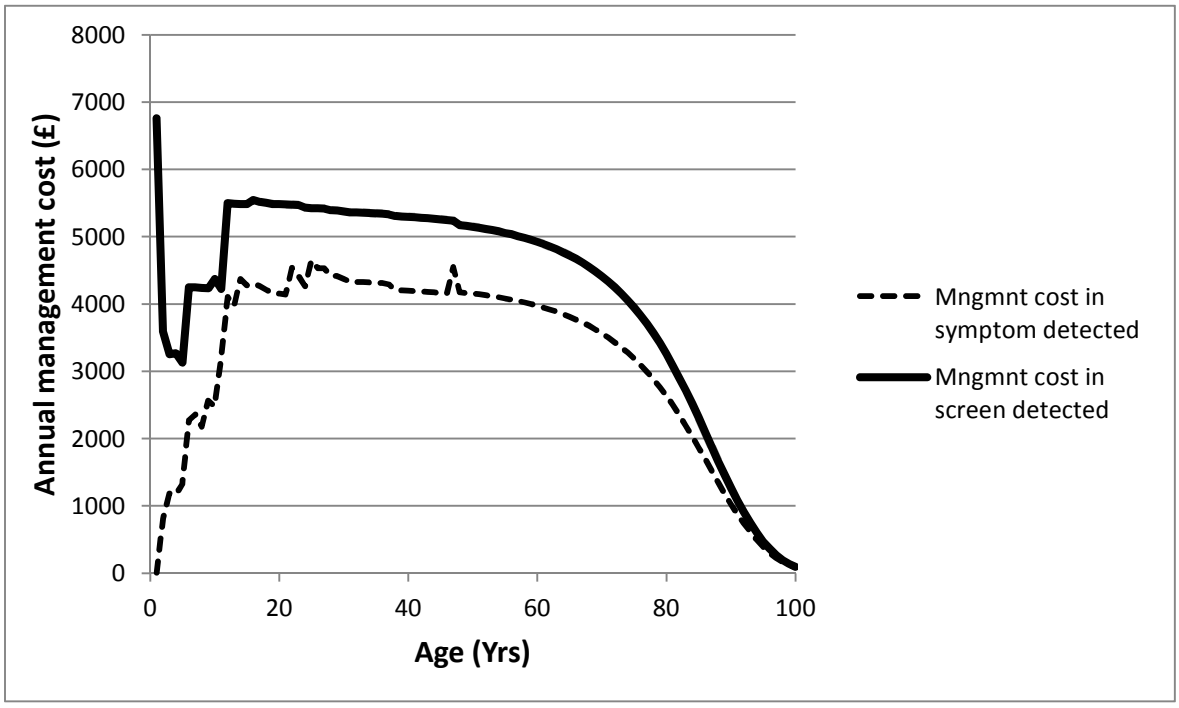
CmngtScrn - Discounted lifetime cost of management of HCY with screening

£235,730 (£174,305, £311,839)

Table A2.4 HCY annual diagnosis and management cost in the screened population

	Appoinments	Bloods	Diet	Other	Total
Diagnosis costs	£360	£115.00			£475
0-11 months	£480.00	£2,990.00	£2,354.40	£498	£6,322.28
12-23 months	£480.00	£702.00	£2,334.12	£108.76	£3,624.88
24-35 months	£360.00	£472.00	£2,334.12	£108.76	£3,274.88
3-4 years	£240.00	£472.00	£2,334.12	£250.20	£3,296.32
4-5 years	£240.00	£472.00	£2,334.12	£108.76	£3,154.88
5-6 years	£240.00	£472.00	£3,477.60	£108.76	£4,298.36
6-7 years	£240.00	£472.00	£3,477.60	£108.76	£4,298.36
7-8 years	£240.00	£472.00	£3,477.60	£108.76	£4,298.36
8-9 years	£240.00	£472.00	£3,477.60	£108.76	£4,298.36
9-10 years	£240.00	£472.00	£3,477.60	£250.20	£4,439.80
10-11 years	£240.00	£472.00	£3,477.60	£108.76	£4,298.36
11-12 years	£240.00	£472.00	£4,777.80	£108.76	£5,598.56
12-13 years	£240.00	£472.00	£4,777.80	£108.76	£5,598.56
13-14 years	£240.00	£472.00	£4,777.80	£108.76	£5,598.56
14-15 years	£240.00	£472.00	£4,777.80	£108.76	£5,598.56
15-16 years	£240.00	£472.00	£4,777.80	£179.44	£5,669.24
16+ years	£240.00	£472.00	£4,777.80	£155.81	£5,645.61

Figure A2.2 Annual age specific diagnosis and management costs for HCY



HEALTH AND SOCIAL CARE IMPACT OF THE HOMOCYSTINURIA

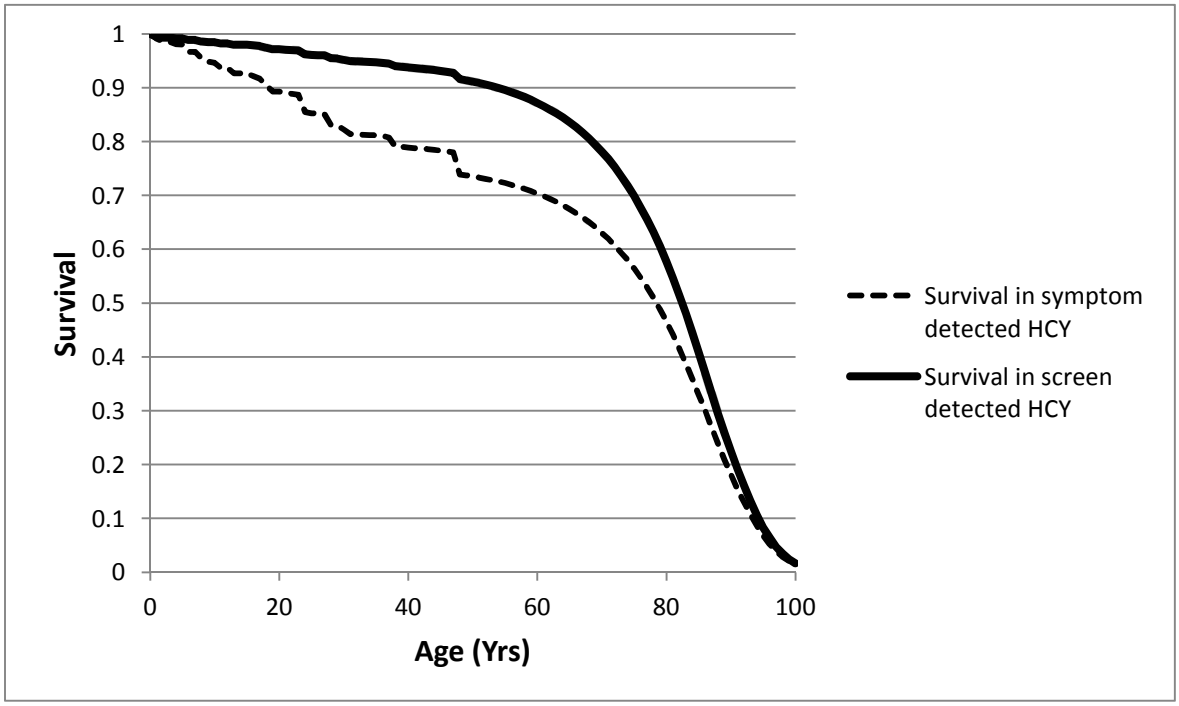
The economic model captures within its scope impact of HCY on early death associated primarily with vascular events, severe developmental delay and ocular problems. It is assumed that screen detected cases are all discovered in the neonatal period. The time profile of symptomatic detection is taken from Taylor.(Taylor, Burke, O'Keefe, Beighi, & Naughton 1998)

Mortality

Age specific all-cause mortality is taken from ONS Interim Life Tables, England & Wales 2008-2010. The mortality impact of symptomatically detected HCY is taken from Mudd(Mudd et al. 1985) using the time to event graphs presented in Figure 6 therein. The model uses the HCY all-types survival estimates. Up to age 15 the all types survival is virtually identical to the estimates for non-responsive HCY and whilst mortality in the non-responsive group deteriorates more quickly survival at the limits of follow-up are similar.

There is substantial evidence suggesting a positive effect of early dietary management with little evidence concerning residual long term mortality. A relative hazard of 0.20 (0.1-0.3) compared to the symptomatically detected population is used in the model. This estimate is based primarily on expert judgement but may be justified by evidence that early commencement of dietary management has been estimated to generate a relative risk of 0.09 (0.036, 0.228) for vascular events, associated mainly with poor dietary compliance and the main cause of mortality.(Yap et al. 2001a) Figure A2.3 presents survival estimates for screen and symptom detected cohorts.

Figure A2.3 HCY Survival under screen and symptom detection



Quality of life

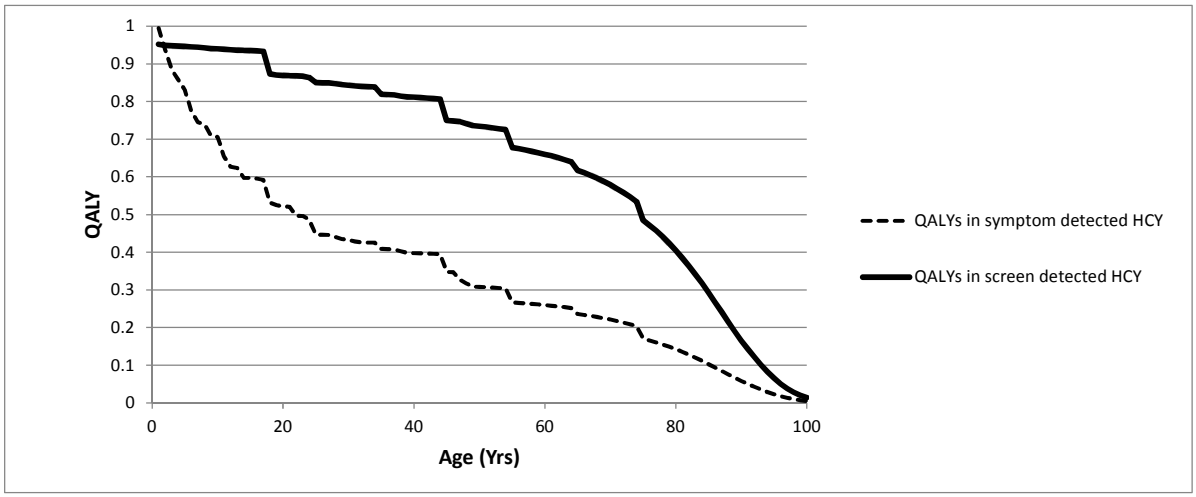
The model focuses on the improvements in quality of life through avoidance of developmental delay consequent on improved early management of HCY made possible by screen detection. It is assumed that the quality of life impact associated with ocular problems and vascular events are subsumed within the development delay.

Mudd(Mudd, Skovby, Levy, Pettigrew, Wilcken, Pyeritz, Andria, Boers, Bromberg, & Cerone 1985) reports a median IQ in symptomatically detected non-responsive HCY patients of 56 corresponding to severe developmental delay. Further the IQ distribution in this population suggests that over 75% have an IQ less than 70, suggesting mild development delay. In the Irish population detected with screening Yap(Yap et al. 2001b) demonstrates that preventive dietary management is capable of producing developmental outcomes equivalent to a cohort of unaffected sibling controls. This effectiveness of early treatment is also supported by Mudd's earlier work (see Figure 2 therein). In the unscreened population the model therefore applies a health related quality of life utility adjustment associated with severe and mild developmental delay to 50% and 25% of the life years accrued with a diagnosed HCY condition. In the screen detected population there is some evidence of mild developmental delay associated primarily with poor dietary compliance in a small subset of the affected children(Yap, Rushe, Howard, & Naughten 2001b) thus a quality of life decrement is applied for 15% of the surviving population, for the remaining 85% a normal age specific health related quality of life utility is applied.(Kind, Hardman, & Macran 1999)

The quality of life decrement for developmental delay severe enough to be characterised by an IQ of less than 55 is estimated from a methodological study undertaken to examine the impact of extending the EQ-5D (3 level) to include a cognitive dimension.(Krabbe et al. 1999) This health status system includes 6 dimensions within its scope; mobility, self-care, usual activities, pain/discomfort, anxiety/depression and cognition. Each attribute is classified into three levels, "no problems" (1), "some problems" (2) and "severe problems" (3). The impact of severe developmental delay is assumed to be characterised by a health state with severe problems in self-care, usual activities and cognitive functioning with no problems in mobility, pain/discomfort and anxiety/depression. This is potentially a conservative assessment as HCY is likely to also impact on mobility and discomfort through its skeletal effects including osteoporosis.

The severe developmental delay EQ-5D+(C) health state 13311-3 is associated with a utility of 0.288 or decrement of 0.712. It should be noted that the EQ5D and also by association the EQ-5D+C are only assessed in the adult population and are known to have difficulties in application to a paediatric age group. With respect to these reservations the above decrement is also applied throughout the early years, this is in preference to including no paediatric quality of life impact. Note also that no quality of life adjustment is made for mild to moderate cognitive impairment in the proportion of the symptomatically detected HCY population with IQ over 55. Figure A2.4 presents the age specific QALYs for the screen and symptom detected HCY populations over the projected lifespan.

Figure A2.4 Age specific QALY impact of screening for HCY



Model parameters:

QiemNoScrn – Average discounted lifetime QALYs for a HCY case under no screening

22.74 (20.61, 25.03)

QiemScrn – Average discounted lifetime QALYs for screen detected HCY

38.40 (35.27, 40.86)

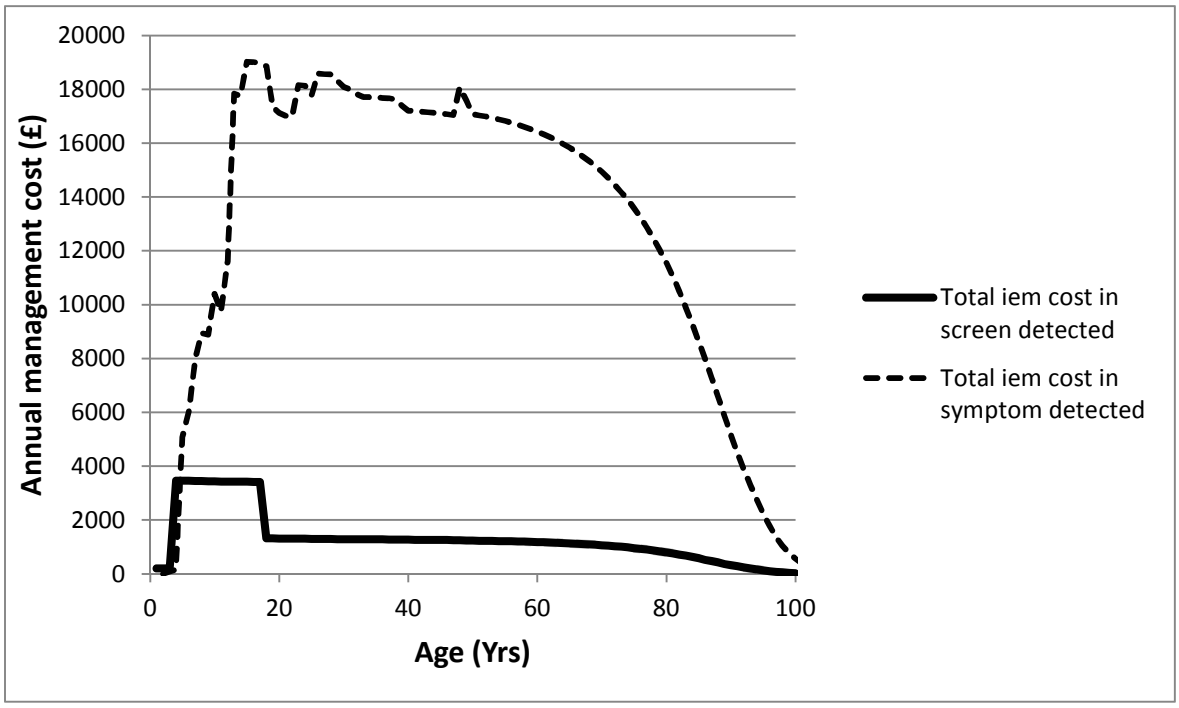
Health and social care costs

Health and social care costs are included in respect of ocular problems and developmental delay. Costs associated with living with developmental delay are estimated from the PSSRU Unit Costs of Health and Social Care 2012,(Curtis 2012) the units costs used are reported in Table A2.5. For severe developmental delay the costs associated with living with low functioning autism (Chapter 8.3.2) are used as a proxy in the paediatric age groups and the costs associated with living in a semi-independent setting are used for adults (Chapter 4.3). For mild developmental delay the costs of caring for someone living with high functioning autism are used as a proxy. Note benefits and voluntary contributions are not included.

The incidence, type and timing of surgery for lens removal and retinal detachment in respect of the ocular problems of HCY are taken from Taylor.(Taylor, Burke, O'Keefe, Beighi, & Naughton 1998) The unit costs of surgery are taken from the National Schedule of Reference Costs 2011-12 for NHS trusts and NHS foundation trusts and are estimated at £197.10 for correcting retinal detachment and £1440.43 for lens removal. Surgery is estimated to be required in 75% of symptomatically detected HCY and the costs are applied at the age of 9 years.

Since evidence suggests that dietary management is effective in avoiding severe developmental delay the health and social care costs associated with long term sequelae of HCY are assumed to be zero.

Figure A2.5 Health and social care costs of managing HCY in screened and symptomatically detected populations



Model parameters:

CiemNoScrn – Average discounted lifetime health/social care costs of symptom detected HCY £704,459 (£518,695, £935,923)

CiemScrn – Average discounted lifetime health/social care costs of screen detected HCY £82,193 (£60,735, £109,292)

Table A2.5 Unit costs used in estimating the cost of developmental delay (Part I – Paediatric)

8.3.2 Children with low-functioning autism (ages 0-17) - Annual cost							8.3.3 Children with high-functioning autism (0-17)		
	Living in residential or foster care			Living in private household with			Living in private household with family		
	Age 0-3	Age 4-11	Age 12-17	Age 0-3	Age 4-11	Age 12-17	Age 0-3	Age 4-11	Age 12-17
Residential/foster care placement	£17,387	£25,037	£35,585	-	-	-	-	-	-
Hospital services	-	£961	£1,769	-	£961	£1,769	-	£866	£866
Other health and social services	£652	£7,699	£446	£652	£7,699	£446	£1,353	£1,353	£1,353
Respite care	-	-	-	-	£3,150	£4,106	-	£7,256	£7,256
Special education	-	£10,189	£30,772	-	£10,189	£30,772	-	£13,018	£13,018
Education support	-	£1,320	£1,111	-	£1,320	£1,111	-	£607	£607
Treatments	-	£20	£17	-	£20	£17	-	£165	£165
Help from voluntary organisations	-	-	-	-	£940	£107	-	-	-
Benefits	-	-	-	£4,187	£4,458	£4,458	£523	£523	£523
Lost employment (parents)	-	-	-	-	£2,325	£2,325	-	£241	£241
Total (Excluding benefits, help from voluntary, lost employment)				£652	£23,339	£38,221	£1,353	£23,265	£23,265

Table A2.5 Unit costs used in estimating the cost of developmental delay (Part II – Adult)

4.3 Adult semi-independent living settings			**4.2 Fully-staffed living settings - PSSRU 2012**	
Costs and unit estimation	**2011/2012 value**		**Costs and unit estimation 2011/2012 value**	
A. Capital costs	£52.00	per week	£77.00	per week
B. Staffing (direct and non-direct staffing)	£259.00	per week	£948.00	per week
C. On-site administration	£10.00	per week	£29.00	per week
D. Agency overheads	£64.00	per week	£153.00	per week
E. Personal living expenses	£264.00	per week (food, utilities, personal care and leisure)	£264.00	per week
F. Hospital	£10.00	per week	£8.00	per week
G. Community	£15.00	per week	£18.00	per week
H. Day Service	£130.00	per week	£236.00	per week
Use of facility by client		52.18 weeks per annum		52.18 weeks per annum
Multiplier for level of disability		Higher levels of ability: 0.82 x (B to H), Lower levels of ability: 1.60 x (B to H)	Higher levels of ability: 0.82 x (B to H), Lower levels of ability: 1.60 x (B to H)	
Per resident week (A to D)	**£385.00**		**£1,208.00**	
Care package (A to H)	**£804.00**		**£1,734.00**	
Annual cost	£34,282.56	Higher level ability	£73,937.76	Higher level ability
	£41,808.00		£90,168.00	
	£66,892.80	Lower level ability	£144,268.80	Lower level ability

APPENDIX 3 – ISOVALERIC ACIDAEMIA

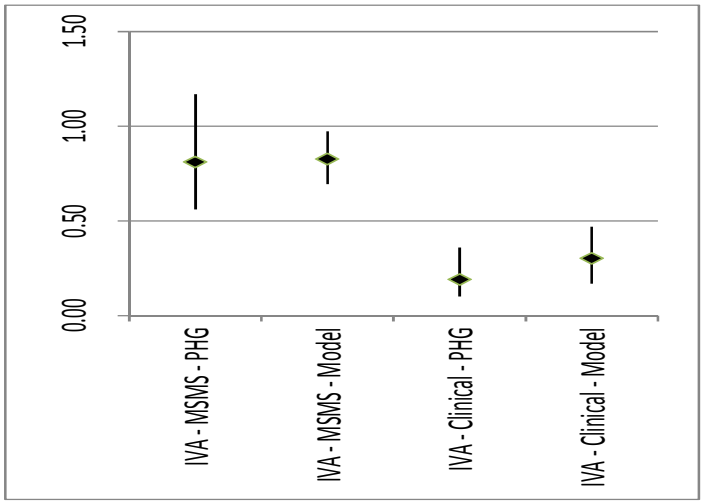
OVERVIEW

This appendix includes a description of the derivation of input parameters for the economic evaluation of screening for IVA.

PREVALENCE

The birth prevalence estimates of IVA are presented in Figure A3.1. The PHG report finds a markedly higher prevalence of IVA in the MSMS screening studies than is discovered in the symptomatically detected series. The primary cause of this discrepancy is most likely to be the existence of a common mutation that is associated with a potentially asymptomatic phenotype and has been estimated to occur in 68% of screen detected cases. (Ensenauer, Vockley, Willard, Huey, Sass, Edland, Burton, Berry, Santer, Grunert, Koch, Marquardt, Rinaldo, Hahn, & Matern 2004)

Figure A3.1 Birth prevalence of IVA per 100,000 births



Model parameters:

PincScrn **-**Birth prevalence with screening 0.83 (0.69, 0.97)

PincNat **-** Birth prevalence without screening 0.30 (0.17. 0.47)

TEST CHARACTERISTICS

The sensitivity and specificity of the MSMS device in the mass screening setting is estimated from the data extracted in the PHG systematic review update. A logit model is used within a Bayesian synthesis to estimate these independently.

Model parameters:

PSens - Sensitivity for IVA is estimated at 93.80% (56.46%, 99.96%)

PSpec - Specificity for IVA is estimated 99.99% (99.94%, 100.00%)

DIAGNOSIS AND MANAGEMENT OF IVA

The next three tables list the resources used in the management of IVA in terms of staff time, blood tests taken and supplements prescribed. They are split into diagnosis costs in Table A3.1, regular appointments in Table A3.2 and supplements prescribed in Table A3.3 .

Table A3.1 IVA diagnosis costs

Cost of 1st appointment	
Staff	90 mins Consultant paediatrician 90 mins Specialist nurse 90 mins Dietician
Bloods	Plasma quantitative amino acids Urinary/organic acids Blood plasma acyl carnatine DNA IVA
Other	Carnitine 100mg/kg/day
Cost of 2nd appointment (Diagnosis confirmed)	60 mins Consultant paediatrician 60 mins Specialist nurse 60 mins Dietician
Cost of 2nd appointment (False positive)	30 mins Consultant paediatrician 30 mins Specialist nurse

The appointments in Table A3.2 are for screened non-mild cased of IVA. Screened mild cases of IVA are assumed to have no diet supplement or carnitine costs and to have half the number of appointment and blood tests as a screened non-mild case of IVA. Symptomatic detected IVA cases are assumed to be managed as high risk type.

A proportion of IVA patients are tube fed. Marjorie Dixon provided us with an estimate of 21% (6/29) for the proportion for the analysis. The cost of their feed is included in the analysis (nutrini and paediasure) but the cost of the nasogastric tube or gastrostomy is not. It is also assumed that tube feeding stops at age 16, paediatric seravit is also stopped and the amount of carnitine is reduced from 100mg/kg/day to 50mg/kg/day. The amount of paediatric seravit given is based on the recommended dose for the age group.

Table A3.2 IVA appointments

Age	Staff	Blood
1st Year (excluding diagnosis appointments)	30 mins Consultant paediatrician x3 30 mins Specialist nurse x3 30 mins Dietician x3 30 mins Dietician x3 (additional apps)	FBC x3 Ca, Pi, LFT x3 Plasma amino acids & ammonia x3 Free carnitines & acyl carnitine x3 Micronutrients
2nd to 6th Year	30 mins Consultant paediatrician x4 30 mins Specialist nurse x4 30 mins Dietician x4	FBC x4 Ca, Pi, LFT x4 Plasma amino acids & ammonia x4 Free carnitines & acyl carnitine x4 Micronutrients
7th to 16th Year	30 mins Consultant paediatrician x2 30 mins Specialist nurse x2 30 mins Dietician x2	FBC x2 Ca, Pi, LFT x2 Plasma amino acids & ammonia x2 Free carnitines & acyl carnitine x2 Micronutrients
16+	30 mins Consultant	FBC Ca, Pi, LFT Plasma amino acids & ammonia Free carnitines & acyl carnitine Micronutrients

Table A3.4 presents the annual costs for the diagnosis and management of IVA in the screened populations with high and low risk variants of IVA. Under no screening it is assumed that diagnosis costs occur in the year of symptomatic presentation(Grunert et al. 2012) but are the same as for screen diagnosis of high risk variant IVA, similarly it is assumed management costs (not including health and social care costs of sequelae) once diagnosed are similar. Dietary management is assumed to be life-long.

The annual costs of diagnosis and management projected over a full life course are presented in Figure A3.2.

Table A3.3 IVA Supplements

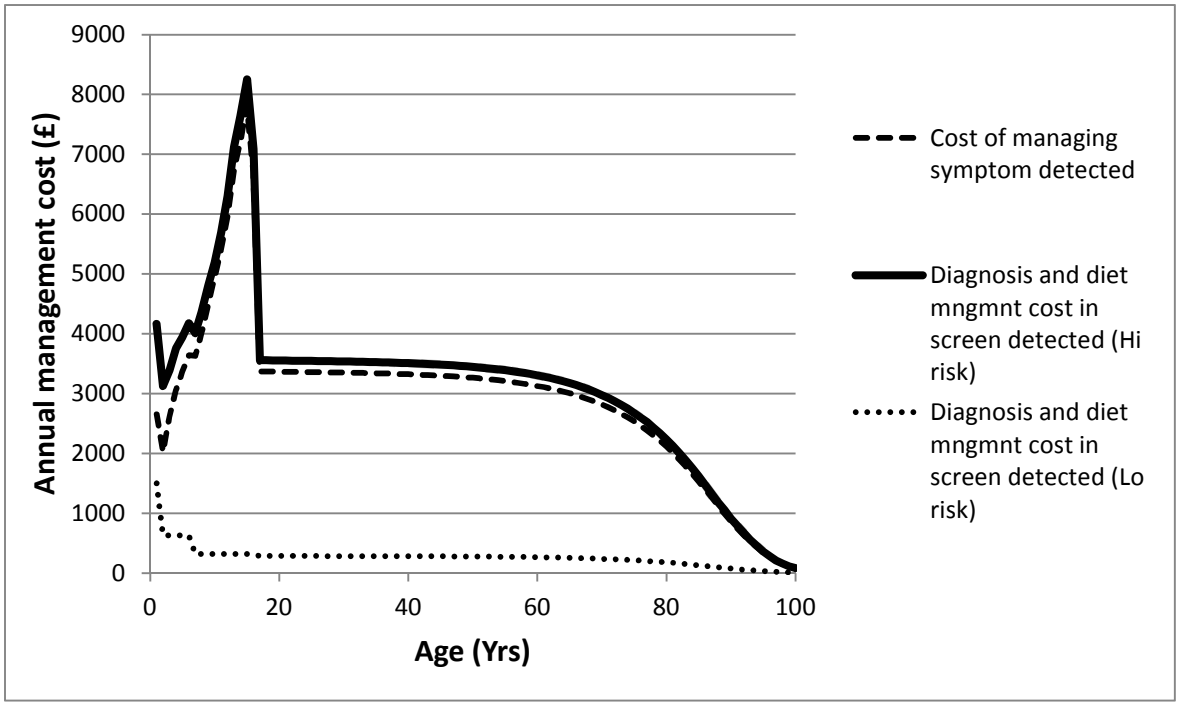
Age	Product
1st Year	Carnitine 100mg/kg/day Energivit 30ml/kg/day IVA anamix 30ml/kg/day
2nd Year	Carnitine 100mg/kg/day Paediatric seravit 17g per day Nutrini 200ml one per day
3rd Year	Carnitine 100mg/kg/day Paediatric seravit 18g per day Nutrini 200ml one per day
4th Year	Carnitine 100mg/kg/day Paediatric seravit 20g per day Nutrini 200ml one per day
5th Year	Carnitine 100mg/kg/day Paediatric seravit 21g per day Nutrini 200ml one per day
6th Year	Carnitine 100mg/kg/day Paediatric seravit 23g per day Nutrini 200ml one per day
7th Year	Carnitine 100mg/kg/day Paediatric seravit 24g per day Nutrini 200ml one per day
8th Year	Carnitine 100mg/kg/day Paediatric seravit 25g per day Nutrini 200ml one per day
9th Year	Carnitine 100mg/kg/day Paediatric seravit 27g per day Paediasure 500ml one per day
10th Year	Carnitine 100mg/kg/day Paediatric seravit 28g per day Paediasure 500ml one per day
11th Year	Carnitine 100mg/kg/day Paediatric seravit 30g per day Paediasure 500ml one per day
12th Year	Carnitine 100mg/kg/day Paediatric seravit 31g per day Paediasure 500ml one per day
13th Year	Carnitine 100mg/kg/day Paediatric seravit 33g per day Paediasure 500ml one per day
14th Year	Carnitine 100mg/kg/day Paediatric seravit 34g per day Paediasure 500ml one per day
15th Year	Carnitine 100mg/kg/day Paediatric seravit 35g per day Paediasure 500ml one per day
16th Year	Carnitine 100mg/kg/day

16+	Carnitine 50mg/kg/day

Table A3.4 IVA annual diagnosis and management cost in the screened population

Screened - high risk						**Screened - low risk**		
	Consultations	Bloods	Extra dietician time	Diet	Total	Consultations	Bloods	Total
Diagnosis false +ive	£463	£456		£21	£940			
Diagnosis true +ive	£600	£456		£21	£1,077	£600	£456	£1,077
0-11 months	£360	£573	£51	£2,460	£3,444	£180	£287	£467
1-2 years	£480	£776		£2,389	£3,645	£240	£388	£628
2-3 years	£480	£776		£2,713	£3,969	£240	£388	£628
3-4 years	£480	£776		£3,132	£4,388	£240	£388	£628
4-5 years	£480	£776		£3,351	£4,607	£240	£388	£628
5-6 years	£480	£776		£3,628	£4,884	£240	£388	£628
6-7 years	£240	£394		£4,058	£4,692	£120	£197	£317
7-8 years	£240	£394		£4,466	£5,100	£120	£197	£317
8-9 years	£240	£394		£4,991	£5,625	£120	£197	£317
9-10 years	£240	£394		£5,441	£6,075	£120	£197	£317
10-11 years	£240	£394		£6,033	£6,667	£120	£197	£317
11-12 years	£240	£394		£6,736	£7,370	£120	£197	£317
12-13 years	£240	£394		£7,706	£8,340	£120	£197	£317
13-14 years	£240	£394		£8,303	£8,937	£120	£197	£317
14-15 years	£240	£394		£9,027	£9,661	£120	£197	£317
15-16 years	£240	£394		£7,665	£8,299	£120	£197	£317
16+ years	£79	£203		£3,885	£4,167	£79	£203	£282

Figure A3.2 Annual age specific diagnosis and management costs for IVA



Model parameters:

Cconf – Confirmation cost in false positives for IVA £896 (£807, £983)

CmngtNoScrn – Discounted lifetime cost of management of IVA without screening

£171,859 (£126,781, £228,948)

CmngtScrn - Discounted lifetime cost of management of IVA with screening

£69,704 (£51,541, £92,209)

HEALTH AND SOCIAL CARE IMPACT OF THE ISOVALERIC ACIDAEMIA

The economic model captures within its scope impact of IVA on mortality and neurocognitive outcomes. It is assumed that screen detected cases are all discovered in the neonatal period. The time profile of symptomatic detection is taken from Grunert.(Grunert, Wendel, Lindner, Leichsenring, Schwab, Vockley, Lehnert, & Ensenauer 2012)

Mortality

Age specific all-cause mortality is taken from ONS Interim Life Tables, England & Wales 2008-2010. The mortality associated with symptomatically detected IVA occurs in the first two years of life and primarily in the neonatal period.(Grunert, Wendel, Lindner, Leichsenring, Schwab, Vockley, Lehnert, & Ensenauer 2012) Furthermore, in the Grunert series 25% of deaths occur within the first seven days, it is assumed that this same mortality rate occurs in the high risk subgroup of the screen detected population. It is assumed that mortality after the first seven days is avoided in the screen detected group and that survival is unaffected in the low risk subgroup. Figure A3.3 presents the estimated survival in the symptomatic and screen detected IVA populations.

Quality of life

The model focuses on the improvements in quality of life through avoidance of neurocognitive impairments associated with late diagnosis of IVA. Grunert retrospectively analysed 21 patients symptomatically diagnosed with IVA and reviewed and analysed a 155 cases reported in the published literature. Table A3.5 presents the distribution of neurocognitive impairments found in late and early diagnosed survivors (one death was recorded in the early diagnosed group), where early diagnosis is defined as being in the first five weeks of life.

Quality of life decrements associated with the differing levels of neurocognitive impairment are estimated from the methodological study by Krabbe.(Krabbe, Stouthard, Essink-Bot, & Bonsel 1999) The 'learning disabilities' decrement is assumed to be equivalent to the contribution of the 'some problems' level of the cognition attribute with a decrement of 0.14 QALYS. The decrement associated with 'mild retardation' is assumed to be equivalent to 'severe problems' level contribution with a decrement of 0.3 QALYs. Severe retardation is estimated to be associated with a decrement equivalent to that estimated for severe development delay 0.712 QALYs and described in Appendix 2 HCY. Average quality of life decrements associated with neurocognitive outcomes from early and late diagnosis are thus estimated as 0.04 QALYs and 0.18 QALYS respectively.

Figure A3.3 IVA Survival under screen and symptom detection

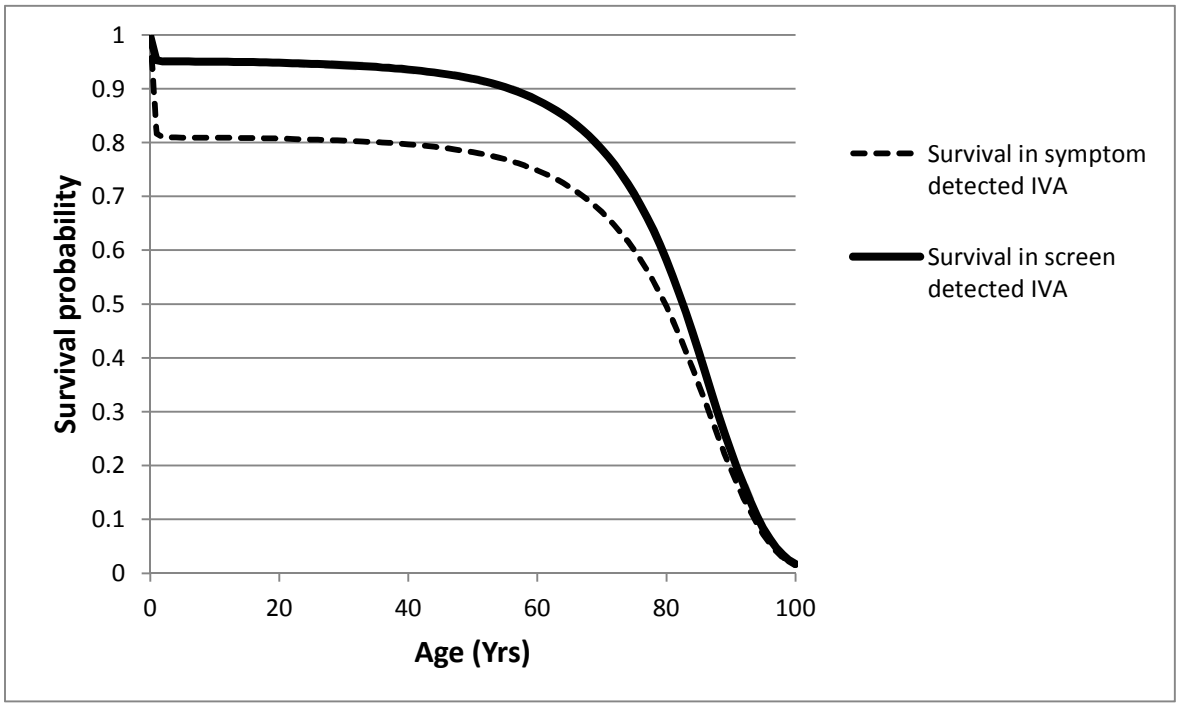
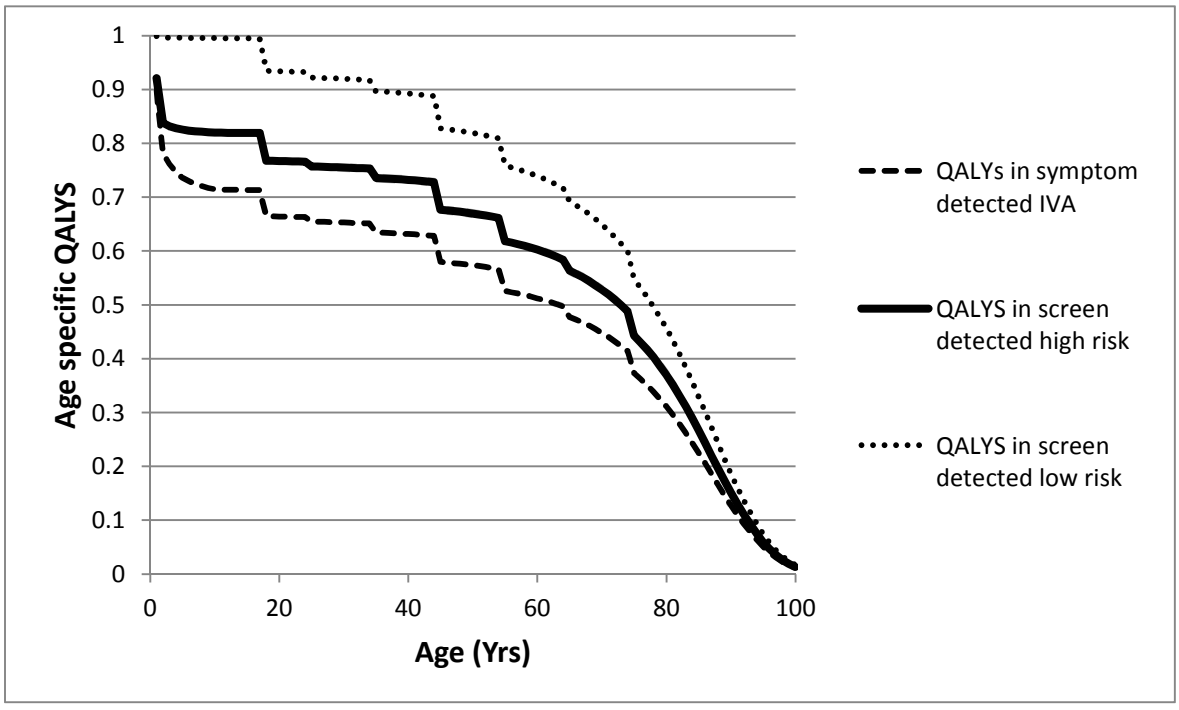


Table A3.5 Neurocognitive outcomes associated with early and late diagnosis of IVA

Diagnosis	Normal	Learning disabilities	Mild retardation	Severe retardation	Grand Total
early (<=5wks)	9 (82%)	1 (9%)	1 (9%)	(0%)	11
late	3 (33%)	4 (44%)	1 (11%)	1 (11%)	9
Grand Total	12	5	2	1	20
QALY decrements	0	0.145	0.302	0.712	

The proportion of symptomatically detected cases arising as early and late diagnoses is taken from Grunert. All screen detected high risk cases are assumed to be diagnosed in the neonatal period, managed accordingly and have similar neurocognitive outcomes to early diagnosed symptomatically detected cases. Screen detected low risk cases are assumed to have normal quality of life outcomes. Figure A3.4 presents the age specific QALYs for the three groups described.

Figure A3.4 Age specific QALYs for screen and symptomatically detected IVA cases



Model parameters:

QiemNoScrn – Average discounted lifetime QALYs for an IVA case under no screening

29.90 (27.10, 32.90)

QiemScrn – Average discounted lifetime QALYs for screen detected IVA

39.29 (36.42, 41.57)

Health and social care costs

Health and social care costs are included in respect of neurocognitive outcomes. The costs estimated for low functioning autism and described in Appendix 2 (HCY) are used as a proxy for the costs associated with both the Grunert 'mild retardation' and 'severe retardation' states in the paediatric age groups. The adult costs of care presented in Table A3.6 are estimated from a study by Willner(Willner et al. 2013) that examined the costs of care for patients with mild to moderate intellectual disabilities in a day services setting again these are used for both the mild and severe retardation states.

As for the quality of life the costs associated with symptomatic detection are estimated from the distribution of neurocognitive outcomes associated with early and late detection. Screen detected high risk cases are assumed to have costs equivalent to the early detected subgroup. No health and social care costs are estimated for low risk screen detected cases.

Model parameters:

CiemNoScrn – Average discounted lifetime health/social care costs of symptom detected IVA

£262,377 (£193,189, £348,586)

CiemScrn – Average discounted lifetime health/social care costs of screen detected IVA

£48,313 (£35,700, £64,242)

Table A3.6 Cost per person per week (£) of health and social care resource use

Willner et al (2013) - patients with mild to moderate intellectual disabilities - setting day services for adults with intellectual disabilities								
Resource type	**Baseline**				**10 month followup**			
	Intervention (n=84)		Control (n=85)		Intervention (n=84)		Control (n=85)	
	Mean cost (£)	SD	Mean cost (£)	SD	Mean cost (£)	SD	Mean cost (£)	SD
Non-accommodation costs								
Daytime activities	403.57	279.37	384.89	309.54	375.74	286.98	310.81	259.64
Psychotropic medication	2.54	8.46	2.79	10.21	2.07	9.72	1.67	8.4
Multidisciplinary meetings	12.17	31.22	10.17	25.8	10.84	33.37	4.52	21.88
Community-based services	43	84.9	28.41	53.21	20.38	45.82	15.66	17.59
Hosptial-based services	7.6	42.08	9.09	64.78	10.82	37.14	3.72	9.89
Subtotal	468.88	264.82	435.35	294.32	419.85	305.11	336.38	270.44
Accommodation costs								
Accommodation staff[a]	483.06	717.68	394.01	551.39	399.57	535.8	394.7	586.45
Accommodation non-staff[a]	117.2	142.13	136.15	148.12	122.24	129.76	126.11	152.27
Domicilary staff[b]	34.62	105.38	3.72	22.99	8.67	55.07	0.22	1.81
Respite care[b]	9.89	37.74	11.16	45.29	19.75	156.39	9.7	34.5
Subtotal	644.77	815.77	545.04	652.16	550.23	655.82	530.73	700.73
Total	**1113.65**	**803.43**	**980.39**	**565.35**	970.08	700.08	867.09	591.51
Total average both groups (2010/11 prices)								982.80
2012/11 (using PSS index)								£1,001.48

[a]For service users living in out-of-family staffed accommodation: intervention group *n* = 36, control group *n* = 41.

[b]For service users living independently, in adult family placements or in family homes: intervention group *n* = 48, control group *n* = 44

APPENDIX 4 – GLUTARIC ACIDURIA TYPE 1

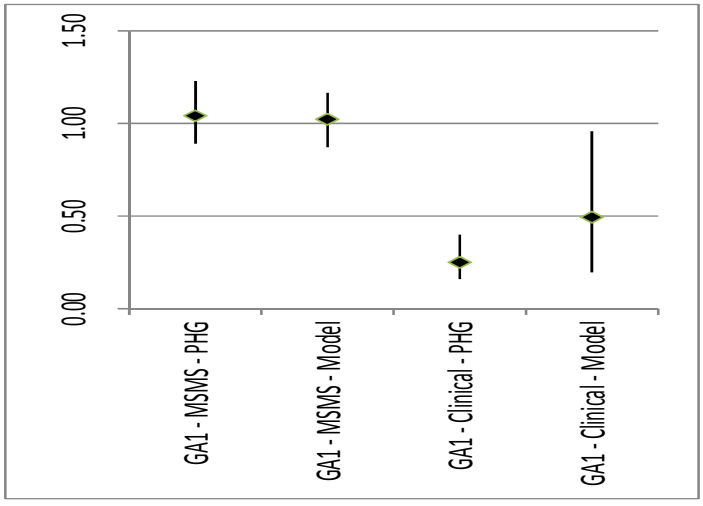
OVERVIEW

This appendix includes a description of the derivation of input parameters for the economic evaluation of screening for glutaric aciduria type 1 (GA1).

PREVALENCE

The birth prevalence estimates of GA1 are presented in Figure A4.1. The PHG report finds a markedly higher prevalence of GA1 in the MSMS screening studies than is discovered in the symptomatically detected series. This discrepancy is remarked by Kolker and ascribed primarily to ascertainment bias the degree of which 'remains obscure'.(Kolker, Garbade, Boy, Maier, Meissner, Muhlhausen, Hennermann, Lucke, Haberle, Baumkotter, Haller, Muller, Zschocke, Burgard, & Hoffmann 2007b) This economic evaluation differentiates between clinic cases that remain undiagnosed and unreported and bias due to screen detected cases that would have otherwise remained asymptomatic. As the proportion in each of these groups is essentially unknown an uniformative bias adjustment is factor is introduced into the model and is shown in Figure A4.2. This factor represents the proportion of the discrepancy between the clinical and screen detected cases that would have remained asymptomatic in the absence of screening. The application of this bias adjustment factor gives rise to the slightly higher mean and greater uncertainty represented in the clinical incidence of GA used in the model (GA1-Clinical – Model) seen in Figure A3.1.

Figure A4.1 Birth prevalence of GA1 per 100,000 births

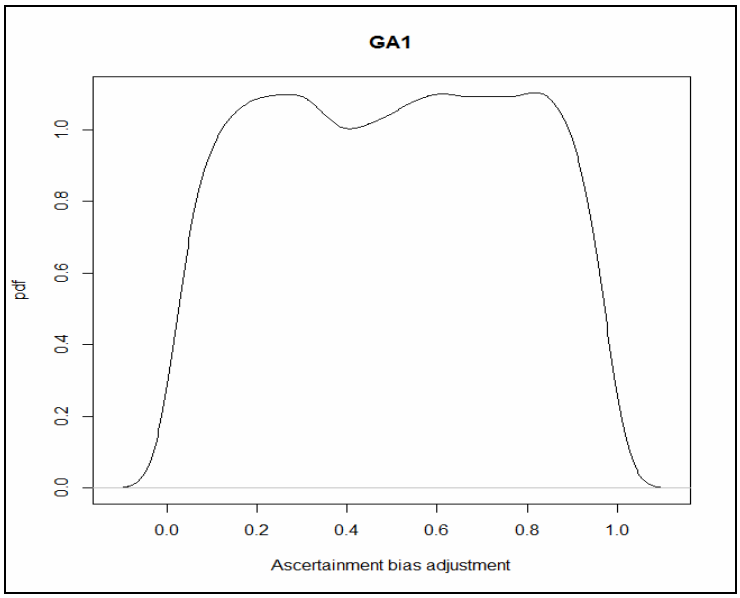


Model parameters:

PincScrn **-**Birth prevalence with screening 1.02 (0.87, 1.17)

***PincNat* -** Birth prevalence without screening 0.47 (0.26. 0.75)

Figure A4.2 Ascertainment bias adjustment for GA1 clinical incidence



TEST CHARACTERISTICS

The sensitivity and specificity of the MSMS device in the mass screening setting is estimated from the data extracted in the PHG systematic review update. A logit model is used within a Bayesian synthesis to estimate these independently.

Model parameters:

PSens - Sensitivity for GA1 is estimated at 90.72% (35.46%, 99.97%)

PSpec - Specificity for GA1 is estimated 99.99% (99.94%, 100.00%)

DIAGNOSIS AND MANAGEMENT OF GA1

The aim for management of patients with GA1 is to avoid the encephalopathic crises that give rise to the long term irreversible neurological health impacts.(Kolker et al. 2007a;Kolker et al. 2011) Preventive care comprises dietary management for the first 6 years of life, and possibly longer, and periodic intensive care during periods of intercurrent illness, the potential trigger episodes of encephalopathic crises. The costs of diet and crisis management are included here. The next three tables list the resources used in the management of GA1 in terms of staff time, blood tests taken and supplements prescribed. They are split into diagnosis costs in Table A4.1, regular appointments in Table A4.2 and supplements prescribed in Table A4.3.

The appointments described in Table A4.2 are for screened patients. Unscreened patients are assumed to incur the diagnosis costs but no further appointment costs. The costs of an unscreened patient are assumed to fall on other services through the complications suffered in the unscreened

population. A dietician (Marjorie Dixon) explained that symptomatically presenting cases of GA1 would be unlikely to be started on GA1 supplements as they would be unlikely to help. The case reports reported substantial dietician time in addition to regular appointments. This was generally weight checks and giving advice to parents over the telephone.

Table A4.1 GA1 Diagnosis Costs

Cost of 1st appointment	
Staff	90 mins Consultant paediatrician 90 mins Specialist nurse 90 mins Dietician
Bloods	Urinary/organic acids Blood plasma acyl carnatine DNA GA1
Other	Carnitine 100mg/kg/day
Cost of 2nd appointment (Diagnosis confirmed)	90 mins Consultant paediatrician 90 mins Specialist nurse 90 mins Dietician
Cost of 2nd appointment (False positive)	Same as above

Table A4.2 GA1 appointments

Age	**Staff**	**Blood**
1st Year (excluding diagnosis appointments)	30 mins Consultant paediatrician x5 30 mins Specialist nurse x5 60 mins Dietician x5 60 mins Dietician x36 (additional apps)	FBC x5 Ca, Pi, LFT x5 Plasma amino acids including tryptophan x5 Free carnitinex5 Micronutrients
2nd to 6th Year	30 mins Consultant paediatrician x4 30 mins Specialist nurse x4 60 mins Dietician x4	FBC x4 Ca, Pi, LFT x4 Plasma amino acids including tryptophan x4 Free carnitinex4 Micronutrients
6-16	20 mins Consultant paediatrician x2 20 mins Specialist nurse x2 30 mins Dietician x2	FBC x2 Ca, Pi, LFT x2 Plasma amino acids & ammonia x2 Free carnitines & acyl carnitine x2 Micronutrients
16+	20 mins Consultant 20 mins Dietician	FBC Ca, Pi, LFT Plasma amino acids & ammonia Free carnitines & acyl carnitine

		Micronutrients

We assumed that patients would receive 100mg/kg/day of carnitine and the 1g protein equivalent/kg/day of a GA1 supplement. For the first year this would be GA1 anamix, followed by GA1 gel. GA1 supplements are stopped at age 6 and the amount of carnitine was reduced to 50mg/kg/day. This decision was taken after discussion with a dietician (Marjorie Dixon) who explained that at this age and in discussion with the parents some centres will stop GA1 supplements.

Table A4.3 GA1 dietary supplements

Age	Product
1st Year	Carnitine 100mg/kg/day GA1 anamix to give 1g of protein equivalent per kg/day
2nd Year	Carnitine 100mg/kg/day GA1 gel to give 1g of protein equivalent per kg/day
3rd Year	Carnitine 100mg/kg/day GA1 gel to give 1g of protein equivalent per kg/day
4th Year	Carnitine 100mg/kg/day GA1 gel to give 1g of protein equivalent per kg/day
5th Year	Carnitine 100mg/kg/day GA1 gel to give 1g of protein equivalent per kg/day
6th Year	Carnitine 100mg/kg/day GA1 gel to give 1g of protein equivalent per kg/day
6 – 16 years	Carnitine 50mg/kg/day

Table A4.4 presents the annual costs for the diagnosis and dietary management of GA1 in the screened populations. Preventive dietary management is assumed to end after the age of 6 years, with follow-up management appointments continuing throughout life. For the screened population it is assumed that all diagnoses occur in the neonatal period.

Without screening it is assumed that all symptomatic diagnoses occur in the first two years of life, primarily associated with first encephalopathic crisis. Dietary management after crisis has not been shown to be effective and no long term dietary costs are included in the model.

Table A4.5 presents the costs of managing encephalopathic crises, the estimated duration of intercurrent illnesses requiring preventive management, the costs of these episodes in children with and without dystonia subsequent to crisis. Table A4.6 presents the estimated frequency of intercurrent illness episodes and the total annual costs of preventive management.

Table A4.4 Annual diagnosis and management cost for GA1 in the screened population

	Appointments	Bloods	Extra dietician time	Diet	Total
Diagnosis costs	£720.00	£376.00	£0.00	£0.00	£1,096.00
0-11 months	£600.00	£955.00	£1,224.00	£2,591.70	£5,370.70
1-2 years	£548.00	£776.00	£0.00	£3,936.28	£5,260.28
2-3 years	£548.00	£776.00	£0.00	£4,209.28	£5,533.28
3-4 years	£548.00	£776.00	£0.00	£5,628.64	£6,952.64
5-6 years	£548.00	£776.00	£0.00	£7,452.56	£8,776.56
6-15 years	£171.33	£394.00	£0.00	£0.00	£565.33
16+ years	£63.67	£203.00	£0.00	£0.00	£266.67

Table A4.5 Duration and costs of encephalopathic crises and episodes of intercurrent illness requiring preventive management

Initial encephelopathic crisis	Mean	Lower	Upper
Duration (days)	24	21	28
NICU/PICU cost per day (XA01Z)	£1,117	£844	£1,307
Dialysis (LD02B)	£198	£167	£167
Dialysis sessions per wk	3		
Total	£ 28,845	£ 19,218	£ 38,606
Proportion severe	100%		
Proportion with dystonia	100%		
Secondary encephelopathic crisis	Mean	Lower	Upper
Duration	4	2	7
NICU/PICU cost per day (XA01Z)	£1,117	£844	£1,307
Dialysis	£198	£167	£167
Dialysis sessions per wk	3		
Total	£ 4,808	£ 1,830	£ 9,652
Preventive emergency hospital admission			
Duration - Normal child (days)	3	2	4
NICU/PICU cost per day (XA05Z)	£440	£347	£480
Total	£1,321	£695	£1,920
Duration - Dystonic child (days)	4	2	7
NICU/PICU cost per day HD (XA02Z)	£795	£662	£927
Total	£3,181	£1,324	£6,486

The estimates of episode frequency and duration are obtained from an expert panel and the unit costs are taken from the National Schedule of Reference Costs 2011-12. Kolker(Kolker et al. 2006) provides the distribution of number of encephalopathic episodes in a symptomatically detected population, with an average estimate of 1.4 episodes. Thus the estimated average cost of managing encephalopathic crises in the symptomatically detected population is £30,900.

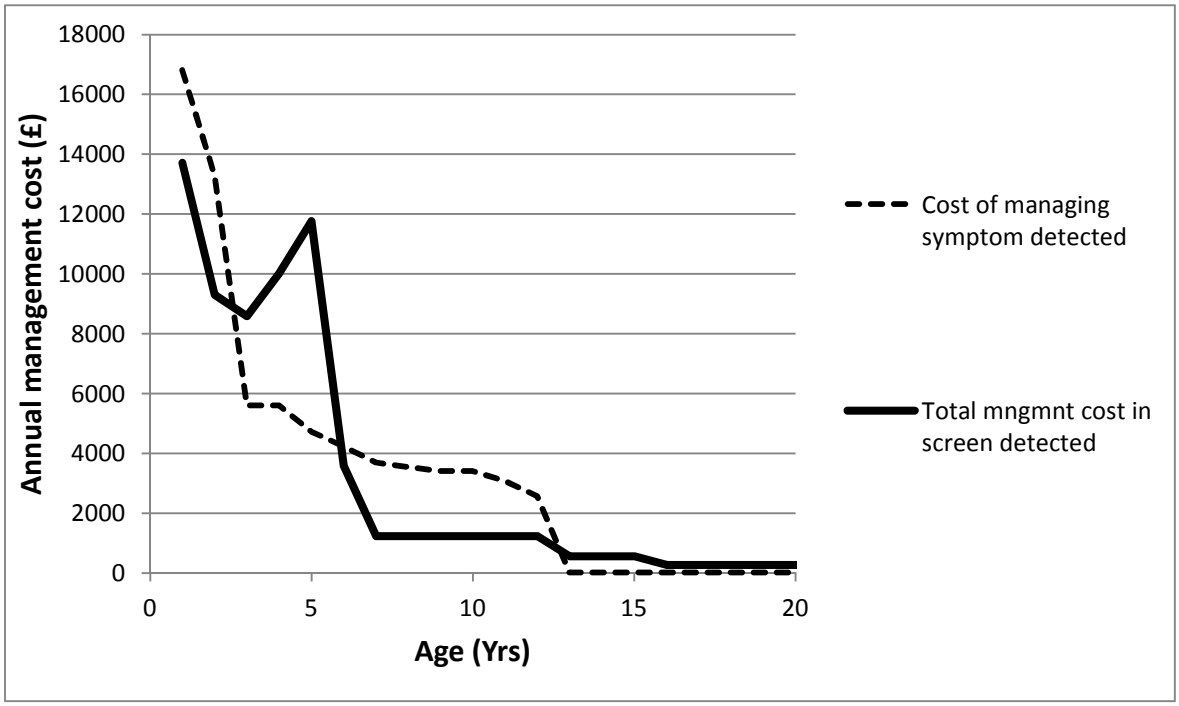
Table A4.6 Frequency and annual costs of episodes of intercurrent illness requiring preventive management.

Age (years)	Episode frequency			Preventive episodes requiring hospitalisation	
	Mid	Min	Max	Asymptomatic	With dystonia
1	4	2	6	£5,283	£3,391
2	2	1	4	£2,641	£6,362
3	2	1	4	£2,641	£6,362
4	2	1	4	£2,641	£6,362
5	2	1	4	£2,641	£6,362
6	2	1	4	£2,641	£6,362
6 - 12[a]	2	1	4	£0	£6,362

a) For children with dystonia only

The annual costs of diagnosis, dietary and preventive management over the first 20 years of life are presented in Figure A4.3, note that this does not include the cost of managing sequelae of crises.

Figure A4.3 Annual age specific diagnosis and management costs for GA1



Model parameters:

Cconf – Confirmation cost in false positives for GA1 £1,052 (£948, £1,154)

CmngtNoScrn – Discounted lifetime cost of management of GA1 without screening

£65,383 (48,233, £87,106)

CmngtScrn - Discounted lifetime cost of management of GA1 with screening

£70,793 (£52,346, £93,650)

HEALTH AND SOCIAL CARE IMPACT OF THE GA1

The economic model captures within its scope the impact of GA1 on mortality and long term sequelae of the encephalopathic crises associated with GA1. Long term neurological disorders following from crises include movement disorders, epilepsy, subdural bleedings and bitemporal arachnoid cysts.

Mortality

Age specific all-cause mortality is taken from ONS Interim Life Tables, England & Wales 2008-2010. The mortality associated with symptomatically and screen detected GA1 is based on the data presented by Kolker.(Kolker, Garbade, Boy, Maier, Meissner, Muhlhausen, Hennermann, Lucke, Haberle, Baumkotter, Haller, Muller, Zschocke, Burgard, & Hoffmann 2007b) The Kolker study compares outcomes in 38 patients identified by newborn screening in Germany between 1999 and 2005 with a historical cohort identified symptomatically prior to the establishment of the screening programme. Figure A4.4 presents the estimated survival in the symptomatic and screen detected GA1 populations.

Quality of life

Morbidity in GA1 is mediated by encephalopathic crisis, which is most commonly associated with severe neurological impairment, specifically including dystonia, a complex movement disorder, speech problems, epilepsy and subdural bleedings. In a small proportion of cases neurological disorders can arise without encephalopathic crisis, these are characterised as either late or insidious onset cases and tend to be of a less severe form. Whilst there is much evidence on the extend and incidence of neurological impacts there is no evidence that directly characterises these impacts in terms of quality of life utility. Table A4.7 uses the EQ-5D 3 level system to generate a range of utility values that are used as estimates for the quality of life impact of different health states for the GA1 (and also MSUD and LCHADD) analyses.

Figure A4.4 GA1 Survival under screen and symptom detection

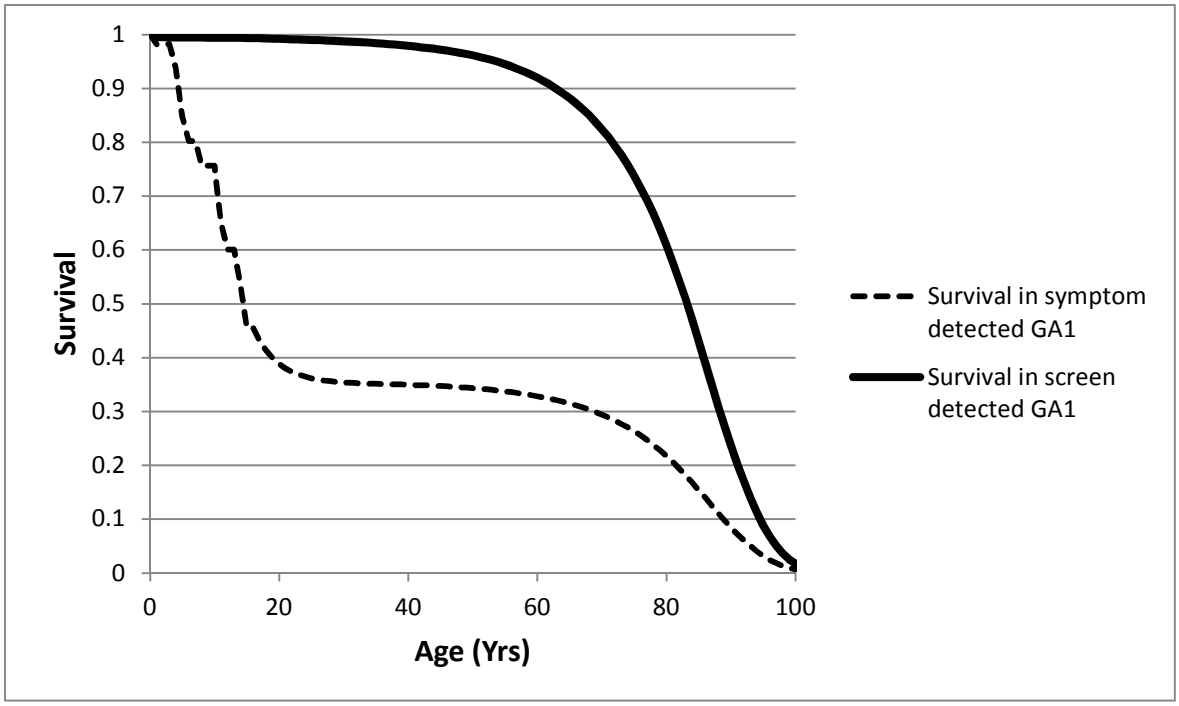


Table A4.7 Quality of life estimates associated with neurocognitive disability health states

EQ5-D_index_calculator.xls			**Mild neurological/psychiatric disability:** Capable of all activities in normal schooling and of living independently undertaking activities of daily living (ADL) with moderate support (incl. autism / ADHD).	**Moderate neurological/psychiatric disability:** Some limitation af activity, requiring significant educational and long term living support, not entirely capable of independent living and requiring a sheltered and supervised environment (incl. autism etc)	**Severe neurological/psychiatric disability:** Dependant for all healthcare and life needs.
	EQ5D-3L (+C)				
		mobility	1	2	3
		self-care	2	2	3
		usual activities	2	2	3
		pain/discomfort	1	2	2
		anxiety/depression	1	2	2
			2	3	3
EQ5D	Without psych	TTO	0.779	0.516	-0.166
		VAS	0.721	0.503	0.075
EQ5D	With psych	TTO	0.708	0.082	-0.331
		VAS	0.658	0.227	0.014
cognition		1	0.08	0.08	0
		2	-0.216	-0.216	
		3			-0.056

The analysis uses the EQ-5D visual analogue scale (VAS) valuation scheme as opposed to the time trade off valuations. For GA1 the quality of life post encephalopathic crisis is assumed to be equivalent to the 'severe' health state, 0.075, with severe problems in mobility, self-care and usual activities and with some problems associated with pain/discomfort and anxiety/depression. For

late/insidious onset disease the quality of life is valued at the moderate health state, 0.503, with some problems in all health state dimensions.

The age distribution of first encephalopathic crisis and the proportion of encephalopathy free symptomatic patients who remain asymptomatic (33%) is taken from Kolker(Kolker, Garbade, Boy, Maier, Meissner, Muhlhausen, Hennermann, Lucke, Haberle, Baumkotter, Haller, Muller, Zschocke, Burgard, & Hoffmann 2007b) as is the proportion of screen detected cases who experience encephalopathic crisis (10.5%). Figure A4.5 presents the age specific health state distributions for the symptomatically and screen detected populations and Figure A4.6 presents the age specific QALYs.

Figure A4.5 Age specific QALYs for screen and symptomatically detected GA1 cases

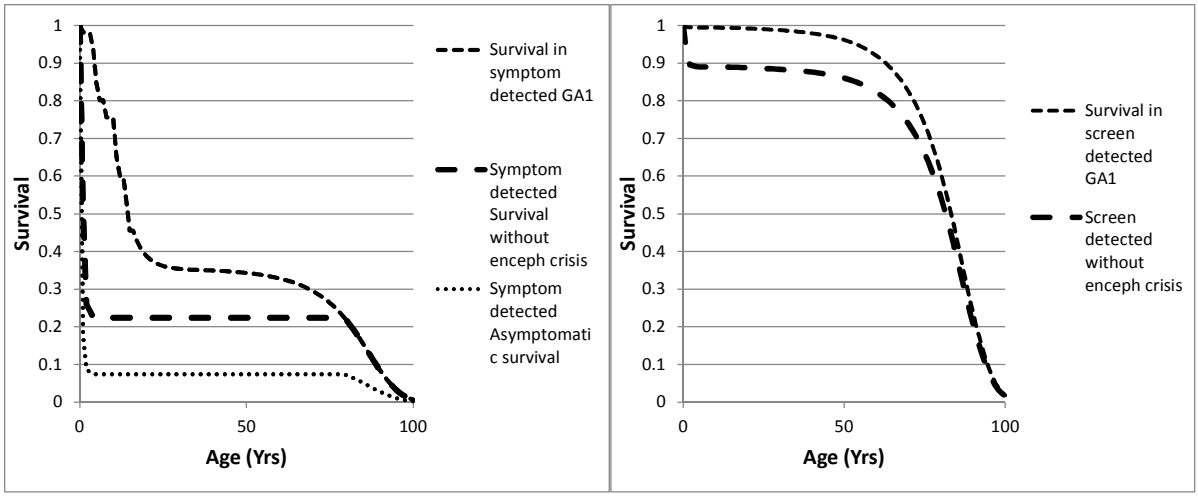
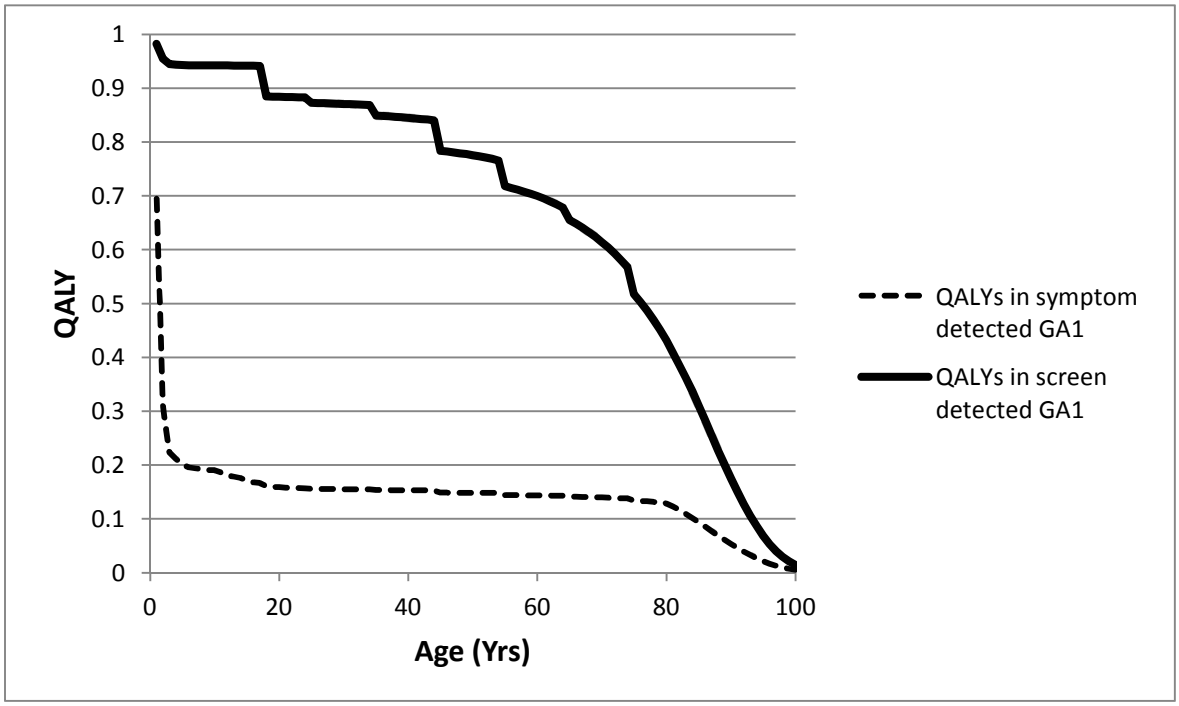


Figure A4.6 Age specific QALYs for screen and symptomatically detected GA1 cases



Model parameters:

QiemNoScrn – Average discounted lifetime QALYs for a GA1 case under no screening

8.40 (7.62, 9.25)

QiemScrn – Average discounted lifetime QALYs for screen detected GA1

39.47 (36.66, 41.69)

Health and social care costs

Health and social care costs are included in respect of neurological impairment. The costs associated with low functioning autism are used as a proxy for the costs of the long term consequences of encephalopathy in the paediatric population, adult costs are assumed to be as for those living in a semi-independent living setting, see Table A2.5. These costs estimates are likely to underestimate the long term costs associated with encephalopathy subsequent to GA1. Figure A4.7 presents the age distribution of costs of care for screen and symptomatically detected GA1 patients.

Model parameters:

CiemNoScrn – Average discounted lifetime health/social care costs of symptom detected GA1

£549,529 (£404,619, £730,087)

CiemScrn – Average discounted lifetime health/social care costs of screen detected GA1

£170,644 (£126,095, £226,905)

APPENDIX 5 – MAPLE SYRUP URINE DISEASE

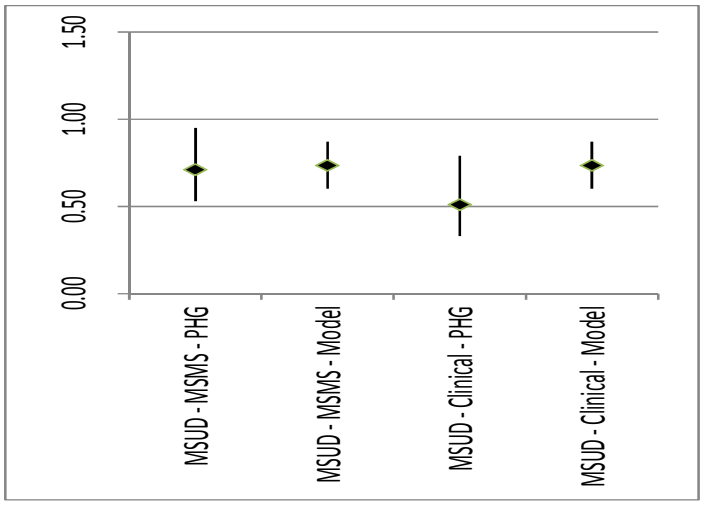
OVERVIEW

This appendix includes a description of the derivation of input parameters for the economic evaluation of screening for Maple Syrup Urine Disease (MSUD). MSUD has three main variants classic, constituting around 75%-80%, intermediate and intermittent. Newborn screening with MSMS is able to identify the classic type and a part of the intermediate type equivalent to approximately 10-20% intermediate/intermittent group. The model therefore focuses on classic and screen detectable intermediate MSUD.

PREVALENCE

The birth prevalence estimates of MSUD are presented in Figure A5.1. The PHG report finds a slightly higher estimate of prevalence in the screen detected series than with symptomatic detection. However it is not clear how well the screening based studies capture the non-screen detectable cases, the apparent consistency in prevalence estimates therefore may misrepresent a degree of overdetection or ascertainment bias in the underlying data.

Figure A5.1 Birth prevalence of MSUD per 100,000 births



Model parameters:

PincScrn **-**Birth prevalence with screening 0.74 (0.60, 0.87)

PincNat **-** Birth prevalence without screening 0.73 (0.60, 0.87)

TEST CHARACTERISTICS

The sensitivity and specificity of the MSMS device in the mass screening setting is estimated from the data extracted in the PHG systematic review update. A logit model is used within a Bayesian synthesis to estimate these independently.

Model parameters:

PSens - Sensitivity for MSUD is estimated at 88.47% (16.55%, 100.00%)

PSpec - Specificity for MSUD is estimated 99.99% (99.97%, 100.00%)

DIAGNOSIS AND MANAGEMENT OF MSUD

Management of MSUD comprises life-long dietary management and episodic intensive care either in response to encephalopathic crisis or preventatively in during periods of intercurrent illness, the potential trigger episodes of encephalopathic crises. The costs of diet and crisis management are included here. The next three tables list the resources used in the management of MSUD in terms of staff time, blood tests taken and supplements prescribed. They are split into diagnosis costs in Table A5.1, regular appointments in Table A5.2 and supplements prescribed in Table A5.3.

Table A5.1 MSUD Diagnosis Costs

Cost of 1st appointment	
Staff	60 mins Consultant paediatrician 60 mins Specialist nurse 60 mins Dietician
Bloods	Urinary/organic acids Blood plasma AA DNA MSUD
Cost of 2nd appointment (Diagnosis confirmed)	30 mins Consultant paediatrician 30 mins Specialist nurse 30 mins Dietician
Cost of 2nd appointment (False positive)	Same as above

Table A5.2 MSUD appointments

Age	**Staff**	**Blood**
1st Year (excluding diagnosis appointments)	30 mins Consultant paediatrician x4 30 mins Specialist nurse x4 30 mins Dietician x4	Weekly BCAA monitoring until 8 weeks Bi-weekly BCAA thereafter
2nd year onwards	30 mins Consultant paediatrician x4 30 mins Specialist nurse x4	Bi-weekly BCAA monitoring

	30 mins Dietician x4	

We assume that patients would receive 3g/kg/day of MSUD Anamix infant feed initially moving to 3g/kg/day MSUD gel/Anamix junior over the course of the first year, with this diet continuing throughout life. In addition isoleucine and valine supplements are given, initially at 200mg per day each but quickly rising to 300mg per day, again supplementation is assumed to be lifelong.

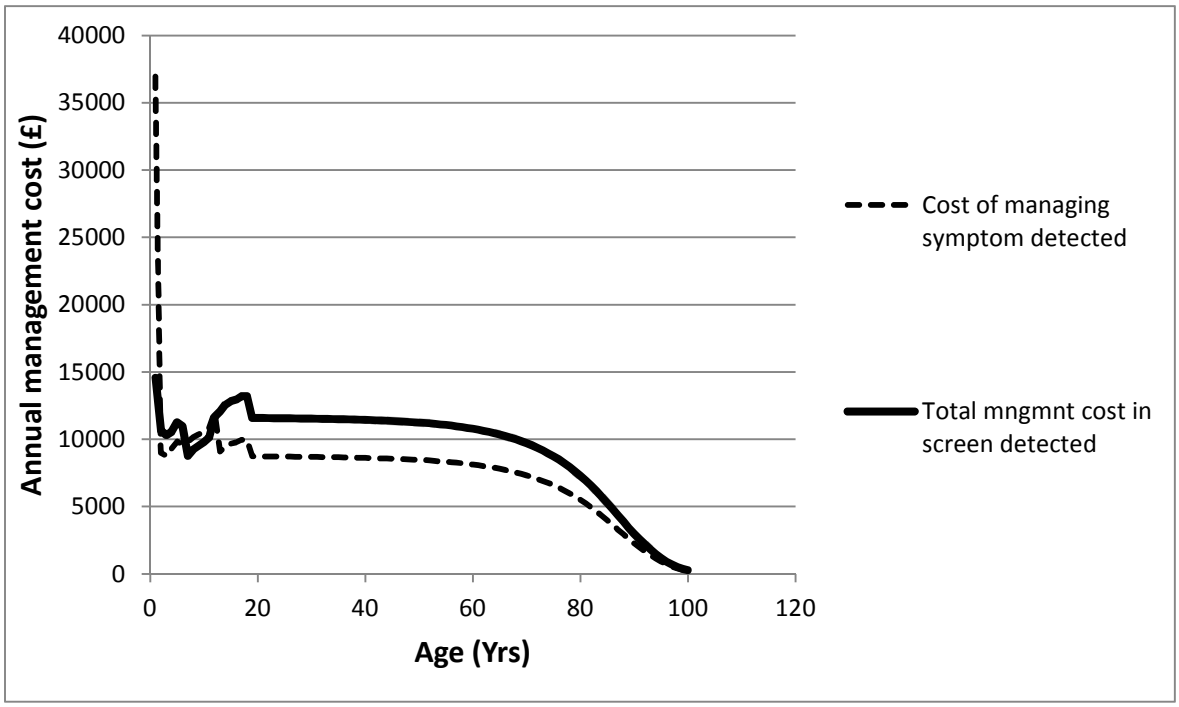
Table A5.3 presents the annual costs for the dietary management of MSUD in the screened populations. Without screening it is assumed that all symptomatic diagnoses occur in the first two years of life, primarily associated with first encephalopathic crisis.

All symptomatic and 10% of screen detected(Simon et al. 2006) cases of MSUD are assumed to experience at least one episode of encephalopathic crisis.

The duration of encephalopathic crises and duration and frequency of intercurrent illness requiring preventive hospitalisation are as for GA1 and are described in Table A4.5 and Table A4.6.

The annual costs of diagnosis, dietary and preventive management for MSUD over life are presented in Figure A5.2, note that this does not include the cost of managing sequelae of crises.

Figure A5.2 Annual age specific diagnosis and management costs for MSUD



Model parameters:

Cconf – Confirmation cost in false positives for MSUD £582 (£524, £638)

CmngtNoScrn – Discounted lifetime cost of management of MSUD without screening

£445,933 (£326,976, £589,323)

CmngtScrn - Discounted lifetime cost of management of MSUD with screening

£531,328 (£392,616, £706,507)

Table A5.3 Annual diagnosis and management cost for MSUD in the screened population (2nd year onwards)

Age	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19+
Consultant paediatrican x 30 mins (x4)	£314	£314	£314	£314	£314	£314	£314	£314	£314	£314	£314	£314	£314	£314	£314	£314	£314	£314	£314
Specialist nurse x 30 mins (x4)	£98	£98	£98	£98	£98	£98	£98	£98	£98	£98	£98	£98	£98	£98	£98	£98	£98	£98	£98
Dietician x 30 mins (x4)	£68	£68	£68	£68	£68	£68	£68	£68	£68	£68	£68	£68	£68	£68	£68	£68	£68	£68	£68
Bi-weekly BCAA monitoring	£313	£313	£313	£313	£313	£313	£313	£313	£313	£313	£313	£313	£313	£313	£313	£313	£313	£313	£313
MSUD Gel/MSUD Anamix Junior g/kg	3	2	2	2	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1	1
daily g	34.5	28.2	33	36.2	30.6	34.8	39	44.55	50.25	57.45	66	74.25	84.3	89.7	92.1	97.5	97.5	65	65
period g	12592.5	10293	12045	13213	11169	12702	14235	16260.8	18341.3	20969.3	24090	27101.3	30769.5	32740.5	33616.5	35587.5	35587.5	23725	23725
units	14.47	11.83	13.84	15.19	12.84	14.60	16.36	18.69	21.08	24.10	27.69	31.15	35.37	37.63	38.64	40.91	40.91	27.27	27.27
cost	£2,413	£1,973	£2,308	£2,532	£2,140	£2,434	£2,728	£3,116	£3,515	£4,019	£4,617	£5,194	£5,897	£6,275	£6,442	£6,820	£6,820	£4,547	£4,547
Isoleucine supplement daily mg	300	300	300	300	300	300	300	300	300	300	300	300	300	300	300	300	300	300	300
period mg	109500	109500	109500	109500	109500	109500	109500	109500	109500	109500	109500	109500	109500	109500	109500	109500	109500	109500	109500
units	73.00	73.00	73.00	73.00	73.00	73.00	73.00	73.00	73.00	73.00	73.00	73.00	73.00	73.00	73.00	73.00	73.00	73.00	73.00
cost	£3,567	£3,567	£3,567	£3,567	£3,567	£3,567	£3,567	£3,567	£3,567	£3,567	£3,567	£3,567	£3,567	£3,567	£3,567	£3,567	£3,567	£3,567	£3,567
Valine supplement daily mg	300	300	300	300	300	300	300	300	300	300	300	300	300	300	300	300	300	300	300
period mg	109500	109500	109500	109500	109500	109500	109500	109500	109500	109500	109500	109500	109500	109500	109500	109500	109500	109500	109500
units	73.00	73.00	73.00	73.00	73.00	73.00	73.00	73.00	73.00	73.00	73.00	73.00	73.00	73.00	73.00	73.00	73.00	73.00	73.00
cost	£3,567	£3,567	£3,567	£3,567	£3,567	£3,567	£3,567	£3,567	£3,567	£3,567	£3,567	£3,567	£3,567	£3,567	£3,567	£3,567	£3,567	£3,567	£3,567
Move towards protein exchanges	£1,141	£1,141	£1,141	£1,901	£1,901	£1,901	£2,282	£2,282	£2,282	£2,282	£3,803	£3,803	£3,803	£3,803	£3,803	£3,803	£3,803	£3,803	£3,803
Total	£11,481	£11,040	£11,376	£12,360	£11,968	£12,262	£12,936	£13,324	£13,723	£14,227	£16,346	£16,923	£17,626	£18,004	£18,172	£18,549	£18,549	£16,276	£16,276

HEALTH AND SOCIAL CARE IMPACT OF THE MSUD

The economic model captures within its scope the impact of MSUD on mortality and long term neurological disorders.

Mortality and Quality of life

Age specific all-cause mortality is taken from ONS Interim Life Tables, England & Wales 2008-2010. The mortality and morbidity associated with symptomatically and screen detected MSUD is based primarily on expert judgement. The proportions in each variant and mortality rates in the first month of life are given in Table A5.4

Table A5.4 MSUD variant proportions and early mortality rates

	Variant	Central	Min	Max
Variant proportions	Classical	77.5%	75.0%	80.0%
	Intermediate (detectable)	3.4%	10.0%	20.0%
	Other~	19.1%		
Death in first month of life (symptom det)	Classical	35.0%	20.0%	50.0%
	Intermediate (detectable)			
	Other~		0.0%	
Death in first month of life (screen det)	Classical	7.5%	5.0%	10.0%
	Intermediate		0.0%	
	Other~		0.0%	

For the purposes of the model neurological morbidity associated with MSUD has been classified into four health states;

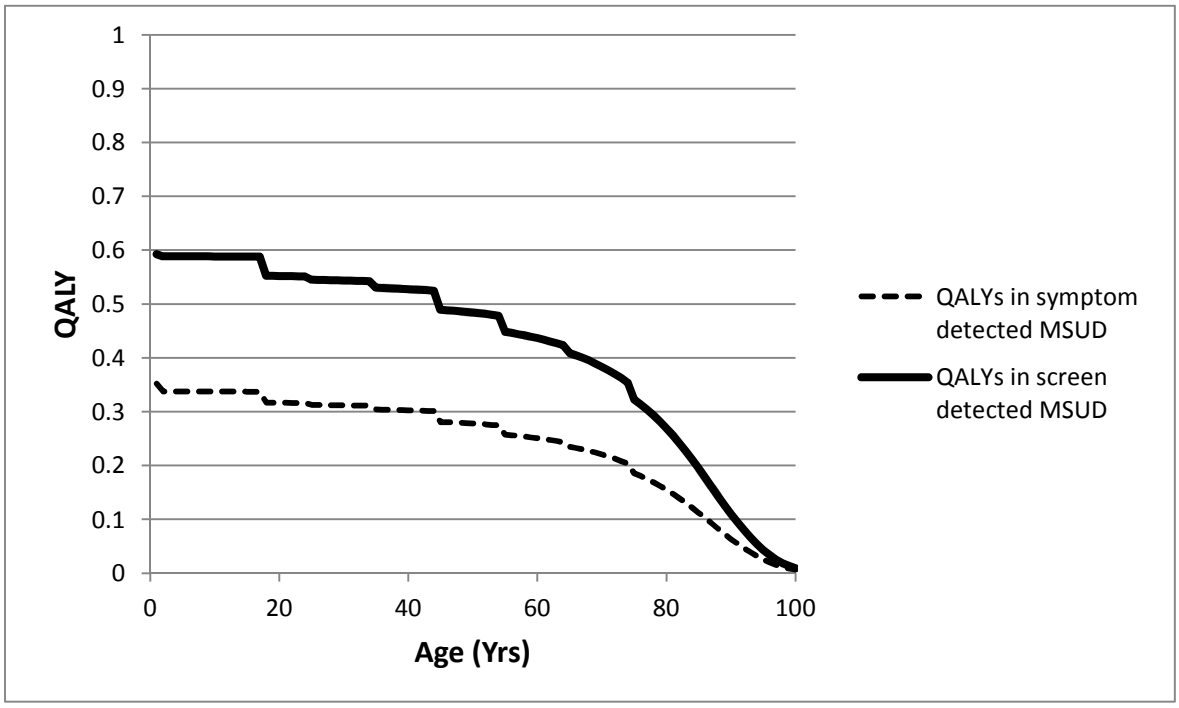
- Mild neurological/psychiatric disability: Capable of all activities in normal schooling and of living independently undertaking activities of daily living (ADL) with moderate support (incl. autism / ADHD).
- Moderate neurological/psychiatric disability: Some limitation of activity, requiring significant educational and long term living support, not entirely capable of independent living and requiring a sheltered and supervised environment (incl. autism etc).
- Severe neurological/psychiatric disability: Dependant for all healthcare and life needs.
- Normal: capable of all normal activities

Health related quality of life utility estimates based upon the EQ-5D system for the above health states are shown in Table A4.7. The proportions in each health state category associated with symptomatic and screen detected MSUD are given in Table A5.5 and the resultant age specific quality of life estimates over life are in Figure A5.3.

Table A5.5 Neurological health state outcomes for screen and symptom detected MSUD

Morbidity in symptom detected classic MSUD	Normal	10%	5%	15%
	Mild	50%	35%	75%
	Moderate	30%	20%	45%
	Severe	10%	5%	15%
Morbidity in screen detected classic MSUD	Normal	40%	15%	45%
	Mild	40%		
	Moderate	17.5%	15%	20%
	Severe	2.5%	0%	5%
Morbidity in symptom detected intermediate MSUD	Normal	35%	30%	40%
	Mild	55%	45%	65%
	Moderate	10%	5%	15%
	Severe	0%	0%	0%
Morbidity in screen detected intermediate MSUD	Normal	100%	0%	0%
	Mild	0%	0%	0%
	Moderate	0%	0%	0%
	Severe	0%	0%	0%

Figure A5.3 Age specific QALYs for screen and symptomatically detected MSUD cases



Model parameters:

QiemNoScrn – Average discounted lifetime QALYs for a MSUD case under no screening

14.17 (12.84, 15.59)

QiemScrn – Average discounted lifetime QALYs for screen detected MSUD

24.73 (23.29, 26.19)

Health and social care costs of MSUD

Health and social care costs included in respect of neurological impairment health states are given in Table A5.6. The adult costs of social care in the mild group are taken from the total annual cost for an adult with low functioning ASD included in the PSSRU 2012. The adult costs for moderate and severe states are taken from the PSSRU costs associated with semi-independent and fully staffed living settings respectively, see Table A2.5 (Part 2). The paediatric costs for mild and moderate impairment are taken from PSSRU costs for high and low functioning autism respectively, see Table 2.5 (Part 1). The paediatric costs for severe impairment are calculated from the age profile of costs from the moderate category.

Table A5.6 Health and social care costs associated with neurological impairment

Age (yrs)	0	4	12	18
Mild	£1,353	£23,265	£23,265	£9,009
Moderate	£652	£23,339	£38,221	£41,808
Severe	£1,406	£50,336	£82,432	£90,168

Model parameters:

CiemNoScrn – Average discounted lifetime health/social care costs of symptom detected MSUD

£585,845 (£431,359, £778,335)

CiemScrn – Average discounted lifetime health/social care costs of screen detected MSUD

£432,070 (£318,740, £575,621)

APPENDIX 6 – LONG CHAIN HYDROXY ACYL COA DEHYDROGENASE DEFICIENCY

OVERVIEW

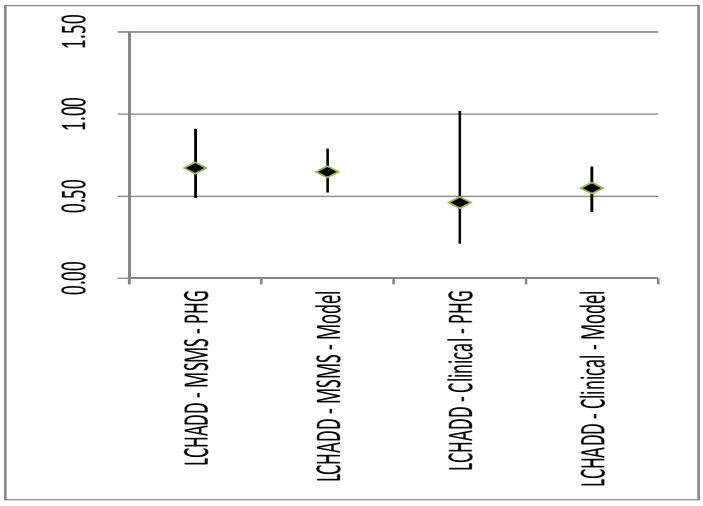
This appendix includes a description of the derivation of input parameters for the economic evaluation of screening for long chain hydroxy acyl CoA dehydrogenase deficiency (LCHADD).

It should be noted that LCHADD is indistinguishable from a deficiency of the trifunctional enzyme in which LCHADD activity is one component, by screening assays based upon individual metabolites or profiles. Indeed, it is often unclear in the literature whether isolated LCHADD deficiency or the absence of one or more components of the trifunctional protein complex (variously described as TFP or MTP) is being described. In addition, while genetically defined LCHADD seems more or less distinct, MTP can have a range of clinical presentations from severe neonatal onset within the first few days of life that may well prove fatal in infancy despite prompt treatment to a milder form that may not present until adolescence with peripheral neuropathy and there is a spectrum in between. Although due to these difficulties with nomenclature, reliable data is difficult find, it seems that MTP is more common than isolated LCHADD in many settings. These considerations make reliable predictions in relation to prevalence of the disease and the effectiveness and cost effectiveness of screening for this continuum of patients difficult. The economic results and conclusions are therefore subject to greater uncertainty than has been captured purely within the parameterisation of the model.

PREVALENCE

The birth prevalence estimates of LCHADD are presented in Figure A6.1. The PHG report finds a slightly higher estimate of prevalence in the screen detected series than with symptomatic detection.

Figure A6.1 Birth prevalence of LCHADD per 100,000 births



Model parameters:

PincScrn **-**Birth prevalence with screening 0.65 (0.52, 0.79)

PincNat **-** Birth prevalence without screening 0.55 (0.40, 0.68)

TEST CHARACTERISTICS

The sensitivity and specificity of the MSMS device in the mass screening setting is estimated from the data extracted in the PHG systematic review update. A logit model is used within a Bayesian synthesis to estimate these independently.

Model parameters:

PSens - Sensitivity for LCHADD is estimated at 89.35% (38.34%, 99.89%)

PSpec - Specificity for LCHADD is estimated 100.00% (99.98%, 100.00%)

DIAGNOSIS AND MANAGEMENT OF LCHADD

Management of LCHADD comprises dietary management for the first two years of life and episodic intensive care either in response to encephalopathic crisis or preventatively during periods of intercurrent illness, the potential trigger episodes of encephalopathic crises. The costs of diet and crisis management are included here. The next three tables list the resources used in the management of LCHADD in terms of staff time, blood tests taken and supplements prescribed. They are split into diagnosis costs in Table A6.1, regular appointments in Table A6.2 and supplements prescribed in Table A6.3.

Table A6.1 LCHADD Diagnosis Costs

Cost of 1st appointment	
Staff	60 mins Consultant paediatrician 60 mins Specialist nurse 60 mins Dietician
Bloods	Urinary/organic acids Blood acylcarnites Genetic confirmation
Cost of 2nd appointment (Diagnosis confirmed)	30 mins Consultant paediatrician 30 mins Specialist nurse 30 mins Dietician
Cost of 2nd appointment (False positive)	Same as above

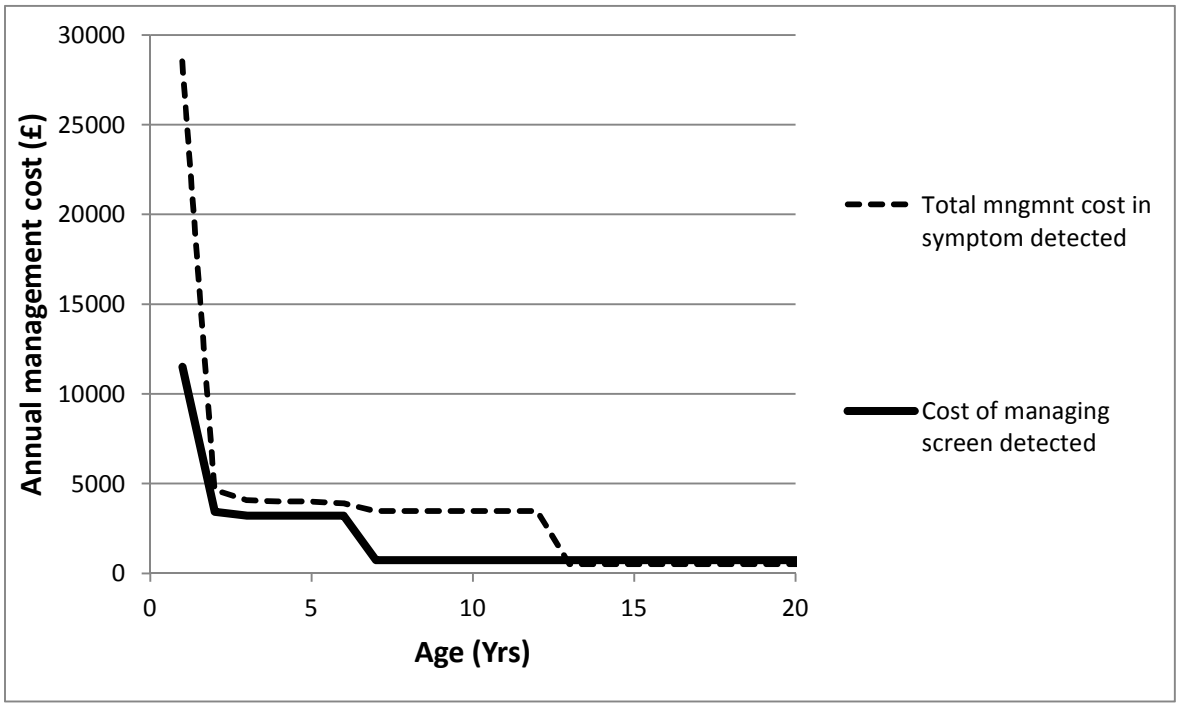
Table A6.2 LCHADD appointments

Age	Staff	Blood
1st Year (excluding diagnosis appointments)	30 mins Consultant paediatrician x4 30 mins Specialist nurse x4 30 mins Dietician x4	Weekly plasma amino acids until 4 months Bi-weekly plasma amino acids thereafter
2nd year onwards	30 mins Consultant paediatrician x4 30 mins Specialist nurse x4 30 mins Dietician x4	Bi-weekly plasma amino acids

We assume that screen detected patients would receive Lipistart sufficient to deliver 2g/kg/day of protein for the first 2 years of life, that all diagnoses occurs in the neonatal period and that costs of management thereafter arise from quarterly consultations. For symptomatically diagnosed patients all diagnoses occur in the first two years of life(Sykut-Cegielska et al. 2011) and we assume that dietary management and regular appointments follow the pattern for screen detected cases.

We assume that 78% of symptomatic (den Boer et al. 2002)and 15% of screen detected cases of LCHADD experience at least one episode of encephalopathic crisis. The duration of encephalopathic crises and duration and frequency of intercurrent illness requiring preventive hospitalisation are as for GA1 and are described in Table A4.5 and Table A4.6. The annual costs of diagnosis, dietary and preventive management for LCHADD over life are presented in Figure A6.2, note that this does not include the cost of managing sequelae of crises.

Figure A6.2 Annual age specific diagnosis and management costs for LCHADD



Model parameters:

Cconf – Confirmation cost in false positives for LCHADD £555 (£500, £609)

CmngtNoScrn – Discounted lifetime cost of management of LCHADD without screening

£81,900 (£60,418, £109,110)

CmngtScrn - Discounted lifetime cost of management of LCHADD with screening

£56,578 (£41,835, £74,845)

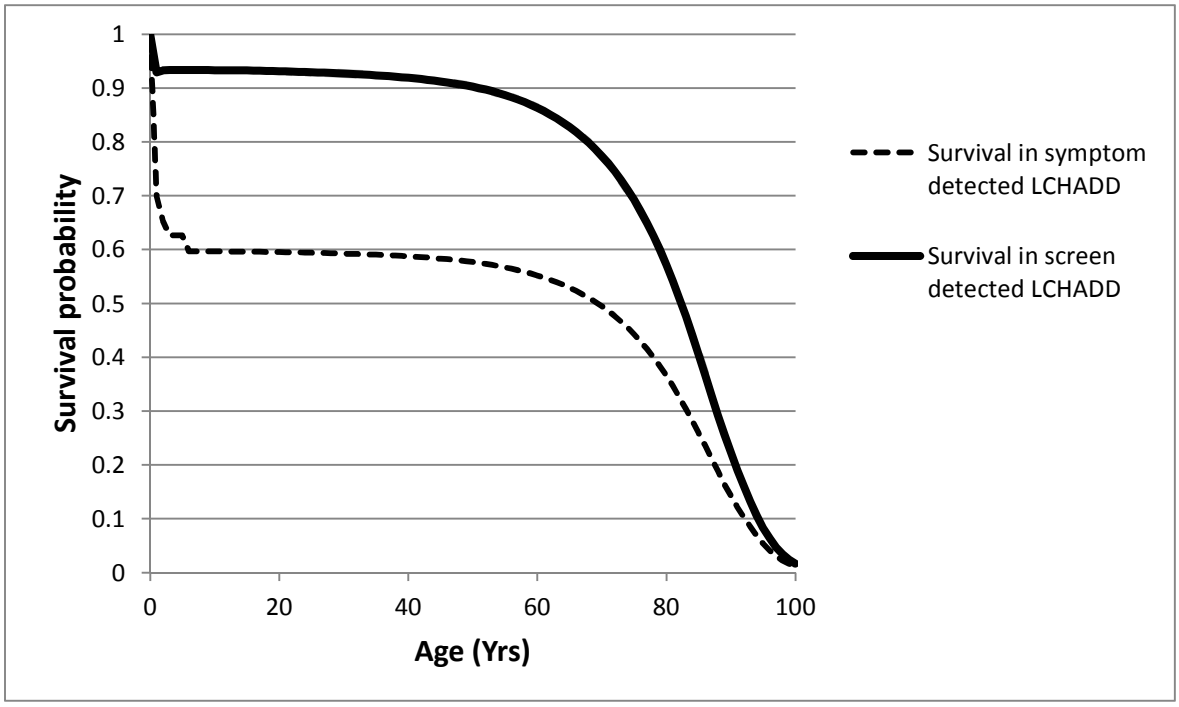
HEALTH AND SOCIAL CARE IMPACT OF THE LCHADD

The economic model captures within its scope the impact of LCHADD on mortality and long term neurological disorders.

Mortality and Quality of life

Age specific all-cause mortality is taken from ONS Interim Life Tables, England & Wales 2008-2010. Mortality in screen and symptomatically detected LHADD over the first 8 years of life is taken from Sykut-Cegielska (Sykut-Cegielska, Gradowska, Piekutowska-Abramczuk, Andresen, Olsen, Oltarzewski, Pronicki, Pajdowska, Bogdanska, Jablonska, Radomyska, Kusmierska, Krajewska-Walasek, Gregersen, & Pronicka 2011) giving the overall survival shown in Figure A6.3.

Figure A6.3 Survival in the screen and symptomatically detected LCHADD



For the purposes of the model neurological morbidity associated with LCHADD has been classified into four health states as used for the evaluation of MSUD;

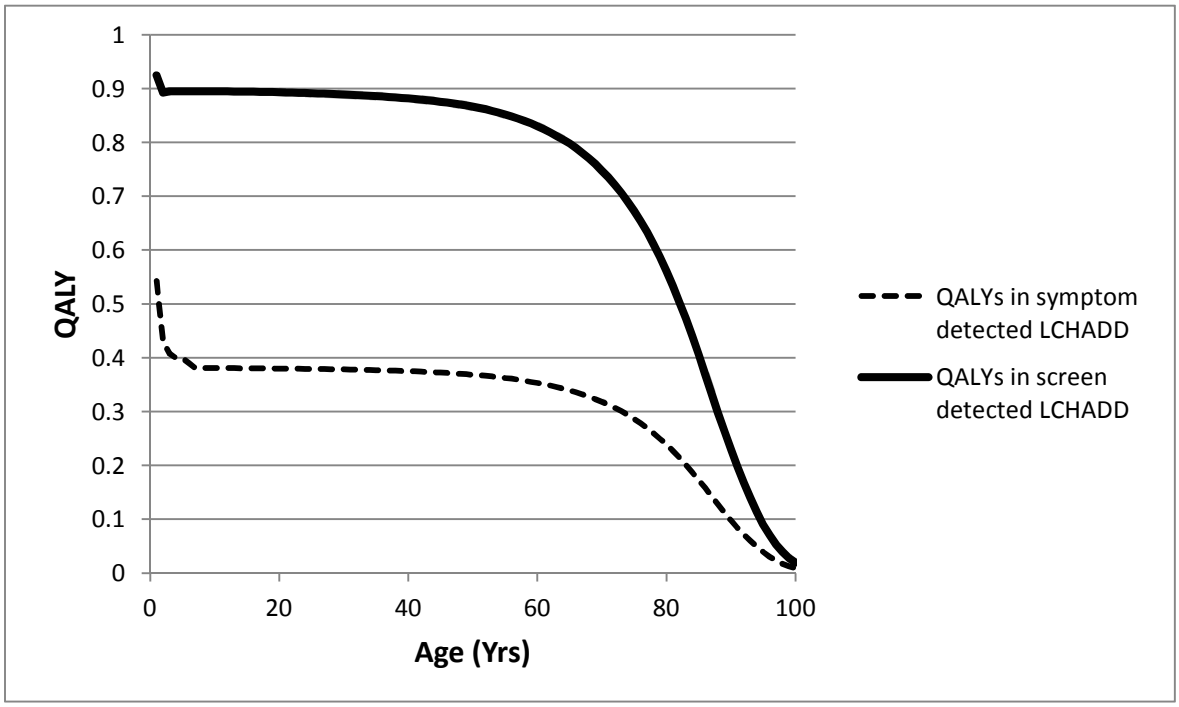
- Mild neurological/psychiatric disability: Capable of all activities in normal schooling and of living independently undertaking activities of daily living (ADL) with moderate support (incl. autism / ADHD).
- Moderate neurological/psychiatric disability: Some limitation of activity, requiring significant educational and long term living support, not entirely capable of independent living and requiring a sheltered and supervised environment (incl. autism etc).
- Severe neurological/psychiatric disability: Dependant for all healthcare and life needs.
- Normal: capable of all normal activities

Health related quality of life utility estimates based upon the EQ-5D system for the above health states are shown in Table A4.7. The proportions in each health state category associated with symptomatic and screen detected LCHADD are given in Table A6.3 and the resultant age specific quality of life estimates over life are in Figure A6.4.

Table A6.3 Neurological health state outcomes for screen and symptom detected LCHADD

Morbidity in symptom detected LCHADD	Normal	12%	5%	15%
	Mild	50%	20%	60%
	Moderate	30%	15%	40%
	Severe	8%	2%	10%
Morbidity in screen detected LCHADD	Normal	100%		
	Mild	0%		
	Moderate	0%		
	Severe	0%		

Figure A6.4 Age specific QALYs for screen and symptomatically detected LCHADD cases



Health and social care costs of LCHADD

Health and social care costs included in respect of neurological impairment associated with LCHADD are assumed to be as for MSUD and are described in Appendix 5 and detailed in Table A5.6. The distribution of health states is described in Table A6.3 and the implied annual health and social care costs are presented in Figure A6.5.

Model parameters:

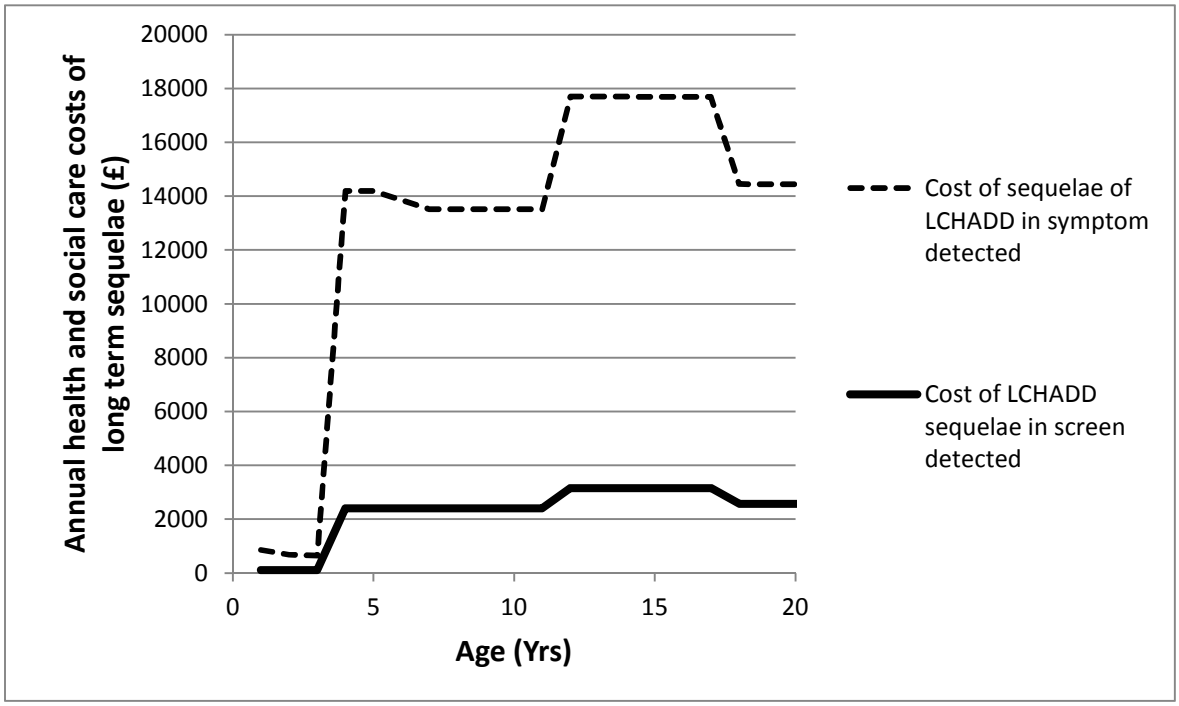
CiemNoScrn – Average discounted lifetime health/social care costs of symptom detected LCHADD

£636,641 (£468,760, £845,822)

CiemScrn – Average discounted lifetime health/social care costs of screen detected LCHADD

£113,268 (£83,698, £150,613)

Figure A6.5 Annual health and social care costs associated with LCHADD



APPENDIX A7 ECONOMIC MODEL INPUT PARAMETERS FOR ALL INBORN ERRORS OF METABOLISM

Table A7 Input parameters list

MSUD	Mean	95% CI	
CiemNoScrn	£ 585,845	£ 431,359	£ 778,335
CmngtNoScrn	£ 445,933	£ 326,976	£ 589,323
QiemNoScrn	14.17	12.84	15.59
CiemScrn	£ 432,070	£ 318,740	£ 575,621
CmngtScrn	£ 531,328	£ 392,616	£ 706,507
QiemScrn	24.73	23.29	26.19
Cconf	£ 582	£ 524	£ 638
Cscrn	£ 0.12	£ 0.08	£ 0.15
Psens	88.47%	16.55%	100.00%
Pspec	99.99%	99.97%	100.00%
PincScrn	7.35E-06	6.02E-06	8.72E-06
PincNat	7.35E-06	6.023E-06	8.72E-06
Pab	1	1	1
Qnorm	41.79	40.14	43.45

HCY	Mean	95% CI	
CiemNoScrn	£ 704,459	£ 518,695	£ 935,923
CmngtNoScrn	£ 172,197	£ 127,031	£ 229,408
QiemNoScrn	22.74	20.61	25.03
CiemScrn	£ 82,193	£ 60,735	£ 109,292
CmngtScrn	£ 235,730	£ 174,305	£ 311,839
QiemScrn	38.40	35.27	40.86
Cconf	£ 475	£ 428	£ 521
Cscrn	£ 0.12	£ 0.08	£ 0.15
Psens	93.26%	48.90%	99.98%
Pspec	99.95%	99.75%	100.00%
PincScrn	7.38E-06	5.34E-06	9.54E-06
PincNat	7.20E-06	5.1921E-06	9.37E-06
Pab	1	1	1
Qnorm	41.79	40.15	43.43

IVA	Mean	95% CI	
CiemNoScrn	£ 262,377	£ 193,189	£ 348,586
CmngtNoScrn	£ 171,859	£ 126,781	£ 228,958
QiemNoScrn	29.90	27.10	32.90
CiemScrn	£ 48,313	£ 35,700	£ 64,242
CmngtScrn	£ 69,704	£ 51,541	£ 92,209
QiemScrn	39.29	36.42	41.56
Cconf	£ 896	£ 807	£ 983
Cscrn	£ 0.12	£ 0.08	£ 0.15
Psens	93.80%	56.46%	99.96%
Pspec	99.99%	99.94%	100.00%
PincScrn	8.26E-06	6.93E-06	9.73E-06
PincNat	3.01E-06	1.67E-06	4.69E-06
Pab	0.98	0.93	1.00
Qnorm	41.79	40.14	43.45

Table A7 (Contd) **Input parameters list**

GA1	Mean	95% CI	
CiemNoScrn	£ 549,529	£ 404,619	£ 730,087
CmngtNoScrn	£ 65,383	£ 48,233	£ 87,106
QiemNoScrn	8.40	7.62	9.25
CiemScrn	£ 170,644	£ 126,095	£ 226,905
CmngtScrn	£ 70,793	£ 52,346	£ 93,650
QiemScrn	39.47	36.66	41.69
Cconf	£ 1,052	£ 948	£ 1,154
Cscrn	£ 0.12	£ 0.08	£ 0.15
Psens	90.72%	35.46%	99.97%
Pspec	99.99%	99.95%	100.00%
PincScrn	1.02E-05	8.72E-06	1.17E-05
PincNat	4.66E-06	2.587E-06	7.48E-06
Pab	0.50	0.20	0.80
Qnorm	41.79	40.14	43.45

LCHADD	Mean	95% CI	
CiemNoScrn	£ 636,641	£ 468,760	£ 845,822
CmngtNoScrn	£ 81,900	£ 60,418	£ 109,110
QiemNoScrn	17.80	16.13	19.59
CiemScrn	£ 113,268	£ 83,698	£ 150,613
CmngtScrn	£ 56,578	£ 41,835	£ 74,845
QiemScrn	41.20	39.25	42.99
Cconf	£ 555	£ 500	£ 609
Cscrn	£ 0.12	£ 0.08	£ 0.15
Psens	89.35%	38.34%	99.89%
Pspec	100.00%	99.98%	100.00%
PincScrn	6.47E-06	5.23E-06	7.89E-06
PincNat	5.48E-06	4.0317E-06	6.79E-06
Pab	1	1	1
Qnorm	41.79	40.14	43.45

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