UK National Screening Committee

Newborn screening for Mucopolysaccharidosis I

External review against programme appraisal criteria for the UK National Screening Committee (UK NSC)

Version: Draft 1

Bazian Ltd.

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The UK NSC advises Ministers and the NHS in all four UK countries about all aspects of screening policy. Its policies are reviewed on a 3 yearly cycle. Current policies can be found in the policy database at http://www.screening.nhs.uk/policies and the policy review process is described in detail at http://www.screening.nhs.uk/policyreview

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Abbreviations List

ERT	Enzyme replacement therapy
GAG	Glycoaminoglycan
MPS I	Mucopolysaccharidosis I
H	Hurler
HS	Hurler-Scheie
HSCT	Haematopoietic stem cell transplantation
HTA	Health technology assessment
MS/MS	Tandem mass spectrometry
NPV	Negative predictive value
PPV	Positive predictive value
S	Scheie
Sn	Sensitivity
Sp	Specificity
UKNSC	United Kingdom National Screening Committee

Plain English Summary

This document reviews evidence published between 2004 and 2014 on newborn screening for mucopolysaccharidosis type I (MPS I).

MPS I is a rare, inherited condition that prevents the body's cells processing molecules such as proteins, carbohydrates and fats. The right levels of these molecules are essential to the functioning of organs such as the heart, lungs, skin, bones and tissues such as blood vessels and tendons.

In MPS I the gradual build up of two carbohydrates can cause a wide range of health problems. It can also cause the early death of those affected. But the effects of MPS I are not always the same. Because of this it is usually split into two forms, a severe form and an 'attenuated' form, which is slower to develop and is sometimes quite mild.

Newborn screening has been suggested as it might find babies with MPS I before they become ill. The aim of screening would be to improve the health of the baby and to improve the experience of their families. But this review of the evidence found a number of problems which would prevent the UKNSC recommending a screening programme. These were:

- that there was a very small amount of information on important issues which need to be understood before a screening programme is recommended in the UK
- MPS I is rare. It is thought to affect about 1 baby in every 90,000 born in the UK each year. The severe form is thought to affect 1 in every 130,000 and the milder form is thought to affect 1 in every 400,000 babies. Where screening tests have been introduced a higher number of babies with MPS I have been found, but the number is uncertain because there haven't been many screening studies.
- Some, but not all, babies with the severe form of MPS 1 can be identified before they become ill by testing their genes. The 'attenuated' form of MPS 1 cannot currently be identified in this way.
- a reliable test is essential to make the screening programme work well. From the very small amount of available information it can be seen that not all of those with positive test results would have MPS 1 and some would receive information that may cause unnecessary anxiety and uncertainty about the baby's future health. There is also not enough information available on the accuracy of these tests.
- in order to recommend a screening programme, early treatment as a result of screening should improve the child's health compared with later treatment following the onset of illness. Currently, treatment of severe MPS I usually takes place within the time recommended as beneficial by European guidelines and it isn't clear that earlier treatment following screening would improve the child's health any further.
- very little information was found about parental attitudes towards earlier diagnosis of MPS I. One small survey of parents of MPS 1 children suggested there would be support for this. A minority of parent were concerned because of the limited effectiveness of treatment, the loss of a 'carefree' period in which they could bond with the child and in which a gradual process of awareness of the illness might help them understand the diagnosis better.

Because of these uncertainties the review concluded that a screening programme should not be introduced in the UK.

Executive Summary

This document reviews the literature published between 2004 and 2014 on newborn screening for mucopolysaccharidosis type I (MPS I).

MPS I is a lysosomal storage disorder. These are rare genetically inherited metabolic conditions affecting the ability of lysosomes to process biological compounds, such as proteins, carbohydrates and lipids, within cells. Accumulation of these compounds results in distortion of the cells and the clinical problems associated with each condition. This is linked to reduction in the level of enzyme activity required in the metabolic process.

MPS I can be caused by over 100 mutations in the IDUA gene which are all inherited in an autosomal recessive pattern. Reduced or eliminated activity of the enzyme α-L-iduronidase causes progressive accumulation of two mucopolysaccharides, dermatan sulphate and heparan sulphate. These are essential for the development and functioning of a broad range of organs and tissues such as the heart, lungs, skin, bones, blood vessels and tendons. They are also essential for biological processes such as angiogenesis and blood coagulation. This explains the potentially multisystem nature of MPS I.

Classification of the condition continues to evolve and this complicates discussion. Reference is made to three distinct phenotypes Hurler Syndrome, a severe form with onset in the first year, Scheie Syndrome, usually the mildest form with onset later in childhood, and Hurler-Scheie Syndrome, an intermediate form in terms of onset and severity. As overlap between, and variation, within these phenotypes has been observed attention now focuses on two broader classifications: severe and attenuated forms.

A 1997 HTA systematic review of screening for a range of metabolic disorders considered lysosomal storage disorders as a group and found that:

- the UK incidence was unknown
- an ethical, safe, simple and robust screening test was not available
- an effective treatment was not available and
- it was uncertain whether treating in the period before symptom onset would improve outcomes

Newborn screening for MPS I, and other lysosomal storage disorders, is a relatively novel development which has been stimulated by developments in treatment, exploration of testing options and interest in a wider range of benefits that might be gained from screening.

The current review explores the volume, quality and direction of the literature published since 2004 and focuses on key questions relating to the HTA's conclusions. The aim of the review is to inform discussion on whether the recent evidence provides a sufficient basis on which to recommend the introduction of a screening programme for MPS I in the UK. The conclusion of the review is that this is not the case at present. The volume of literature was very limited and imposed limitations on the ability to draw clear conclusions in key areas. For example:

- several registry based studies reported MPS 1 by phenotype. A UK registry study suggested that the overall incidence of MPS 1 is approximately 1:93,480 and the incidence of HurlerSyndrome is approximately 1:132,298. The remaining phenotypes are rarer at approximately 1:400,000.

This is an important development from the situation in 1997. Studies of screening suggest that the overall incidence of MPS 1 might be higher, but this is uncertain.

- there is evidence linking a high proportion of the severe form of MPS 1 to nonsense mutations and to particular homozygous and compound heterozygous genotypes. However the proportion varied between the small studies which were included in the review. It is acknowledged in the literature that, outside of these well-known mutations, prediction of the form MPS I is challenging on the basis of other types of mutation and the many genotypes which have been observed in MPS 1 patients.
- screening programmes involve more than just a test, but a reliable test is essential to a well-functioning screening programme. Only three studies reporting test performance outcomes for MPS 1 were identified. One study did not identify any MPS 1 cases. The remaining two looked at different approaches to testing newborn bloodspot specimens to detect low α-L-iduronidase levels. However these were unable to report key performance measures such as sensitivity, specificity and negative predictive value from the observed results.

  The positive predictive value *(*the probability that a baby with a positive test result has MPS 1) was 10.5% in one study and 33.3% in the other. The volume of literature was a key constraint and further studies would be needed to gather information on key outcomes.
- early interventions arising from screening should improve outcomes compared to later treatment on the basis of clinical presentation. The review did not identify any studies comparing the treatment of presymptomatic MPS I with symptomatically detected cases. In addition, optimum timing of treatment initiation was difficult to identify from the small number of papers exploring the relationship between timing of treatment and outcome. The papers reported a relatively small number of outcomes when compared to the broad range of problems associated with MPS 1 and conflicting results about the importance of treatment timing were reported.
- four papers reported outcomes related to stem cell transplantation (HSCT) for the severe form of MPS I. A delay of six months between the median age diagnosis and median age at initiation of treatment was reported and the reasons for this are uncertain. The median age at treatment initiation is reported to be within European guideline recommendations and it is also uncertain whether earlier treatment as a consequence of screening would lead to further improvement in outcomes.
- the debate about newborn screening has changed considerably since the publication of the HTA study in 1997. One small qualitative study explored parent's attitudes towards a hypothetical early MPS I diagnosis in relation to five themes associated with reduction of the diagnostic odyssey. The study pointed to broad support for earlier diagnosis. However a minority of parents qualified this by introducing concerns about the limitations and burden of current treatment options, the loss of a 'carefree' period in which they could bond with the child and in which a gradual awareness of the illness might facilitate acceptance of the diagnosis.

The potential impact of false positive and indeterminate results was not addressed in the study. A UKNSC document exploring the literature on these themes more generally can be accessed at www.screening.nhs.uk/policydb_download.php?doc=455

The review concluded that, at present, the evidence base is too limited in terms of volume, quality and consistency to recommend a UK screening programme for MPS I.

Introduction

Mucopolysaccharidosis I

Mucopolysacchardosis type I (MPS I) is a rare, autosomal recessive, lysosomal storage disorder caused by a deficiency of α-L-iduronidase, an enzyme required for the degradation of two main glycoaminoglycans (GAG), dermatan sulphate and heparin sulphate.[1] The accumulation of these GAGs in various organs and tissues of MPS I patients results in progressive multi-organ deterioration which, in severe cases, results in death during childhood.[2]

MPS I has traditionally been classified into three syndromes according to disease severity: Hurler (most severe), Hurler-Scheie (intermediate), and Scheie (least severe). Due to an overlap in biochemical and clinical features among these three syndromes, recent literature tends to classify affected individuals as having severe or attenuated MPS I phenotypes, with Hurler-Scheie and Scheie syndromes often combined in the attenuated group.[3, 4]

Severe disease (Hurler syndrome) is associated with early symptom onset, including umbilical or inguinal hernia and frequent upper respiratory infections in the first year of life,[3] substantial developmental delay and neurodegeneration. After age one, additional progressive symptoms are seen, including coarsening of facial features, joint stiffness and contractures, short stature, hepatosplenomegaly, and respiratory and heart disease.[1, 3] Symptoms progress rapidly and death, generally due to cardiorespiratory failure, generally occurs within the first ten years of life.[1, 3, 4]

Scheie syndrome is marked by later onset, less rapid progression and does not involve neurodegeneration, while Hurler-Scheie syndrome sees patterns of onset, progression and severity between the Hurler and Scheie phenotypes, and involves mild or no central nervous system involvement.[4]

Basis for current recommendation

The UK National Screening Committee (UKNSC) has never formally reviewed newborn screening for MPS I. A 1997 Health Technology Assessment (HTA)[5] on screening for inborn errors of metabolism suggested that screening for lysosomal storage disorders did not meet key criteria as there was no test and, in most cases, the conditions were untreatable. There was also uncertainty regarding the incidence of lysosomal storage disorders and whether there was a period before onset of symptoms in which treatment could improve outcomes.

Current update review and approach taken

The current review was prepared by Bazian Ltd., and then adapted in discussion with the UK National Screening Committee. The review considers whether the volume and direction of the published evidence produced between 2004 and 2014 indicates that newborn screening for mucopolysaccharidosis type I should be recommended in the UK. Six main criteria will be considered, with particular focus given to areas the 1997 HTA identified as uncertain, or supported by insufficient evidence. The main criteria and key questions reviewed are presented in Table 1.

Table 1. Key questions for current Mucopolysaccharidosis I evidence review

Criterion	Key Questions (KQ)	# Studies Included
2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage	2a: What is the evidence base (in terms of study type and volume) informing assumptions about the overall incidence, phenotype distribution and timing of presentation of MPS I? How do studies relating to these factors in clinically presenting MPS I data compare with that from publications reporting on screen detected MPS I?	14
	2b: What proportion of newborns with MPS I genotypes express the respective clinical phenotypes?	3
	2c: Is the progression to disease understood, are there any modulating factors which promote expression of the phenotype?	3
	2d: Has a disease marker, or set of markers, been identified for screening and diagnostic purposes.	2
5. There should be a simple, safe, precise and validated screening test.	5: Has the clinical value of newborn screening tests for MPS I been established in prospective studies of large, unselected or representative, populations?	3
8. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.	8: Has an agreed diagnostic pathway been established for presymptomatic (e.g. cascade testing of siblings) or screen detected MPS I and are the biomarkers sufficiently predictive of phenotype at the point of testing? Is it clear which interventions should be offered to those with MPS I diagnosed presymptomatically or through screening?	0

10. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.	10: What is the evidence base (in terms of study type and volume) relating to the improvement in treatment outcomes that will be achieved by screening?	6
14. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public.	14: What is the evidence base (in terms of study type and volume) relating to the wider benefits of screening for MPS I (e.g. reproductive decision making, diagnostic odyssey etc.)?	1
16. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (i.e. value for money). Assessment against this criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource.	16: Have any studies of the cost effectiveness of screening for MPS I been published?	0

The key questions were derived from the 2004 HTA review and through discussion amongst UKNSC members and members of the UKNSC Fetal Maternal & Child Health Subgroup. Discussion between Bazian Ltd and the UKNSC Secretariat further developed the questions and provided information required for developing the search strategy**.**

Each criterion was summarised as 'met', 'partially met' or 'not met' by considering the results of the included studies in light of the volume, quality and consistency of the body of evidence. Several factors were assessed to determine the quality of the identified evidence, including study design and methodology, risk of bias, directness and applicability of the evidence. Factors that were determined to be pertinent to the quality of the body of evidence identified for each criterion are outlined in the results section as well as the comment section of the Appendix tables.

For Criterion 5, quality assessment focused on four main domains: patient selection, the index test, the reference standard, and flow and timing of index test and reference standard. Each domain was assessed for risk of bias, and the first three domains were assessed for applicability to a potential UK screening programme population. Details of these assessments can be found in the comment section of the Appendix tables.

A systematic literature search of three databases was searched for studies published between 2004 and 2014. The search strategy is detailed in the appendix. Overall, the search yielded 1,676 references addressing MPS I. Of these, 229 were assessed as being potentially relevant to the key questions outlined in Table 1. These studies were further filtered at title and abstract level, and 132 were selected for appraisal at full text. Each section below provides information on the evidence selection process and number of included studies for the given criterion. Selection and appraisal of studies was undertaken by one reviewer, with any queries resolved through discussion with a second reviewer, or with the UKNSC. The review was checked within Bazian Ltd's quality assurance process.

Appraisal against UK NSC Criteria

These criteria are available online at http://www.screening.nhs.uk/criteria.

2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage

While MPS I is now widely considered to exist as a spectrum from severe to attenuated forms, three distinct phenotypes are typically referred to:

- Hurler, the most severe form, marked by symptom onset in the first year of life, cognitive impairment presenting within the first years of life and death generally within the first decade of life,
- Hurler-Scheie, an intermediate form, with symptom onset by the age of six, variable survival and mild or absent cognitive impairment, and
- Scheie, the mildest form, with later symptom onset and mortality, and no cognitive impairment.

There is recognised overlap among the three phenotypes, which complicates classification.

Common MPS I mutations of the IDUA gene include W402X, which has a reported frequency of approximately 50% of IDUA mutant alleles in Northern Europe, the UK and North America; Q70X, which is reportedly more frequent in Scandinavia and Russia than in other countries; and P533R, which is found among Italian and Spanish populations. [6] Over 100 IDUA mutations have been reported, but genotype-phenotype relationships have been challenging to establish due to genotypic heterogeneity.[7]

Current UKNSC key question

The current review focuses on evidence surrounding the epidemiology, phenotype distribution, natural history and genotype-phenotype correlations in MPS I. The key questions for this section are:

2a: What is the evidence base (in terms of study type and volume) informing assumptions about the overall incidence, phenotype distribution and timing of presentation of MPS I?

How do studies relating to these factors in clinically presenting MPS I data compare with that from publications reporting on screen detected MPS I?

2b: What proportion of newborns with MPS I genotypes express the respective clinical phenotype?

2c: Is the progression to disease understood, are there any modulating factors which promote expression of the phenotype?

2d: Has a disease marker, or set of markers, been identified for screening and diagnostic purposes?

Description of the evidence

Overall, 31 studies were identified as potentially relevant during title and abstract sifting and further assessed at full text. All study types were considered, including studies analysing registry data. Evidence from UK, European, North American, Australia and New Zealand populations was prioritised.

Of the 31 studies assessed at full text, 13 were included in the final analysis. The main reasons for exclusion were lack of relevant data on epidemiology, natural history or genotype-phenotype relationship.

Results

Key Question 1a: 1a: Overall incidence, phenotype distribution and timing of presentation of MPS I in screen vs. clinically detected patients.

Incidence

Six studies were identified that presented information on the epidemiology of MPS I. Overall MPS I incidence estimates in Europe derived from disease registries or multiple case ascertainment sources ranged from 1:144,203 in Germany to 1:93,480 in the UK. MPS I is more frequently detected in screened populations (1:35,700 to 1:17,643) compared to clinical registry data (1:911,043 to 1:93,480). For the individual phenotypes, European estimates ranged from 1:163,548 to 1:120,938 for Hurler, 1:3,352,731 to 1:410,822 for Hurler-Scheie and 1:1,915,846 1:1,419,202 for Scheie. Full details of epidemiological data are presented in Table 2 and the appendix tables.

Overall, greater variation in MPS I incidence was seen in the attenuated phenotypes. This variation may be due to difficulties distinguishing between the Hurler-Scheie and Scheie variants, or lower case ascertainment due to milder symptoms and late diagnosis.

Table 2. MPS I epidemiology

Author Year	Country	Source	Period	Cases detected (source population)	Incidence			
					MPS I	H	HS	S
Moore 2008	UK	Registry	1981-2003	196 (NR)	1:93,480°	1:132,298°	1:410,822°	1:1,419,202°
Murphy 2009	Rep. of Ireland	Clinical	2001-2006	31 (366,883)	NR	1:26,206[a] 1:371[b] 1:120,938[c]	NR	NR
Baehner 2005	Germany	Multiple	1980-1995	93 (13,410,924)	1:144,203	1:163,548	1:3,352,731	1:1,915,846
Boy 2011	Brazil	Multiple	2008	68 (2,700,000)	1:2,700,000[§]	NR	NR	NR
Lin 2009	Taiwan	Multiple	1984-2004	130 (6,377,299)	1:911,043	1:1,594,325	1:3,188,650	1:6,377,299
Lin 2013	Taiwan	Screen	2008-2013	2 (35,285)	1:17,643	NR	NR	NR
Scott 2013	USA	Screen	NR	3 (106,526)	1:35,700°	-	-	-

[§] Estimated minimum prevalence; ° Reported as birth prevalence, however, calculated in the same manner as incidence estimates from the other included studies ; [a] Incidence in overall population; [b] Incidence in Traveller population; [c] Incidence in non-Traveller population; H Hurler; HS Hurler Scheie; S Scheie

Phenotype distribution

Nine studies were identified that presented information on the phenotype distribution across MPS I cases. Overall, the number of cases included in the identified studies tended to be small (three of the studies included fewer than 100 cases), so variation in distribution frequencies across the phenotypes is expected. Across European studies, 58.8% to 88.2% of detected MPS I cases were the severe Hurler variant (70.7% in the UK); 4.3% to 22.8% were Hurler-Scheie, and 3.2% to 14.7% were classified as Scheie. As with incidence figures, greater uncertainty can be expected across the attenuated variants due to symptom overlap leading to misdiagnosis, and late onset increasing the risk of under detection. Table 3 presents additional data on phenotype distribution across the identified studies.

Table 3. MPS I Phenotype distribution

Author Year	Country	Period	Source	n= MPS I	H	HS	S
Moore 2008[8]	UK	1981-2003	Registry	167	70.7%	22.8%	6.6%
Murphy 2009[9]	Rep. of Ireland	2001-2006	Clinical	31	83.9%	12.9%	3.2%
Baehner 2005[10]	Germany	1980-1995	Multiple	93	88.2%	4.3%	7.5%
Bertola 2011[6]	Europe	NR	Multiple	102	58.8%	21.6%	14.7%
Lin 2009[11]	Taiwan	1984-2004	Multiple	7	57.1%	28.6%	14.3%
Pastores 2007[12]	Global	2003-unknown	Registry	302	47%	25%	13%
Beck 2014[1]	Global	2003-2013	Registry	987	60.9%	23.0%	12.9%
D'Aco 2012[13]	Global	2003-2010	Registry	891	57.0%	23.5%	10.9%
Munoz-Rojas 2011[14]	Global	Unknown-2008	Registry	845	58%	23%	11%

H Hurler; HS Hurler Scheie; S Scheie

NB. Phenotype distributions may not sum to 100% in each study due to unknown/unclassified cases.

Pastores 2007, Beck 2014, D'Aco 2012, and Munoz-Rojas 2011 analysed data from the same international MPS I registry, and include overlap in populations assessed.

Timing of symptom onset and age at diagnosis

Four studies were identified that reported the timing of symptom onset, and six reported the timing of diagnosis among MPS I patients. Four of the studies assessed data from the same international MPS I registry, and have overlapping patient samples. One UK study reported age of symptom onset among 25 clinically presenting attenuated MPS I patients.

Overall, the studies reported increasing age of symptomatic presentation in the milder variants of the condition. Based on international registry data, patients in the Hurler phenotype initially experience symptoms at age 6 months, Hurler-Scheie patients between the ages of 1.4 to 2.0 years, and Sheie patients between the ages of 3.0 and 5.4 years. Sheie patients in the UK and Europe are reported to exhibit symptoms earlier than other parts of the world, although no statistical test of the difference in presentation confirms this difference. See Table 4 for further details.

The same pattern was detected in terms of timing of diagnosis, with median age under one year among Hurler patients, between 3 and 4 years among Hurler-Scheie patients, and between 7 and 9 years among Scheie patients.

Table 4. MPS I timing of symptom onset and age of diagnosis (years)

Author Year	Country	Period	Source	Median age (range)			
				MPS I	H	HS	S
Age at symptom onset							
Beck 2014[1]	Europe	2003-2013	Registry	NR	0.5 (NR)	2.0 (NR)	4.9 (NR)
Beck 2014[1]	Global	2003-2013	Registry	NR	0.5 (NR)	1.8 (NR)	5.3 (NR)
D'Aco 2012[13]	Global	2003-2010	Registry	NR	0.5 (0-6.5)	1.9 (0-12.4)	5.4 (0-33.8)
Thomas 2010[15]	Global	2003-2008	Registry	NR	NR	NR	5.4 (0-33.8)
Vijay 2005[7]	UK	NR	Clinic	2.0 (0.33-9) attenuated only	NR	1.4 (0.33-6)	3.0 (0.75-9)
Age at diagnosis							
Vijay 2005[7]	UK	NR	Clinic	5.0 (1.3-40) attenuated only	NR	4 (1.3-32)	7 (2.5-40)
Murphy 2009[9]	Rep. of Ireland	2001-2006	Clinical	NR	Clinical: NR (0.25-7) Cascade test: NR (AN-.75)	Clinical: NR (4-7.5)	Clinical: 8 (n=1)
Beck 2014[1]	Europe	2003-2013	Registry	NR	0.9 (NR)	3.6 (NR)	9.4 (NR)

Beck 2014[1]	Global	2003-2013	Registry	NR	1.0(NR)	4.0 (NR)	9.4 (NR)
Pastores 2007[12]	Global	2003-unknown	Registry	NR	0.8 (0 -23.8)	3.8 (0-38.7)	9.4 (0.0-54.1)
D'Aco 2012[13]	Global	2003-2010	Registry	NR	0.8 (0-23.8)	3.8 (0-38.7)	9.4 (0-54.1)
Thomas 2010[15]	Global	2003-2008	Registry	NR	NR	NR	9.8 (0-54.1)
AN: antenatal; Pastores 2007, Beck 2014, D'Aco 2012, Thomas 2010 analysed data from the same international MPS I registry, and include overlap in populations assessed.							

Discussion

Overall, evidence suggests that 1 in 93,000 births in the UK is affected by MPS I, with approximately 1 in 132,000 births diagnosed with MPS I Hurler; these findings are broadly consistent with results from other registry or clinic based studies in Europe. A limited volume of evidence was available regarding the incidence of MPS I in screen detected populations, but this evidence does suggest that screening results in higher frequency estimates compared to estimates derived from registries or clinical data.

The included studies, especially those conducted using registry databases, utilised data over long time periods (as necessary for deriving incidence estimates for rare conditions). However, variation in case definition or diagnostic practice over such time periods could result in inconsistent detection, especially of the more attenuated phenotypes. This is evident by the wide range in ages of symptom onset and diagnosis reported across the studies; some include age of diagnosis into the third decade of life amongst Hurler patients, which is unlikely given the natural history of the more severe phenotype. There is a risk of misclassification/misdiagnosis reflected in the global registry data.

A key limitation of the epidemiology evidence is that case ascertainment methods varied across the studies, but in general relied upon either registry data or data requests from multiple sources. While these studies generally reported that case ascertainment was anticipated to be high, it is unclear if all MPS I cases were included in the studies. Given the inconsistency with incidence figures from screening programmes, the evidence does suggest that such registry or multiple source based case ascertainment methods may underestimate the overall number of MPS I cases in a population, and may misclassify the phenotype distribution across MPS I cases.

The evidence suggests that Hurler is the most frequent phenotype across MPS I cases, followed by Hurler-Scheie and Scheie phenotypes. While a substantial number of studies were included in the assessment, four of the nine studies relied upon the same international MPS I registry database, so there is overlap in the assessed MPS I cases. While four studies were conducted in the UK or other European countries, these tended to include a small number of MPS I cases (n=31 to 167).

Individual phenotype frequency distribution and age at symptom onset are subject to uncertainty due to the overlap in clinical symptoms and the associated potential for misdiagnosis, as well as potential under-diagnosis due to late symptom onset among the most

attenuated MPS I cases. This uncertainty is most likely to impact distribution estimates among Hurler-Scheie and Scheie cases.

Finally, no information was provided regarding detection method in the registry based studies (i.e. clinical presentation vs. cascade testing or population screening), so variation phenotype distribution cannot be assessed according to detection method.

1b: What proportion of newborns with MPS I genotypes express the respective clinical phenotypes?

No studies were identified that directly assessed the proportion of newborns with MPS I genotypes that go on to display clinically relevant phenotypes. Three studies[6, 7, 9] reported on the frequency of genotype among MPS I patients, and found homozygous W402X, Q70X and compound heterozygous W402X or Q70X were common mutations amongst Hurler patients. Genotype was more variable amongst Hurler-Scheie and Scheie patients. See Table 5 and appendix tables for additional details.

Overall, few studies were identified regarding genotypic variation amongst MPS I patients, and none of the identified studies provided robust evidence regarding the genotype-phenotype relationship in the patient population. Extensive allelic heterogeneity was identified, with one study[6] detecting 55 distinct IDUA mutations (35 of which were novel), and 68 distinct genotypes. Such heterogeneity is reported to "often preclude the recognition of correlations between mutant genotypes and variant clinical phenotypes."[6]

The three studies were small in size (largest size n=102), and individual phenotypes had even smaller samples, in some instances a single case. Despite the allelic variety reported, this body of evidence may not fully capture the heterogeneity and distribution of mutations. In MPS I, establishing a genotype to phenotype relationship is further complicated by symptom overlap, especially amongst the more attenuated variants, and lack of standard classification system for patients at the milder end of the MPS I spectrum.

Table 5. Select genotype information for MPS I phenotypes

Author Year	n=	Basis	H	H-S	S
Murphy 2009[9]	31	Individual	n=26 84.6% W402X/W402X 3.8% W402X/Q70X 3.8% W402X/A75T 3.8% W402X/unknown 3.8% Q70X/Q70X	n=4 75% W402X/P496L 25% R89W/C964delC	n=1 100% W402X/C678/7G-A
Bertola 2011[6]	102	Individual	n=60 20.0% W402X/W402X 6.7% W402X/other 15.0% Q70X/Q70X 6.7% Q70X/W402X 6.7% Q70X/P496R 6.7% Q70X/other	n=22 13.6% W402X/other 9.1% P533R/P533R 9.1% Q70X /other 9.1% G51D/other 9.1% C46_57del12/C46_57del12 4.5% R89W/P496R 4.5% P496R/G265R	n=15 26.7% Q70X/other 6.7% L490P/L490P 6.7% G51D/R89Q 6.7% A327P/C878_889dup 6.7% E276K/E276K

Vijay 2005[7]	29	Allelic	-	38 alleles 32% L490P 13% W402X 13% P533R 11% Unidentified 5% Q70X 5% A319V 5% R619X 5% A36E 3% S633L 3% R89Q 3% Q380R 3% R621X	20 alleles 35% W402X 15% 678-7g->a 15% Unidentified 10% L490P 10% P496L 5% Q70X 5% C664insC 5% C974ins12

Discussion

No direct evidence was available regarding the proportion of newborns with MPS I genotypes expressing the relevant clinical phenotypes. Data from three studies was available, however, regarding the proportion of individuals with MPS I phenotypes with IDUA mutant alleles. Two of these studies suggest that there are some common IDUA alleles that are associated with the Hurler phenotype (e.g. homozygous or compound heterozygous W402X and Q70X). However, genotype distribution amongst the more attenuated phenotypes was substantially more variable.

A further limitation of the body of evidence was that each individual study included a small number of patients (n=29 to 102), which was further reduced when analysis was conducted at the phenotype level. For instance, data from the Republic of Ireland suggests that homozygous W402X is associated with the vast majority of MPS I Hurler cases; this study includes just 26 Hurler patients, however, and the high frequency of this particular genotype may reflect the population and small sample size. The association wasn't replicated to such a high degree in the pan European study.

Overall, no evidence was available regarding the disease progression amongst prespecified IDUA mutations, and the identified evidence is insufficient to robustly characterise the genotype-phenotype relationship in MPS I.

1c: Is the progression to disease understood, are there any modulating factors which promote expression of the phenotype?

Five studies[1, 7, 8, 13, 15] were identified that presented information on disease progression amongst MPS I patients, with two[7, 15] of the studies reporting only on the attenuated variants. Symptoms emerge earliest amongst Hurler patients, followed by Hurler-Scheie and Scheie patients. Hernia was consistently reported as one of the earliest symptoms across the three phenotypes, and coarsening facial features present early in the more severe phenotypes. Overlap in common symptoms is evident among the more attenuated phenotypes, especially in the timing of the earliest presenting symptoms such as hernia and joint contractures. Figure 1 presents the timeline of reported symptom onset across MPS I variants.

Aside from symptom onset, limited evidence was available regarding the natural history of MPS I. Data regarding age of death was available from two studies only, and inconsistencies are seen

in these figures. This is likely due to geographic coverage (one study was based on UK registry data, the other on global registry data), and variation in median age of death may be due to differences between health systems in detection and treatment of MPS I.

Discussion

Evidence from five studies suggests that there is a consistent presentation of symptoms in MPS I patients.

Three of the included studies were based on analysis of data from the international MPS I registry, and represents global MPS I experiences that may not fully reflect the UK experience due to variation in disease classification (especially among Hurler-Sheie and Scheie patients), diagnostic odyssey, and participation in the registry. Two of the studies[7, 8] were conducted in the UK. One[8] was a registry based study that included survival analysis among MPS I patients, and the other[7] a small case series among attenuated MPS I patients (Hurler-Scheie and Scheie), and data on symptom onset and progression is difficult to interpret due to the small sample size.

No evidence was identified regarding factors that promote the expression of each of the phenotypes, nor on variation in natural history according to genotype.

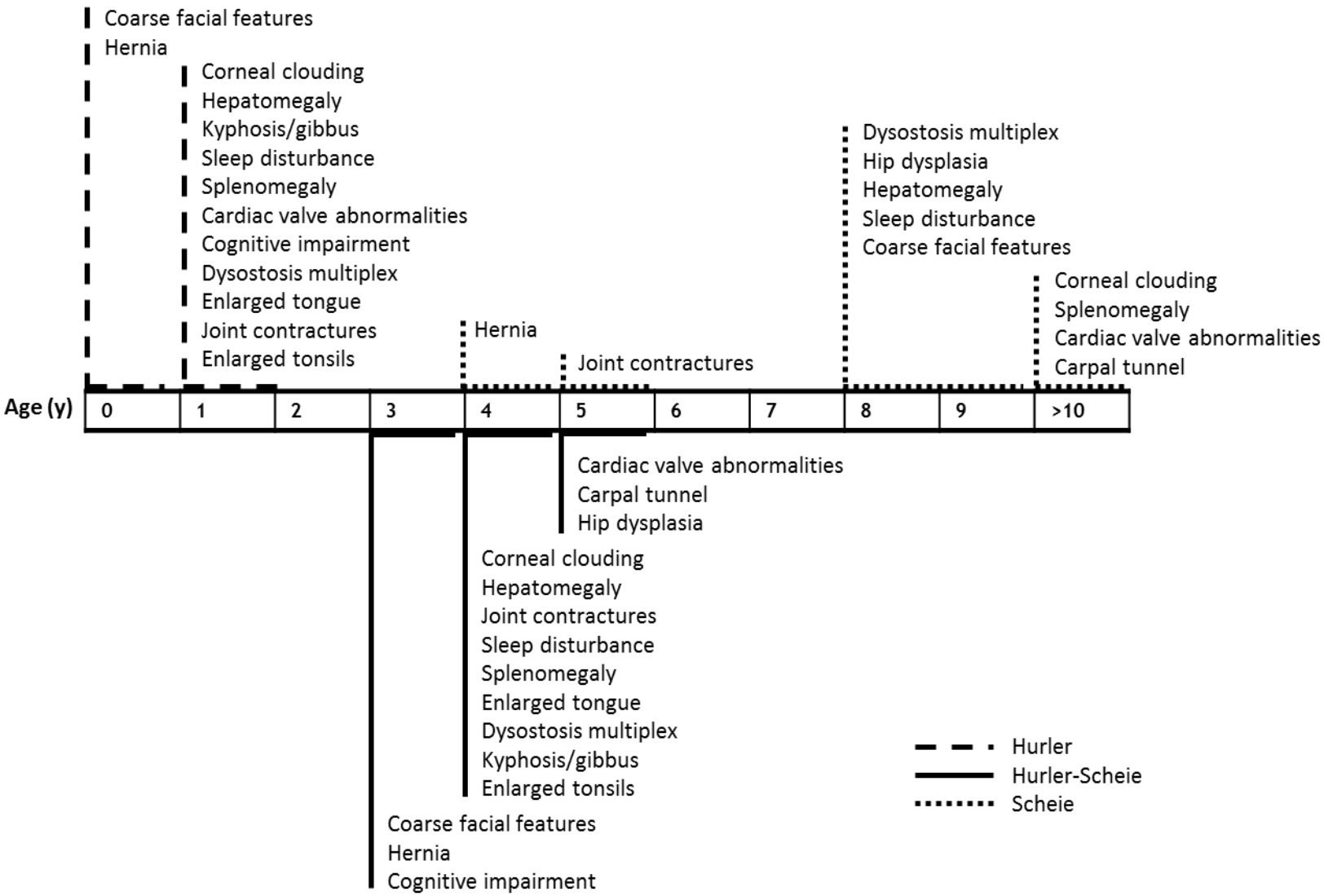

Figure 1. Timeline of symptom onset among Hurler, Hurler-Scheie and Sheie patients, based on MPS I registry data[1, 8, 13, 15]

1d: Has a disease marker, or set of markers, been identified for screening and diagnostic purposes.

The identified screening studies[16, 17] (see Criterion 5) test α-L-iduronidase activity levels in newborn dried blood spots, with follow-up confirmatory testing often involving secondary biochemical confirmation or mutation testing for known MPS I IDUA alleles. Mutation analysis is unlikely to be suitable as a primary screening strategy, due to genotype heterogeneity across MPS I cases.[6, 7, 9] Assessment of urinary GAG concentration has also been suggested as a potential biomarker, but was not assessed in any of the identified pilot screening programmes.

Summary: Criterion 2 partially met. The incidence, phenotype distribution and age of symptom onset among MPS I patients is well established. In Europe, MPS I frequency ranges from 1:144,203 to 1:93,480. Hurler is consistently identified as the most common variant, accounting for 58.8% to 88.2% of MPS I cases, while Hurler-Scheie accounts for 4.3% to 22.8%, and Scheie for 3.2% to 14.7% of cases. A single UK study reported incidence of 1:93,480, and phenotype distribution of 70.7%, 22.8% and 6.6% for Hurler, Hurler-Scheie and Scheie, respectively. Median age of symptom onset was consistently inversely associated with severity of illness, occurring at 0.5 years amongst Hurler patients, between 1.4 to 2.0 years in Hurler-Scheie and 3.0 to 5.4 years in Scheie patients. No evidence was identified, however, regarding variation in these factors according to detection method (i.e. clinical presentation vs. cascade testing or population based screening).

Evidence was identified regarding the genotype-phenotype association in MPS I. While several common genotypes have been observed among MPS I patients, especially in the most severe Hurler variant, extensive allelic heterogeneity across cases combined with difficulties in standardly defining the more attenuated variants make establishing robust genotype-phenotype correlations challenging. No direct evidence was identified regarding the proportion of individuals with common IDUA mutations who express the relevant clinical phenotypes.

Finally, data from an international MPS I registry provides evidence regarding symptom onset over time across the MPS I phenotypes, although overlap among the more attenuated phenotypes was identified. No evidence was identified regarding factors that moderate phenotype expression.

5. There should be a simple, safe, precise and validated screening test.

The primary MPS I biomarker for potential screening tests is α-L-iduronidase activity in dried blood spots (DBS). Challenges regarding the ability of laboratory tests to detect small differences in α-L-iduronidase activity have been reported, undermining the ability of enzymatic assays to predict clinical phenotype.[15]

Several potential methods for MPS I testing have been described in the literature, including tandem mass spectrometry (MS/MS) of enzyme activity[18-22] and fluorometric enzyme assays.[16, 17, 23] Multiplex assays that test for several lysosomal disorders at once have also been described. Some studies suggest that measurement of dermatan and heparin sulphate derived disaccharides using high performance liquid chromatography-tandem mass spectrometry[24] (HPLC-MS/MS) or testing of urinary GAG concentration[25] may be an optional biomarker for screening programmes.

MPS I has been included as part of several recent pilot screening programmes, including in Washington State USA[26] (multiplex MS/MS for lysosomal storage disorders), Italy[17] (fluorometric

enzyme assay for lysosomal storage disorders) and Taiwan[16] (fluorometric enzyme assay for MPS I).

Current UKNSC key question

The current review focuses on the evidence relating to the clinical value of newborn screening tests for MPS I, prioritising prospective studies of large, unselected or representative populations. In the absence of this type of evidence on the clinical validity and utility of the testing strategy, case-control studies assessing the analytical validity of testing strategies were considered.

Description of the evidence

Overall, 37 studies were identified as potentially relevant during title and abstract sifting and further assessed at full text. Prospective cohort studies or programme evaluations of pilot screening programmes were prioritised.

Of the 37 studies assessed at full text, 3 pilot screening programmes[16, 17, 26] were included in the final analysis. The main reasons for exclusion were lack of results specifically for MPS I (e.g. pooled results of multiplex assays for lysosomal storage disorders or all types of mucopolysaccharidoses), and lack of data on test performance (e.g. sensitivity, specificity, positive predictive value or negative predictive value).

The three included studies reported limited results for pilot newborn screening programmes in the USA[26], Taiwan[16] and Italy[17]. The population samples tested in these programmes ranged from 3,403 to 106,526 neonates. All three programmes assessed α-L-iduronidase activity from dried blood spots; two programmes[16, 17] utilised a two-stage fluorometric enzyme assay and one[26] used a multiplex MS/MS testing strategy. Results below are presented for the entirety of the testing strategy (e.g. samples positive after the first and second assays, where applicable); data on first stage positive screens of the Taiwan and Italy programmes can be found in the appendix tables.

All three studies reported results for screen positive individuals only. As such, it is generally not possible to calculate sensitivity, specificity, or negative predictive value (although specificity for the USA programme was calculable based on reported false positive rate). The positive predictive value (PPV) for the two-stage fluorometric enzyme assay ranged from 0% to 10.5% in the two populations assessed (see Table 6), and was 33.3% for the MS/MS strategy.

Table 6. Positive predictive value of MS/MS or fluorometric enzyme assay (FEA) of α-L-iduronidase activity in dried blood spots, results from two pilot screening programmes

Author Year	Country	n=	Cases/ screen positives	Population	Test	Cutoff	Incidence	Results
Scott 2013[26]	USA	106,526	3/9	Screening	MS/MS	1.15 µmol/h/L	1:34,700	Sn: No data Sp: No data NPV: No data PPV: 33.3%
Lin 2013[16]	Taiwan	35,285	2/17	Screening	FEA	9.03 µmol/L blood*20h	1:17,643	Sn: No data Sp: No data NPV: No data PPV: 10.5%*
Paciotti 2012[17]	Italy	3,403	0/3	Screening	FEA	8.2nmol/h/mL	Not calculable	Sn: No data Sp: No data NPV: No data PPV: 0%*
* Reviewer calculated based on limited data on positive screen results only Scott 2013 test identified one carrier (considered a false positive in calculations); true positives classified according to presence of MPS I nucleotide changes not clinical follow-up, unclear if the three detected cases were clinically relevant.								

Discussion

Overall, the three included studies represent a low level of evidence relating to two potential testing strategies (fluorometric enzyme assay and MS/MS assessing α-L-iduronidase activity). Beyond the limited quantity and scope of the included studies, limitations surrounding the testing strategy/results reporting and programme applicability were identified.

In terms of testing strategy and results reporting, the confirmatory diagnostic tests were conducted on screen positive samples only, confirmed MPS I status is only available for a small portion of the population, and the true diagnostic status of screen negative samples is not known. As such, key performance metrics (i.e. sensitivity, specificity, negative predictive value) cannot be determined. The majority of studies identified in the search focused primarily on established reference values for MPS I vs. unaffected individuals, and did not directly address the key question of test performance, while others were used to screen for multiple conditions at once and did not provide results for MPS I specifically.

The reference standard used in Washington State screening programme relied on detection of MPS I associated nucleotide changes to confirm diagnosis; no clinical follow-up was conducted, and no additional confirmatory tests were used to verify case status. It is unclear whether the three detected cases went on to develop MPS I phenotypes. Additionally, the initial MS/MS screen detected at least one MPS I carrier (treated as a false positive in the positive predictive value analysis).

No long term follow-up that would allow for clinical determination of MPS I status in the screened samples was conducted. As positive predictive value is influenced by the prevalence of the condition and population demographics in a given population, this reduces the applicability of studies from other countries that only report PPV to a UK screening programme. For comparison, the UK's estimated birth prevalence of MPS I in a non-screening population is 1:93,480.[8]

While the population screened (i.e. newborns) and the sampling methods used (i.e. DBS) are directly applicable to a UK screening programme, two of the three[16, 17] studies collected DBS samples earlier than is standard in the UK (at 2 to 3 days in the included studies compared to 5 to 8 days in the UK). Whether the differences in sample collection is a critical concern for applicability depends on whether there is variation in α-L-iduronidase activity over the course of the first week of life among MPS I patients. Finally, it is worth noting that none of the screening programmes included information on the ability of the test to distinguish between MPS I severity levels or pseudodeficiency.

Summary: Criterion 5 not met. Insufficient evidence was identified to determine the overall performance of a fluorometric enzyme assay or MS/MS for the detection of MPS I. While three pilot screening studies were identified and included in the review, the only consistent performance metric available was positive predictive value, which is influenced by condition

prevalence in the tested population. As none of the studies was conducted in the UK, this reduces the applicability of the results to a UK screening programme. Based on a single study, MS/MS may offer high specificity and a better PPV than fluorometric enzyme assay, however, the volume of evidence for MS/MS is a key limitation. Additional studies that establish the sensitivity, specificity, positive and negative predictive values of various MPS I testing strategies are required.

8. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.

No studies were identified relating to the agreed diagnostic or treatment pathways for MPS I patients following detection via cascade testing or screening.

Guidelines and consensus statements for the identification and management of MPS I (without consideration of detection methods) suggest that HSCT is appropriate for MPS I Hurler patients under two years of age, as it has been shown to significantly alter cognitive impairment. Identification of an appropriate donor should reportedly focus on a sibling with a genotypically identical histocompatibility antigen, followed by other related donors.[27] There is suggestion that combined ERT and HSCT can be beneficial, especially among patients in poor clinical condition and those with respiratory and cardiologic morbidities.[27]

A Brazilian guideline suggests that difficulty in predicting phenotype at time of disease onset or diagnosis makes identifying patients for whom there exists a favourable risk:benefit ratio for HSCT treatment. [28]

ERT has been recommended for treatment of symptomatic patients at any age with at least one MPS I manifestation known to respond to laronidase (i.e. obstructive, restrictive and interstitial respiratory disease, sleep apnea/hyperpnea syndrome; osteoarticular compromise; or cardiac compromise).[27, 28]

10. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.

Several treatment options have been explored for MPS I. Hematopoietic stem cell transplant (HSCT) was introduced as a treatment for Hurler syndrome in the 1980s, with donor cells serving as a permanent source of enzyme replacement in the blood and nervous system. Originally, stem cells were sourced from the bone marrow, with peripheral blood and umbilical cord blood being more recent sources. HSCT has been reported to increase survival and improve some symptoms, including facial coarseness, hepatosplenomegaly, hearing and heart function; however, variation in clinical outcome has been found.[28] HSCT reportedly does not improve skeletal manifestations (i.e. dysostosis multiplex) or long term corneal clouding.[3, 27, 28] An MPS I management guideline published in 2009 suggested that HSCT prior to the age of 2 years is associated with significantly better development than transplant in older patients.[27] One cross-sectional study of MPS I registry data suggests that mean age of bone marrow transplant in the UK was 1.33 years,[8] while global registry data suggests that mean age of diagnosis among Hurler patients is 0.9 years in Europe.[1] HSCT is reported as the treatment of choice for younger patients with Hurler syndrome,[28] as it is currently the only treatment option capable of passing the blood brain barrier and thus preventing central nervous system deterioration.[2, 29] Graft failure has

been reported as a key limitation of HSCT treatment for Hurler syndrome, and recent studies have focused on the influence of various conditioning regimens and hematopoietic stem cell sources on engraftment and transplantation success.[29]

Enzyme replacement therapy has been an available treatment option for MPS I patients since the early 2000s. Laronidase (recombinant human alpha-L-iduronidase enzyme) is licensed within Europe for treatment of non-neurological symptoms of MPS I, including enlarged liver, stiff joints, reduced lung volume, heart disease and eye disease**.** A key limitation of ERT with laronidase is that nearly all patients develop antibodies against the drug, and it is not suitable for treating the neurological manifestations seen in Hurler patients.

Current UKNSC key question

Interest in screening for MPS I and other lysosomal storage disorders poses questions in regards to treatment timing. For MPS I, this is especially the case as treatment options vary across phenotypes, and recommendations regarding the timing of treatment initiation have previously been made.

The current review focuses on the evidence relating to the improvement in treatment outcomes that will be achieved by screening, prioritising studies of treatment effects in screen detected patients compared to those detected clinically or presymptomatically via cascade testing compared with those detected clinically. In the absence of studies in screened populations or cases detected by cascade testing, studies assessing the impact of early compared late treatment, or that included age of treatment initiation in analyses, were considered.

The current review does not assess or synthesise studies on the general efficacy and safety of HSCT or ERT treatment in the absence of data on either detection method or analysis of effectiveness by age at treatment.

Description of the evidence

Overall, 59 studies were identified as potentially relevant during title and abstract sifting and further assessed at full text. Systematic reviews, randomised controlled trials and cohort studies that assessed treatment effectiveness in screen vs. clinically detected MPS I populations were prioritised, although other study designs were considered. In the absence of such evidence, studies that compared cascade testing to clinical detection, or analysed variation in effectiveness by age at treatment were considered.

Of the 59 studies assessed at full text, 6 were included in the final analysis (one cohort study[30], four case series[2, 29, 31, 32], and one open-label clinical trial[33]). The main reasons for exclusion were lack of data on disease detection (i.e. screen vs. clinically detected), and lack of analysis regarding the association between age at treatment and effectiveness.

Hematopoietic stem cell transplant (HSCT)

Four studies[2, 29-31] were identified that provided information on the effectiveness of HSCT according to patients' age at treatment.

The four studies assessed various outcomes, including cognitive and development function, adaptive functioning, event free survival and survival. Age at initiation of treatment varied widely across the studies, with median age at treatment ranging between 13.1 and 18 months, and overall age at treatment for included patients ranging from 1 to 228 months.

Assessment of the association between age at treatment and HSCT outcomes varied across the four studies. Three studies include age as a continuous variable in analyses.[2, 30, 31] Two of these studies[30, 31] found that age at treatment was not associated with significant differences in adaptive functioning,[31] survival[30] or alive and engrafted status,[30] while the third study[2] reported that younger age at transplant was associated with statistically significant improvements in cognition, although the clinical significance of these improvements is not clear as no scoring scale was reported. The fourth study treated age at treatment as a binary variable (younger or older than the median age of 16.7 months), and found that younger age at treatment was associated with significantly higher risk of event free survival (defined as autologous reconstitution, graft failure or death). See Table 2 for further details on age associated results.

Enzyme replacement therapy (ERT) with laronidase

Two studies[32, 33] were identified that provided information on the effectiveness of ERT across different outcome categories according to patients' age at treatment.

One study found that younger (<2.5 years) Hurler syndrome children experience mental development similar to their unaffected peers, while those receiving treatment later continue to experience flat mental development. The second study generally found no differences between children treated between ages 1 and 3 years and those whose treatment commenced later in life (after age 3) in terms of anthropometric changes; the one statistically significant difference between the two groups was in change in head circumference, and it is unclear whether this difference was clinically as well as statistically significant.

Table 7. Association between age at treatment and various outcomes in MPS I patients

	Study	Patients	Treatment	Age at treatment (months)	Age threshold for analysis	Overall results	Age related results
Survival and transplant success	Boelens 2007[30]	n=146 H	**HSCT**	18 (median) 1 to 96 (range)	Continuous	Alive &Engrafted: 56% Survival: 85%	A&E: OR 0.98 (95% CI 0.96 to 1.01), p=0.23 Survival: OR 1.02 (95% CI 0.99 to 1.05), p=0.23
	Boelens 2013	n=258 H	**HSCT**	16.7 (median) 2.1 to 228 (range)	16.7 months	Event free survival: 63%	<16.7 mo: 71% >16.7 mo: 55% p=0.02 Younger age HR: 1.6 (1.06 to 2.49) p=0.03
Developmental	Poe 2014[2]	n=31 H	**HSCT**	13.8 (median) 2.1 to 34.3 (range)	Continuous	NR	Cognitive development: β=-0.024, p<0.001 Receptive language: β=-0.022, p=0.004 Expressive language: β=-0.023, p=0.01 Adaptive behaviour: β= -0.013, p=0.03

	Study	Patients	Treatment	Age at treatment (months)	Age threshold for analysis	Overall results	Age related results
Developmental	Bjoraker 2006[31]	n=41 H	HSCT	21.7 (mean) 4.1 to 73 (range)	Continuous	Adaptive function declined over time (absolute scores), but improved compared to age-standardised scores	Communication: NS Daily living: NS Socialisation: NS Motor skills: NS
	Wraith 2007	n=20 (16H, 4HS)	ERT	2.9 y (median) 0.5 to 5.1 y (range)	2.5 years	NR	H patients <2.5y and HS patients: developmental gains similar to the non-MPS I population H patients >2.5y: continued on a flat development trajectory (No data)

	Study	Patients	Treatment	Age at treatment (months)	Age threshold for analysis	Overall results	Age related results
Physical	Tylki-Szymanska 2010 [32]	n=14 treated (at age 1y): 7 H untreated (until after age 3): 3 H, 1 HS, 3 S	ERT	4y (median) 1 to 15 y (range)	1 to 3 years (treated vs. not treated)	<u>Mean Δ height (1-3y)</u> Treated: 36.3 cm Untreated: 36.7 cm p=0.84 <u>Mean Δ weight (1-3y):</u> Treated:10.9 kg Untreated: 11.8 kg P=0.36 <u>Mean Δ head cir. (1-3y)</u> Treated: 19.6 cm Untreated: 17.2 cm p=0.018 <u>Mean Δ neck cir. (1-3y)</u> Treated: 19.4 cm Untreated: 17.9 cm p=0.23	NA
	Circumference; HSCT: hematopoietic stem cell transplant; H: Hurler syndrome; HS: Hurler-Scheie; S: Scheie; NR: Not reported; NS: Not significant; Δ: change in						

Discussion

Overall, a limited body of evidence was identified regarding potential benefits of early treatment following screen detection of MPS I. The body of evidence was limited by uncertainties in terms of directness, volume, methodology (e.g. study design and study size), consistency and applicability.

The identified studies provided no direct assessment of potential treatment benefits following screening vs. clinical detection or cascade testing vs clinical detection for MPS I. None of the studies described participants as detected via screening, and the median age of treatment is more aligned with clinical detection than early treatment following screen detection. Additional research regarding effectiveness following detection or treatment during the newborn phase is needed in order to provide directly applicable evidence to support a population based newborn screening programme.

The six included studies represent a limited volume of evidence. Varied outcomes were reported, both in terms of outcome categories and measurements selected, which further reduces the volume of evidence for either HSCT or ERT. For any given treatment-outcome combination, the volume of evidence was limited to 1 to 2 studies.

Study design and size were key limitations across the entire body of evidence. In order to establish the effectiveness of treatment following a screening programme, randomised controlled trials or prospective cohort studies comparing outcomes in screen vs. clinically detected populations would be required. No studies of this type were identified. Six studies, five of which were small case series, were identified that provide some indication of variation in treatment outcomes by age. However, in order to establish variation in treatment effectiveness by MPS I detection method or age of treatment, larger cohort studies or randomised controlled trials are required.

Three of the four HSCT studies were retrospective case series, of relatively small in size (n=31 to 258) and included Hurler syndrome patients with ages ranging from 1 to 228 months at the time of treatment. The prospective study was small in size (n=41), and included only Hurler patients aged 4 to 73 months at treatment initiation.

In addition, evidence on the association between earlier age at treatment and outcomes among Hurler syndrome patients receiving HSCT was inconsistent. For example in the two largest HSCT studies (n=128 and 258), which reported on similar outcome measures (survival and alive and engrafted status vs. graft failure or death [EFS]). The former study reported no significant differences when age was treated as a continuous variable, while the latter study reported significantly better results among patients under 16.7 months of age. Whether this discrepancy is due to differences in sample size, follow-up duration, lag time bias, or statistical approach is unclear. Similarly in other studies no consistent age effect was seen in terms of adaptive functioning, survival or graft success.

Two studies were identified for ERT, which included a total of 34 patients with MPS phenotype heterogeneity. One study provided a narrative analysis of age related outcomes only, with no supporting data. The other study offered compared outcomes between a group of 7 Hurler syndrome patients and a group of 7 patients of mixed phenotype (3 Hurler, 1 Hurler-Scheie, 3 Scheie). Whether the differences in outcomes between the group were due to variation in treatment or variation in disease severity cannot be determined, and multiple potential interpretations of the results are possible (e.g. study underpowered to detect differences, ERT

improved outcomes in treated Hurler group but impact was lost when compared to outcomes in mixed phenotype group, early treatment with ERT is not associated with changes in growth among MPS I patients).

Summary: Criterion 10 not met.

Overall, the studies required to answer the key question were not identified in the literature. Ideally, randomised controlled trials or prospective cohort studies would be needed in order to determine whether there are benefits to early treatment following screen detection. No direct evidence was identified regarding treatment outcomes in screen vs. clinically detected MPS I populations. Low level evidence was identified that was insufficient to draw firm conclusions on the impact of age at treatment on outcomes.

15. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).

Current UKNSC key question

The current review assesses the evidence base relating to the wider benefits of screening for MPS I, including factors such as reproductive decision making and impact on the diagnostic odyssey. No study type restriction was applied to this key question.

Description of the evidence

Overall, 2 studies were identified as potentially relevant during title and abstract sifting and further assessed at full text, and one small qualitative study[34] was selected for inclusion. This study, which consisted of semi-structured interviews of 17 MPS I patients and their parents, found that all patients experienced a prolonged diagnostic odyssey, and that this delay in diagnosis was a negative experience regardless off MPS I phenotype. Additionally, the availability of disease modifying treatments was identified by all participants as an important missed benefit of a hypothetical early diagnosis. Additionally, some parents suggested that an earlier diagnosis would have influenced their decision to have another child. Overall, five key themes were described:

1) delayed diagnosis causing parental frustration
2) delayed diagnosis causing patient frustration
3) hypothetical early diagnosis enabling reproductive decision-making
4) hypothetical early diagnosis enabling focusing on the diagnosis
5) hypothetical early diagnosis enabling timely initiation of treatment

In addition to the potential benefits of an potential earlier diagnosis, some harms were described, including having less time to come to terms with raising a sick child and losing ‘the good years’ of early childhood, when severe symptoms have not set in, to difficult and potentially harmful treatment courses.

Discussion

The single, small, qualitative study represents a limited body of evidence regarding potential wider benefits of a newborn screening programme for MPS I. The study included patients and parents representing the entire MPS I phenotypic spectrum (Hurler, Hurler-Scheie, Scheie), and reported a universally negative experience due to the prolonged diagnosis. While potential

benefits of a hypothetical early diagnosis were described in terms of a shortened diagnostic odyssey, informed reproductive decisions and potential benefits of earlier treatment, harms of potential early detection were described as well, although these are not specifically linked to early detection due to screening. Additionally, the interview questions focused on a hypothetical earlier diagnosis, not on screening specifically. As all patients were detected clinically or through cascade testing, and not following an MPS I screening programme, it is unknown whether the entire screen testing strategy would be acceptable to these patients, and how the balance of benefits vs. harms of such a programme would impact acceptability. Additionally, as no screen detected cases were included in the study, no non-hypothetical comparison can be made between the impact of diagnosis timing on reproductive decisions and diagnostic odyssey.

Summary: Criterion 15 not met. A single, small qualitative study found that participants thought a hypothetical earlier MPS I diagnosis would be beneficial in terms of preventing patient, parent and family stress during the uncertainty of the diagnostic period; allowing for informed reproductive decisions; and initiating a potentially course altering treatment earlier., However the potential benefits and harms described in the study are based on qualitative questions regarding a hypothetical earlier treatment, not a full screening programme. No studies on the comparative experience of screen vs. clinically detected patients and their families were identified.

16. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (i.e. value for money). Assessment against this criterion should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource.

No studies were identified relating to the cost effectiveness of screening for MPS I.

Conclusions and implications for policy

This report assesses newborn screening for mucopolysaccharidosis type I against select UK National Screening Committee (UK NSC) criteria for appraising the viability, effectiveness and appropriateness of a screening programme.

This review assessed key questions to determine if evidence published since 2004 supports a recommendation for newborn screening of MPS I in the UK. No direct evidence was identified regarding the genotype-phenotype progression, or the effectiveness early treatment following screening, and very limited evidence was identified regarding the clinical validity and utility of a screening test. Evidence regarding MPS I frequency, phenotype, and the natural history of symptom onset was identified, but comparison of evidence from screening and registry based studies suggest that the latter may not detect all cases in a population.

The volume, quality and direction of evidence published since 2004 does not indicate that newborn screening for mucopolysaccharidosis type I should be recommended in the UK. Several uncertainties remain across key criteria, including:

- Lack of robust evidence on the genotype to phenotype relationship, especially among the more attenuated phenotypes. While the evidence suggests that nonsense mutations

including W402X and Q70X are associated with the severe Hurler phenotype, it is not clear based on the identified evidence how many individuals with these IDUA mutations will develop severe MPS I, nor how common these mutations are.

- Lack of evidence regarding the performance of available testing strategies, including no available data on the sensitivity and specificity of MS/MS or fluorometric enzyme assays of IDUA activity. Heterozygous carriers will be detected by the test because of low IDUA levels and more information is required on this. An optimum testing strategy could not be determined from the available evidence.
- Lack of evidence of a benefit of early treatment following screen detection or an optimum age for treatment initiation which is dependent on screen detection. No studies were identified that compared treatment outcomes between clinically presenting and screen or cascade detected patients. Evidence from a global MPS I registry suggests that median age of treatment among Hurler patients is approximately 0.9 years, which is within the current European recommendations, and younger than cutoff used in the single study that suggested a potential benefit of cognitive development with earlier treatment (i.e. younger than 16.7 months) In order to establish the additional benefit of early treatment opportunities presented by screen detection, sufficiently large studies that assess variation in outcomes according to age of treatment initiation, with analyses using screening relevant age cutoffs (i.e. newborns or infants), are necessary.
- Available methods for the assessment of α-L-iduronidase activity are unable to distinguish between clinical phenotypes and published clinical guidelines do not address the diagnostic and treatment pathways for MPS I following screen detection. As current treatment options vary according to MPS I phenotype and an optimum time for treatment initiation which is reliant on newborn screening has not been identified, the advantages of screening over current approaches are difficult to discern on the basis of the evidence included in this review.

Search strategy

MEDLINE (Ovid)

1 mucopolysaccharidosis i/ (1563)

2 (Mucopolysaccharidosis or Hurler* or Scheie* or Pfaundler-Hurler* or (alpha-L-Iduronidase adj3 deficiency) or Gargoylism or Lipochondrodystrophy).ti,ab. (4157)

3 MPS 1.ti,ab. (93)

4 Iduronidase/ (542)

5 or/1-4 (4557)

6 limit 5 to english language (3740)

7 limit 6 to yr="2004 -Current" (1609)

EMBASE (Ovid)

1 mucopolysaccharidosis/ or hurler syndrome/ or scheie syndrome/ (2579)

2 (Mucopolysaccharidosis or Hurler* or Scheie* or Pfaundler-Hurler* or (alpha-L-Iduronidase adj3 deficiency) or Gargoylism or Lipochondrodystrophy).ti,ab. (2932)

3 MPS 1.ti,ab. (90)

4 levo iduronidase/ (595)

5 or/1-4 (4195)

6 limit 5 to (english language and yr="2004 -Current") (3057)

7 limit 6 to exclude medline journals (215)

Cochrane Library

Including: Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database (HTA), NHS Economic Evaluation Database (EED)

#1 MeSH descriptor: [Mucopolysaccharidosis I] this term only (15)

#2 (Mucopolysaccharidosis or Hurler* or Scheie* or Pfaundler-Hurler* or Gargoylism or

Lipochondrodystrophy):ti,ab (62)

#3 (alpha-L-Iduronidase near/3 deficiency):ti,ab (3)

#4 "MPS 1":ti,ab (10)

#5 MeSH descriptor: [Iduronidase] this term only (9)

#6 #1 or #2 or #3 or #4 or #5 Publication Year from 2004 to 2014 (65)

Appendices

Appendix number	1
Relevant criteria	2
Publication details	[10] Baehner F, Schmiedeskamp C, Krummenauer F, et al. Cumulative incidence rates of the mucopolysaccharidoses in Germany. J Inherit Metab Dis. 2005;28(6):1011-7.
Study details	Retrospective observational study, Germany
Study objectives	To determine the incidence of mucopolysaccharidoses in Germany.
Inclusions	NR
Exclusions	Prenatal MPS diagnoses
Population	n=93 MPS I cases between 1980 and 1995 in Germany; case ascertainment from several sources, including: membership list from German Society for MPS; patient records from Children's Hospital, University of Mainz and Pediatric Department at the University of Hamburg; laboratory records from five German Universities. All cases confirmed via enzyme assays in serum, leukotypes and/or fibroblasts.
Intervention/test	NA
Comparator	NA
Results	<u>Crude incidence MPS I, 1980 to 1995</u> Overall: 1:144,203 [RC] Hurler: 1:163,548 [RC] Hurler-Scheie: 1:3,352,731 [RC] Scheie: 1:1,915,846 [RC] <u>MPS I Phenotype distribution 1980 to 1995, n (% of MPS I)</u> Hurler: 82 (88.2%) Hurler-Scheie: 4 (4.3%) Scheie: 7 (7.5%)
Comments	Unclear if detected cases represent all MPS cases during the study period; detection difficult due to rarity of MPS, diagnostic difficulties (especially for attenuated phenotypes) and lack of centralised recording and obligatory reporting of cases. Individual phenotype incidence estimates are subject to

	greater uncertainty due to the overlap in clinical symptoms and potential for misdiagnosis. Results may underestimate true incidence in Germany. Incidence figures calculated based on German Bureau of Statistics data on live births from 1980 to 1995. Methods do not confirm that all reported cases were born between 1980 and 1995 vs. diagnosed during that time period; if the latter method was used, results may overestimate MPS I incidence. Detection method of MPS I cases not reported; unclear if cases presented clinically or asymptomatically following cascade-testing.

Appendix number	2
Relevant criteria	2
Publication details	[35] Boy R, Schwartz IV, Krug BC, et al. Ethical issues related to the access to orphan drugs in Brazil: the case of mucopolysaccharidosis type I. J Med Ethics. 2011;37(4):233-9.
Study details	Cross-sectional, Brazil
Study objectives	To determine the demographic profile of MPS I patients in Brazil
Inclusions	NR
Exclusions	NR
Population	MPS I patients in Brazil between January and September 2008; case ascertainment from multiple sources, including physicians, public institutions and non-governmental organisations involved in the diagnosis and management of MPS I. Prevalence estimates based on Brazilian population estimate of 184m.
Intervention/test	NA
Comparator	NA
Results	<u>Estimated minimum MPS I prevalence, 2008</u> Overall: 1:2,700,000
Comments	Figures represent minimum estimated prevalence. Difficulties in case ascertainment (lack of centralised MPS I database/registry, no mandatory reporting) risks underestimating prevalence. No information reported on the number of data requests distribute; response rate and resultant risk of bias unclear. Prevalence estimates based on 'current' (date not reported) Brazilian population of 184 million.

	Detection method of MPS I cases not reported; unclear if cases presented clinically or asymptomatically following cascade-testing.

Appendix number	3
Relevant criteria	2, 5
Publication details	[16] Lin SP, Lin HY, Wang TJ, et al. A pilot newborn screening program for Mucopolysaccharidosis type I in Taiwan. Orphanet J Rare Dis. 2013;8:147.
Study details	Pilot screening programme, Taiwan
Study objectives	To determine whether measuring IDUA activity in dried blood on filter paper was effective in newborn screening for MPS I and to determine the birth prevalence of MPS I in Taiwan.
Inclusions	NR
Exclusions	NR
Population	n=35,285 newborns screened between 1 October, 2008 and 30 April 2013.
Test	Two stage (test/retest using same DBS sample) fluorometric enzyme assay for IDUA activity using DBS collected on third day of life. IDUA threshold: <9.03 µmol/L blood*20hr. Follow-up diagnostic/reference tests: recheck of 2nd DBS; confirmatory tests include urine GAG quantification, urinary GAG two-dimensional electrophoresis, leukocyte IDUA activity, and molecular DNA analysis.
Comparator	NA

<table>
<tr><td>Results</td><td>
Criterion 2

MPS I incidence: 1:17,643

Criterion 5

Stage 1 screen: 58 newborns IDUA activity <9.03 µmol/L blood*20h

Stage 2 screen (same DBS sample): 19 newborns IDUA activity <9.03 µmol/L blood*20h

Diagnostic tests: 2nd DBS sample, 3 newborns had IDUA activity <9.03 µmol/L blood*20h; 2 newborns confirmed MPS I following further diagnostic tests (urine GAG quantification, urinary GAG two-dimensional electrophoresis, leukocyte IDUA activity, and molecular DNA analysis).
<table>
<tr><td></td><td></td><td>Confirmed MPS I status</td><td></td></tr>
<tr><td></td><td></td><td>+</td><td>-</td></tr>
<tr><td rowspan="2">Screening test</td><td>+</td><td>2</td><td>17</td></tr>
<tr><td>-</td><td>NR</td><td>NR</td></tr>
</table>
PPV: 10.5% (Reviewer calculated, based on second stage screen figures)
</td></tr>
<tr><td colspan="2">Quality appraisal
<table>
<tr><th>Question</th><th>Assessment (Y, N, unclear)</th><th>Risk of Bias (low, high, unclear)</th><th>Supporting info</th></tr>
<tr><td colspan="4">Domain I: Patient selection</td></tr>
<tr><td>Consecutive or random sample of population enrolled?</td><td>Unclear</td><td>Unclear</td><td>Reported >35K newborns screened between 2008-2013; does not report programme selection methods.</td></tr>
<tr><td>Case-control design avoided?</td><td>Y</td><td>Low</td><td>Not a case control study.</td></tr>
<tr><td>Inappropriate exclusions avoided?</td><td>Unclear</td><td>Unclear</td><td>Does not report programme selection methods or inclusion/exclusion criteria</td></tr>
<tr><td colspan="4">Domain II: Index Test</td></tr>
<tr><td>Index test results interpreted without knowledge of reference standard results?</td><td>Y</td><td>Low</td><td>Multi-step screening diagnostic process; index test preceded reference standard.</td></tr>
<tr><td>Threshold pre-specified?</td><td>Y</td><td>Low</td><td>Reference values for IDUA activity established using a subsample of DBS</td></tr>
</table>
</td></tr>
</table>

			(n=2,173).
Domain II: Reference standard			
Reference standard likely to correctly classify condition?	Y	Low	Multi-assay diagnostic panel, including urine GAG quantification, urinary GAG two-dimensional electrophoresis, leukocyte IDUA activity, and molecular DNA analysis.
Reference standard results interpreted without knowledge of index test results?	Unclear	Unclear	Blinding of diagnostic assays not reported.
Domain IV: Test strategy flow and timing			
Appropriate interval between index test and reference standard?	Y	Low	No anticipated change in IDUA activity between screening and diagnostic tests; no treatment reported following index test results.
Did all participants receive same reference standard?	N	High	MPS I status of screen negatives not tested; not possible to determine if two true positives represent all MPS I patients from the screening sample.
All patients included in analysis?	N	High	Not possible to calculate Sn, Sp or NPV due to lack of data on negative tests true MPS I status.
Applicability			
Applicable to UK screening population of interest?	Unclear	Unclear	Population (newborns), test methods (DBS) applicable to the UK. Test timing (DBS at day three) is earlier than UK procedures, and the only performance indicator available was PPV, which could vary due to prevalence difference between Taiwan and UK.
Applicable to UK screening test of interest?	N	Unclear	DBS timing earlier than UK, and the only performance indicator available was PPV, which could vary due to prevalence difference between Taiwan and UK.
Target condition measured by reference test applicable to UK screening condition of interest?	Y	Low	MPS I

Other comments

Sn, Sp, NPV cannot be calculated based on reported data. As only screen positive samples underwent confirmatory diagnostic testing, it is not known whether incidence figures represents the true burden of MPS I in this population; if the samples included any false negative screen tests, the 1:17,643 may underestimate the true incidence. Reference IDUA values: Newborn control – 9.03 to 69.52 µmol/L blood*20h MPS I Carriers – 9.40 to 19.82 µmol/L blood*20h (4 parents of confirmed MPS I patients)

Appendix number	4
Relevant criteria	2
Publication details	[8] Moore D, Connock MJ, Wraith E, et al. The prevalence of and survival in Mucopolysaccharidosis I: Hurler, Hurler-Scheie and Scheie syndromes in the UK. Orphanet J Rare Dis. 2008;3:24.
Study details	Retrospective observational study, UK
Study objectives	To assess the prevalence and natural history of MPS I in the UK.
Inclusions	Inclusion in the Society for Mucopolysaccharide Diseases registry (UK).
Exclusions	NR
Population	n=196 patients with longitudinal data in Society for Mucopolysaccharide Diseases registry over the period of 1981 to 2003.
Intervention/test	NA
Comparator	NA
Results/outcomes	<u>Birth prevalence of MPS I, 1981 to 2003 [RC]</u> Overall: 1:93,480 Hurler: 1:132,298 Hurler-Scheie: 1:410,822 Scheie: 1:1,419,202 <u>MPS I Phenotype distribution 1981 to 2003, n= (% of MPS I)</u> Hurler: 118 (70.7%) Hurler-Scheie: 38 (22.8%) Scheie: 11 (6.6%) <u>Mortality 1981 to 2005, % (n)</u> Overall: 43.4% (85/196) Hurler: 55.2% (79/143)

	Hurler-Scheie: 12.2% (5/41) Scheie: 8.3% (1/12) <u>Median survival, years (95% CI)</u> Overall: 11.6 (9.5 to 13.7) Hurler: 8.7 (7.6 to 9.7) Hurler-Scheie: Median not calculable; mean 21.6 (19.3 to 24.0) Scheie: Not calculable
Comments	2003 selected in order to prevent biases due to late diagnosis among younger cases. Of the 196 MPS I patients 85 had died. Registry attempts to enrol all MPS patients in the UK; coverage is reported as very high/near complete. Prevalence estimates based on three year average MPS I births and three year average births in England and Wales, to account for year on year variations in diagnoses. Survival analysis included all available registry data (1981 to 2005). Detection method of MPS I cases not reported; unclear if cases presented clinically or asymptomatically following cascade-testing.

Appendix number	5
Relevant criteria	2
Publication details	[9] Murphy AM, Lambert D, Treacy EP, et al. Incidence and prevalence of mucopolysaccharidosis type 1 in the Irish republic. Arch Dis Child. 2009;94(1):52-4.
Study details	Retrospective observational study, Republic of Ireland
Study objectives	To assess the incidence and prevalence of MPS I in Ireland.
Inclusions	NR
Exclusions	NR
Population	N=31 MPS I patients in Ireland between 2001 and 2006; case ascertainment via database and chart review from the two specialist centres treating MPS I.
Intervention/test	NA
Comparator	NA
Results	<u>Incidence of MPS I Hurler, 2001 to 2006 [RC]</u> Overall: 1:26,206

	Traveller: 1:371 Non-Traveller: 1:120,938 <u>MPS I Phenotype distribution among prevalent cases 2002, n= (% of MPS I)</u> Hurler: 26 (83.9%) Hurler-Scheie: 4 (12.9%) Scheie: 1 (3.2%) <u>Age at diagnosis among prevalent Hurler cases 2002, range</u> Clinical presentation (n=14): 3 months to 7 years Family screening (n=12): Antenatal to 9 months <u>Age at diagnosis among prevalent Hurler-Scheie cases 2002, range</u> Clinical presentation (n=4): 4 to 7.5 years <u>Age at diagnosis of prevalent Scheie case 2002</u> Clinical presentation (n=1): 8 years <u>Genotype among prevalent MPS I cases, 2002</u> Hurler: 22/26 (84.6%) W402X/W402X; 1/26 (3.8%) W402X/Q70X; 1/26 (3.8%) W402X/A75T; 1/26 (3.8%) W402X/unknown; 1/26 (3.8%) Q70X/Q70X 12/12 (100%) detected via family screening W402X/W402X 10/14 (71.4%) detected clinically W402X/W402X Hurler-Scheie: 3/4 (75%) W402X/P496L; 1/4 (25%) R89W/C964delC Scheie: 1/1 (100%) W402X/C678/7G-A
Comments	Over half of Hurler patients detected via cascade testing; may account for high prevalence of homozygous W402X in this small subgroup. Small study (n=31) with high proportion of cases in Irish Traveller population; may not be representative of UK cases as a whole.

Appendix number	6
Relevant criteria	2
Publication details	[12] Pastores GM, Arn P, Beck M, et al. The MPS I registry: design, methodology, and early findings of a global disease registry for monitoring patients with Mucopolysaccharidosis Type I. Mol Genet Metab. 2007;91(1):37-47.
Study details	Cross-sectional study, Global
Study objectives	To present early findings from the global MPS I registry

Inclusions	NR
Exclusions	NR
Population	n=302 MPS I cases enrolled in the global MPS I registry since October 2003; enrolment in the registry is voluntary. All included cases had confirmed diagnosis by enzyme assay or mutation analysis.
Intervention/test	NA
Comparator	NA
Results	Phenotype distribution Hurler: 47% Hurler-Scheie: 25% Scheie: 13% Unknown: 15% Age of diagnosis (years) among cases with neither family history nor presymptomatic diagnosis, median (range) Hurler: 0.8 (0.2 to 6.8) Hurler-Scheie: 3.9 (0.2 to 36.1) Scheie: 9.3 (1.9 to 54.1) Unknown: 4.8 (0.3 to 14.7) Interval from symptom onset to diagnosis (years) among cases with neither family history nor presymptomatic diagnosis, median (range) Hurler: 0.3 (0.0 to 2.3) Hurler-Scheie: 0.9 (0.0 to 9.3) Scheie: 1.5 (0.0 to 47.3) Unknown: 0.2 (0.0 to 1.8)
Comments	Completeness of enrolled patients unclear. Phenotype distribution based on prevalent (living cases), unclear if distribution is representative of all MPS I patients. Age at diagnosis available for clinically presenting cases with no family history only.

Appendix number	8
Relevant criteria	2
Publication details	[6] Bertola F, Filocamo M, Casati G, et al. IDUA mutational profiling of a cohort of 102 European patients with mucopolysaccharidosis type I: identification and

	characterization of 35 novel alpha-L-iduronidase (IDUA) alleles. Hum Mutat. 2011;32(6):E2189-210.
Study details	Cross-sectional, Europe
Study objectives	To determine genotype of a cohort of MPS I patients and identify novel IDUA alleles
Inclusions	NR
Exclusions	NR
Population	n=102 unrelated individuals (37 Italian, 23 Polish, 21 Turkish, 18 Spanish, and 3 patients each from Hungary, Serbia and Greece) with clinically and biochemically diagnosed MPS I. Patients recruited via their attending clinicians or through Genzyme Corporation as part of a global project to register all MPS I patients. All 14 exons, splice junctions and proximal portions of the 5' and 3' untranslated regions of the IDUA genes of the 102 unrelated MPS I patients were investigated by DNA sequence analysis.
Intervention/test	NA
Comparator	NA
Results	<u>Phenotype distribution, n (%)</u> Hurler: 60/102 (58.8%) Hurler-Scheie: 22/102 (21.6%) Scheie: 15/102 (14.7%) Intermediate Hurler/Hurler-Scheie: 1/102 (1.0%) Intermediate Hurler-Scheie/Scheie: (1.0%) Unknown: 3/102 (2.9%) <u>Mutational analysis</u> 55 distinct IDUA mutations were identified, including: 22 missense mutations (40%), 14 splice site alterations (25%), 9 micro-deletions (16%), 5 nonsense mutations (9%), 3 micro-duplications (5%), 1 translational initiation site mutation (2%) and 1 no-stop mutation (2%). 35/55 (64%) mutations were novel. High mutational heterogeneity; 68 distinct genotypes were identified. 45/102 (44%) were either homozygous for common W402X (n=12), Q70X (n=9) and P533R (n=3) mutations, other known mutations (n=7) or novel lesions (n=14). 55/102 (54%) were compound heterozygous (including n=7 with an unidentified second mutant IDUA allele).

	2/102 (2%) had no identified IDUA mutations. IDUA mutation frequency in 102 MPS I patients Q70X: 18.6% W402X: 18% G51D: 4.9% P496R: 4.4% P533R: 3.9% A327P: 2.4% 46_57del12: 3.9%
Comments	Unclear how complete/representative the included patients were of all MPS I patients in the participating countries. Applicability of the identified genotypes to at UK population is unclear. "Extensive allelic heterogeneity often precludes the recognition of correlations between mutant genotypes and variant clinical phenotypes." "Another factor limiting our ability to define effective genotype-phenotype correlations was probably our difficulty in attributing one or other clinical phenotype in a given case, bearing in mind that the clinical spectrum of disease in MPS I is in reality a continuum of phenotypes with gradually changing severity. This is particularly true for the so called 'intermediate form', where it is difficult to be truly objective, especially when the patients are young at the time of diagnosis and there is no standardized scoring index of severity." "The existence of dramatic differences in mutational heterogeneity and mutation prevalence highlights the importance of multi-national screening studies in helping to elucidate the genotype-phenotype relationship in disorders such as MPS I that are characterized by extensive allelic heterogeneity."

Appendix number	9
Relevant criteria	2
Publication details	[14] Munoz-Rojas MV, Bay L, Sanchez L, et al. Clinical manifestations and treatment of mucopolysaccharidosis type I patients in Latin America as compared with the rest of the world. J Inherit Metab Dis. 2011;34(5):1029-37.
Study details	Cross-sectional, Global
Study objectives	To compare MPS I phenotype distribution and natural history between Latin America and the rest of the world
Inclusions	Confirmed MPS I diagnosis

<table>
<tr><td>Exclusions</td><td>None</td></tr>
<tr><td>Population</td><td>Patients enrolled in the global MPS I registry as of September 2009.</td></tr>
<tr><td>Intervention/test</td><td>NR</td></tr>
<tr><td>Comparator</td><td>NR</td></tr>
<tr><td>Results</td><td><u>Phenotype distribution, n (%)</u>
<table>
<tr><td>Phenotype</td><td>Global (n=845)</td><td>Latin America (n=118)</td><td>Rest of World (n=727)</td></tr>
<tr><td>Hurler</td><td>489 (58%)</td><td>37 (31%)</td><td>452 (62%)</td></tr>
<tr><td>Hurler-Scheie</td><td>196 (23%)</td><td>43 (37%)</td><td>153 (21%)</td></tr>
<tr><td>Scheie</td><td>91 (11%)</td><td>12 (10%)</td><td>79 (11%)</td></tr>
<tr><td>Unknown</td><td>69 (8%)</td><td>26 (22%)</td><td>43 (6%)</td></tr>
</table></td></tr>
<tr><td>Comments</td><td>Registry allows posthumous enrolment in order to enhance data on MPS I natural history.

Unclear how complete/representative registry is, but authors report “the design and methodology of the program have enabled the acquisition of a population sample that is diverse in its composition and representative of the heterogeneous nature of MPS I.”

Age of symptom onset and diagnosis displayed graphically, but data cannot be extracted with precision.</td></tr>
</table>

Appendix number	10
Relevant criteria	2
Publication details	[1] Beck M, Arn P, Giugliani R, et al. The natural history of MPS I: global perspectives from the MPS I Registry. Genet Med. 2014;16(10):759-65.
Study details	Prospective cohort study, Global
Study objectives	To describe the natural history of MPS I.
Inclusions	Enrolment in the MPS I Registry as of August 2013. No treatment, or data prior to treatment.
Exclusions	NR
Population	987 patients enrolled in the MPS I Registry as of August 2013. Geographic distribution: Europe (45.5%), North America (34.8%), Latin America (17.3%), Asia Pacific (2.4%).

Intervention/test	NA
Comparator	NA
Results/outcomes	Phenotype distribution, n (%) Hurler: 601 (60.9%) Hurler-Scheie: 227 (23.0%) Scheie: 127 (12.9%) Unknown: 32 (3.2%) Median age (years) at symptom onset, Overall/Europe Hurler: 0.5/0.5 Hurler-Scheie: 1.8/2.0 Scheie: 5.3/4.9 Median age (years) at diagnosis, Overall/Europe Hurler: 1/0.9 Hurler-Scheie: 4.0/3.6 Scheie: 9.4/9.4 Median age (years) at treatment initiation, Overall/Europe Hurler: 1.5/1.4 Hurler-Scheie: 8.0/6.8 Scheie: 16.9/16.9 Symptom presentation by phenotype, age of onset (%) **Hurler** Before age 1: Hernia (58.9%), Coarse facial features (86.4%) Aged 1-2: Kyphosis/gibbus (70.0%), dysostosis multiplex (43.6%), corneal clouding (70.9%), hepatomegaly (70.0%), sleep disturbances/snoring (51.6%), enlarged tongue (41.3%), splenomegaly (50.9%), cognitive impairment (46.4%), cardiac valve abnormalities (48.9%), enlarged tonsils (28.6%), joint contractures (37.9%) **Hurler-Scheie:** Before age 3: none Age 3-3.9: Hernia (59.9%), Coarse facial features (72.7%), Cognitive impairment (31.3%) Age 4-4.9: enlarged tongue (38.3%), sleep disturbances/snoring (48.9%), enlarged tonsils (33.0%), dysostosis multiplex (37.4%), joint contractures (57.3%), corneal clouding (68.3%), hepatomegaly (66.5%), kyphosis/gibbus (33.5%), splenomegaly (47.1%)

	Age >5: Cardiac valve abnormalities (59.0%), hip dysplasia (25.6%), carpal tunnel syndrome (27.8%) **Scheie:** Before age 4: none Age 4-4.9: Hernia (53.5%), Age 7-7.9: Joint contractures (69.3%) Age 8-9.9: Dysostosis multiplex (35.4%), Hip dysplasia (25.2%), Sleep disturbances/snoring (26.8%), Coarse facial features (48.0%), Hepatomegaly (48.0%) Age >10: Corneal clouding (70.1%), splenomegaly (27.6%), cardiac valve abnormalities (67.7%), carpal tunnel syndrome (51.2%)
Comments	Detection methods not reported (unclear proportion of included patients detected clinically vs. cascade screening). Same registry as that presented in Pastores 2007 (later analysis date with more participants; some overlap exists with first 302 patients enrolled).

Appendix number	11
Relevant criteria	2
Publication details	[13] D'Aco K, Underhill L, Rangachari L, et al. Diagnosis and treatment trends in mucopolysaccharidosis I: findings from the MPS I Registry. Eur J Pediatr. 2012;171(6):911-9.
Study details	Prospective registry study, Global
Study objectives	To assess the epidemiology and natural history of MPS I globally.
Inclusions	NR
Exclusions	NR
Population	n=891 patients enrolled in the international MPS I registry as of March 2010. Geographic distribution: 46.6% Europe and the Middle East, 35.1% North America, 14.9% Latin America, and 3.4% Asia Pacific.
Intervention/test	NA
Comparator	NA
Results	<u>Phenotype distribution, n (%)</u> Hurler: 508 (57.0%) Hurler-Scheie: 209 (23.5%) Scheie: 97 (10.9%)

	Unknown: 77 (8.6%) <u>Age (years) at symptom onset, median (range)</u> Hurler: 0.5 (0.0 to 6.5) Hurler-Scheie: 1.9 (0.0 to 12.4) Scheie: 5.4 (0.0 to 33.8) <u>Age (years) at diagnosis, median (range)</u> Hurler: 0.8 (0.0 to 23.8) Hurler-Scheie: 3.8 (0.0 to 38.7) Scheie: 9.4 (0.0 to 54.1) <u>Age (years) at treatment initiation, median (range)</u> Hurler: 1.4 (0.1 to 31.2) Hurler-Scheie: 8.6 (0.3 to 47.2) Scheie: 17.1 (3.1 to 62.9) <u>Age (years) at death, median (range)</u> Hurler: 3.8 (0.4 to 27.2) Hurler-Scheie: 17.4 (7.5 to 30.3) Scheie: 29.0 (17.4 to 46.6)
Comments	Range of age at diagnosis, treatment and death amongst Hurlers patients suggests misdiagnosis/misclassification. Discrepancy in age at treatment and age of death range amongst Hurler patients (maximum age in mortality range is less than the maximum reported age of treatment value, suggesting inconsistencies or errors in data reporting). Risk of incomplete/missing/inaccurate data due to voluntary enrolment in MPS I registry, loss to follow-up and lack of standardisation in patient assessments. Additionally, not all doctors who treat MPS I patients use the registry.

Appendix number	12
Relevant criteria	2
Publication details	[15] Thomas JA, Beck M, Clarke JT, et al. Childhood onset of Scheie syndrome, the attenuated form of mucopolysaccharidosis I. J Inherit Metab Dis. 2010;33(4):421-7.
Study details	Prospective registry study, Global

Study objectives	To assess the natural history of MPSI Scheie patients.
Inclusions	NR
Exclusions	NR
Population	n=78 Scheie patients enrolled in the MPS I registry from October 2003 and October 2008. Mean (SD) age 22.9y (13.6), median (range) 17.5y (1.8 to 62.9).
Intervention/test	NA
Comparator	NA
Results	Age (years) at symptom onset, median (range) 5.4 (birth to 33.8) Age (years) at diagnosis, median (range) 9.8 (antenatal to 54.1) Natural history of symptom onset by age (n=72) Age <5: Hernia Age 5-12: 18 clinical features, mostly involving infiltration and enlargement of soft tissues or joint and bone complications. Adolescence: scoliosis, carpal tunnel syndrome, and congestive heart failure Early Adulthood: glaucoma, cardiomyopathy, and myelopathy No single symptom emerged as the first sign in a majority of patients. Hernia and joint contractures each appeared as a first sign in approximately 30%, but hernia was more often reported as an isolated finding at birth or within the first year of life, whereas joint contractures usually appeared after age 2 and more often in conjunction with other disease manifestations. Median (range) number of clinical features per patient: 7 (0–15). % reporting top five features, median age onset (% reporting) Cardiac valve abnormalities: 7.2y (87.7%) Joint contractures: NR (>90%) Corneal clouding: 9.1y (81.8%) Carpal tunnel syndrome: 13.1y (66.7%) Hernia: 3.3y (65.1%) % Scheie patients reporting top five most prevalent features 5: 31.0% 4: 18.3% 3: 25.4% 2: 14.1%

	1: 5.6% 0: 5.6%
Comments	Two participants diagnosed presymptomatically due to sibling with MPS I, one antenatal diagnosis, one at age 5. "Three syndromes are not rigorously defined and cannot currently be distinguished by biochemical criteria or genotype in most cases." Syndrome classification depends on the judgement of the treating clinician, and may not be standard across all included patients. Misclassification suggested by some features, including diagnosis before age 18 months, and presence of coarse facial features and cognitive impairment, not typical features of the Scheie phenotype. Despite this being one of the larger cohorts of Scheie patients, the sample sizes is still small, limiting conclusions on the natural history of this rare phenotype.

Appendix number	13
Relevant criteria	2
Publication details	[7] Vijay S, Wraith JE. Clinical presentation and follow-up of patients with the attenuated phenotype of mucopolysaccharidosis type I. Acta Paediatr. 2005;94(7):872-7.
Study details	Case series, UK
Study objectives	To assess the heterogeneity and severity of symptoms amongst attenuated MPS I patients.
Inclusions	Attendance at the MPS clinic in Machester.
Exclusions	NR
Population	n=29 (19 female/10 male) attenuated MPS I (i.e. Hurler-Scheie or Scheie) patients; year of study not reported.
Intervention/test	NA
Comparator	NA
Results/outcomes	<u>Age (years) of symptom onset, median (range)</u> Attenuated (n=25): 2 (0.33 to 9) Hurler-Scheie (n=15): 1.4 (0.33 to 6) Sheie (n=10): 3 (0.75 to 9) <u>Age (years) of diagnosis, median (range)</u>

Attenuated (n=25): 5 (1.3 to 40)
Hurler-Scheie (n=15): 4 (1.3 to 32)
Sheie (n=10): 7 (2.5 to 40)

Symptoms at clinical presentation and overall, %

Symptom	At presentation			Developed over time		
	Total	H-S	S	Total	H-S	S
Joint stiffness	44%	40%	50%	86%	79%	100%
Corneal clouding	28%	13%	50%	83%	89%	70%
Recurrent ENT	20%	27%	10%	62%	58%	70%
Umbilical hernia	16%	27%	10%	72%	74%	70%
Hearing	12%	20%	-	52%	47%	60%
Fixed flexion	8%	-	20%	24%	16%	40%
Coarse facial	8%	13%	-	66%	79%	40%
Hepatomegaly	8%	13%	-	55%	63%	40%
Squint	8%	13%	-	7%	11%	-
Motor delay	8%	13%	-	-	-	-
Short stature	8%	13%	-	-	-	-
Delayed speech	8%	7%	10%	34%	37%	30%

Genotype, number of alleles (% of total alleles)

Mutation	Total	H-S	S
L490P	14 (24%)	12 (32%)	2 (10%)
W402X	12 (21%)	5 (13%)	7 (35%)
P533R	5 (9%)	5 (13%)	-
Q70X	3 (5%)	2 (5%)	1 (5%)
678-7g->a	3 (5%)	-	3 (15%)
P496L	2 (3%)	-	2 (10%)
A319V	2 (3%)	2 (5%)	-
R619X	2 (3%)	2 (5%)	-
A36E	2 (3%)	2 (5%)	-
S633L	1 (2%)	1 (3%)	-
R89Q	1 (2%)	1 (3%)	-
Q380R	1 (2%)	1 (3%)	-
R621X	1 (2%)	1 (3%)	-
C664insC	1 (2%)	-	1 (5%)
C974ins12	1 (2%)	-	1 (5%)
Unidentified	7 (12%)	4 (11%)	3 (15%)

Comments

ENT: ear, nose and throat

4 patients detected via cascade screening; not included in symptom

	onset/diagnosis data. Small sample size should be considered when interpreting frequency distributions

Appendix number	14
Relevant criteria	2, 5
Publication details	[26] Scott CR, Elliott S, Buroker N, et al. Identification of infants at risk for developing Fabry, Pompe, or mucopolysaccharidosis-I from newborn blood spots by tandem mass spectrometry. J Pediatr. 2013;163(2):498-503.
Study details	Pilot screening programme, USA
Study objectives	To determine the performance of a multiplex MS/MS assay of lysosomal storage disorders in a screening population.
Inclusions	NR
Exclusions	NR
Population	n=106,526 DBS samples from newborns (sex not reported) in Washington State, USA. Years of sample collection not reported.
Test	Multiplex MS/MS for three lysosomal storage disorders (Pompe disease, Fabry disase, MPS I) using DBS; day of collection not. α-L-iduronidase threshold 1.15 µmol/h/L (<32% of average population enzyme activity levels). Diagnosis in positive screens was confirmed by sequence analysis using a second punch from the same DBS sample.
Comparator	NA
Results/outcomes	**Criterion 2** Birth prevalence: 1:35,700 (95% CI 1:1243,000 to 1:11,000) **Criterion 5** 9 neonates screened positive for reduce α-L-iduronidase activity; 3/9 confirmed via sequence analysis. 1 of the false positives (according to MPS I related nucleotide changes) was a carrier, 2 were the result of poor punch cards, and three had no identifiable MPS I mutations (wild type/wild type).

		MPS I consistent nucleotide changes	
		+	**-**
Screening test	**+**	3	6

	-	NR	NR

PPV: 33% (95% CI 8% to 65%)

Quality appraisal

Question	Assessment (Y, N, unclear)	Risk of Bias (low, high, unclear)	Supporting info
Domain I: Patient selection			
Consecutive or random sample of population enrolled?	Unclear	Low	NR, but >100,000 samples from an existing newborn screening programme; low risk of bias.
Case-control design avoided?	Y	Low	Not case control
Inappropriate exclusions avoided?	Unclear	Low	No exclusion criteria reported, however, risk of bias low based on use of NBS sample.
Domain II: Index Test			
Index test results interpreted without knowledge of reference standard results?	Y	Low	Staged testing strategy, screen test conducted and analysed prior to reference test.
Threshold pre-specified?	Y	Low	Threshold set at <32% total sample activity. Sample drawn from existing NBS programme.
Domain III: Reference standard			
Reference standard likely to correctly classify condition?	Unclear	Unclear	No clinical follow-up to confirm diagnosis, confirmation based on presence of MPS I associated mutations. Three samples had nucleotide changes consistent with MPS I; one sample identified as a carrier of a known mutation; three samples had no identified nucleotide change; two had low activity due to poor punch from DBS card. Unclear if the three samples with no identified nucleotide change had novel or 'private' mutations that could account for low enzyme activity.
Reference standard results interpreted without knowledge of	Unclear	Unclear	Reference test conducted for screen positive samples only; unclear whether reference test was blinded to original

index test results?			screening result.
Domain IV: Test strategy flow and timing			
Appropriate interval between index test and reference standard?	Y	Low	Index and reference test conducted using same DBS sample (different punches).
Did all participants receive same reference standard?	N	High	MPS I status of screen negatives not tested; not possible to determine if 3 true positives represent all MPS I patients from the screening sample.
All patients included in analysis?	N	High	Not possible to calculate Sn, or NPV due to lack of data on negative tests true MPS I status.
Applicability			
Applicable to UK screening population of interest?	Unclear	Unclear	Population (newborns), sample source (DBS) applicable to the UK. Test timing is not reported, and the only performance indicator reported was PPV, which could vary due to prevalence difference between Italy and UK. Specificity was calculated assuming that FPR=1-Sp; however, the derivation of the FPR was not explicitly reported in the study.
Applicable to UK screening test of interest?	Y	Low	MS/MS of DBS is applicable to a UK screening programme
Target condition measured by reference test applicable to UK screening condition of interest?	Y	Low	MPS I

Other comments

Average enzyme levels of whole sample: 3.6 µmol/h/L.

Sn, Sp, NPV cannot be calculated based on reported data.

The reference standard used to confirm MPS I status was MPS II associated nucleotide changes, and not based on clinical follow-up. It is unclear if all three of the detected cases were ultimately clinically significant (i.e. developed one of the MPS I phenotypes).

<table>
<tr><td>Appendix number</td><td>15</td></tr>
<tr><td>Relevant criteria</td><td>2, 5</td></tr>
<tr><td>Publication details</td><td>[17] Paciotti S, Persichetti E, Pagliardini S, et al. First pilot newborn screening for four lysosomal storage diseases in an Italian region: identification and analysis of a putative causative mutation in the GBA gene. Clin Chim Acta. 2012;413(23-24):1827-31.</td></tr>
<tr><td>Study details</td><td>Pilot screening programme, Italy</td></tr>
<tr><td>Study objectives</td><td>To report the outcomes of a 2.5 year pilot screening programme for four lysosomal storage disorders, including MPS I.</td></tr>
<tr><td>Inclusions</td><td>NR</td></tr>
<tr><td>Exclusions</td><td>NR</td></tr>
<tr><td>Population</td><td>n=3,403 newborns (1,702 male/1,701 female) in Umbria, Italy born between January 2010 and June 2012.</td></tr>
<tr><td>Test</td><td>Two stage multiplex fluorometric enzyme assay for four lysosomal storage disorders (Pompe disease, Gaucher disease, Fabry disase, MPS I) using DBS collected on day 2 of life. α-L-iduronidase threshold 8.2nmol/h/mL (<25% of average control enzyme activity levels). Positive screens retested (using sample from second DBS), and diagnosis confirmed by assessing enzyme activity in purified leukocytes (whole blood sample).</td></tr>
<tr><td>Comparator</td><td>NA</td></tr>
<tr><td>Results/outcomes</td><td>Criterion 5

13 neonates screened positive for reduce α-L-iduronidase activity; 3/13 confirmed low α-L-iduronidaseactivity upon retest of second DBS. 0/3 diagnosed with MPS I following leukocyte testing.

<table>
<tr><td colspan="2"></td><td>Confirmed MPS I status</td><td></td></tr>
<tr><td colspan="2"></td><td>+</td><td>-</td></tr>
<tr><td rowspan="2">Screening test</td><td>+</td><td>0</td><td>3</td></tr>
<tr><td>-</td><td>NR</td><td>NR</td></tr>
</table>

PPV: 0% (Reviewer calculated, based on second stage screen figures)</td></tr>
<tr><td colspan="2">Quality appraisal
<table>
<tr><th>Question</th><th>Assessment (Y, N,</th><th>Risk of Bias (low, high,</th><th>Supporting info</th></tr>
</table></td></tr>
</table>

	unclear)	unclear)	
Domain I: Patient selection			
Consecutive or random sample of population enrolled?	Y	Low	Consecutive newborns over 2.5 years.
Case-control design avoided?	Y	Low	Cohort study
Inappropriate exclusions avoided?	Unclear	Low	No exclusion criteria reported, however, risk of bias low based on enrolment of consecutive neonates across region.
Domain II: Index Test			
Index test results interpreted without knowledge of reference standard results?	Y	Low	Staged testing strategy, screen test conducted and analysed prior to reference test.
Threshold pre-specified?	Unclear	Unclear	Threshold set at <25% normal median activity. Reported as "in each analysis, DBS samples obtained from patients and healthy individuals were used as controls." Unclear how reference range was established, and whether these samples were obtained from a separate (previous) cohort.
Domain III: Reference standard			
Reference standard likely to correctly classify condition?	Y	Low	Reference test leukocyte α-L-iduronidase activity from new whole blood sample.
Reference standard results interpreted without knowledge of index test results?	Unclear	Unclear	Reference test conducted for screen positive samples only; unclear whether leukocyte enzymatic assay was blinded to original screening result.
Domain IV: Test strategy flow and timing			
Appropriate interval between index test and reference standard?	Unclear	Low	No anticipated change in α-L-iduronidase activity between screening and diagnostic tests; no treatment reported following index test results.
Did all participants receive same reference standard?	N	High	MPS I status of screen negatives not tested; not possible to determine if 0 true positives represent all MPS I patients from the screening sample.

All patients included in analysis?	N	High	Not possible to calculate Sn, Sp or NPV due to lack of data on negative tests true MPS I status.
Applicability			
Applicable to UK screening population of interest?	Unclear	Unclear	Population (newborns), sample source (DBS) applicable to the UK. Test timing (DBS at day two) is earlier than UK procedures, and the only performance indicator available was PPV, which could vary due to prevalence difference between Italy and UK.
Applicable to UK screening test of interest?	N	Unclear	DBS timing earlier than UK, and the only performance indicator available was PPV, which could vary due to prevalence difference between Taiwan and UK.
Target condition measured by reference test applicable to UK screening condition of interest?	Y	Low	MPS I

Other comments

Sn, Sp, NPV cannot be calculated based on reported data.

Due to rarity of MPS I, sample size unlikely to be large enough to identify cases. Cannot precisely determine incidence of MPS I in Italy based on current screening programme sample.

Appendix number	16
Relevant criteria	10
Publication details	[31] Bjoraker KJ, Delaney K, Peters C, et al. Long-term outcomes of adaptive functions for children with mucopolysaccharidosis I (Hurler syndrome) treated with hematopoietic stem cell transplantation. J Dev Behav Pediatr. 2006;27(4):290-6.
Study details	Prospective case series, USA
Study objectives	To assess the long term outcomes in children with Hurler Syndrome who have received haematopoietic stem cell transplant (HSCT), specifically in the area of adaptive functioning.
Inclusions	Diagnosis of MPS IH (Hurler Syndrome), inclusion in the University of Minnesota database.

<table>
<tr><td>Exclusions</td><td>NR</td></tr>
<tr><td>Population</td><td>n=41 children (16 female, 25 male) with severe MPS I phenotype (characterised by affected CNS, the presence of 2 severe mutations, or the severity and early onset of presenting symptoms) who underwent HSCT between 1983 and 2002. Mean age at transplant: 21.7 months (SD: 11m; Range: 4.1 to 73m). Average follow-up: 67.2 months (SD 46.5m; Range: 2 to 21 years post-transplant). All patients remained fully or partially donor-engrafted at follow-up.</td></tr>
<tr><td>Intervention</td><td>Hematopoietic stem cell transplant (cell source not defined)</td></tr>
<tr><td>Comparator</td><td>n=43 untreated controls for age equivalent correlation analysis (i.e. slope results). 35 controls completed baseline but not follow-up assessments (24 died in transplant, 11 lost to follow-up); 7 children were not transplanted; 1 child received HSCT, but was not engrafted.</td></tr>
<tr><td>Outcome</td><td>Change in adaptive function domains (personal and social sufficiency in the areas of communication, daily living skills, socialisation, motor) as measured on the Vineland Adaptive Behaviour Scales (VABS) assessed at baseline (pre-transplant) and at least every year post-transplant. Lower scores indicate greater deficiency in adaptive functioning.</td></tr>
<tr><td>Results</td><td>Mean (SD) standard scores and slopes (Spearman’s Rho [SD]) based on age standardised scores for VABS function domains
<table>
<tr><th></th><th>Communication</th><th>Daily Living</th><th>Socialisation</th><th>Motor</th></tr>
<tr><td>Baseline</td><td>88.7 (13.5)</td><td>87.1 (16.5)</td><td>94.4 (12.7)</td><td>86.5 (11.8)</td></tr>
<tr><td>1y post HSCT</td><td>82.6 (12.9)</td><td>75.9 (12.6)</td><td>85.3 (8.7)</td><td>73.6 (15.0)</td></tr>
<tr><td>2y post HSCT</td><td>74.5 (17.8)</td><td>69.9 (17.7)</td><td>77.0 (12.7)</td><td>65.3 (14.4)</td></tr>
<tr><td>3y post HSCT</td><td>68.2 (18.9)</td><td>66.9 (22.1)</td><td>80.7 (21.8)</td><td>59.7 (18.7)</td></tr>
<tr><td>4-8y post HSCT</td><td>63.5 (22.1)</td><td>58.1 (26.7)</td><td>75.4 (22.9)</td><td>ND</td></tr>
<tr><td>Slope</td><td>0.52 (0.46)</td><td>0.52 (0.50)</td><td>0.66 (0.82)</td><td>0.49* (0.35)</td></tr>
</table>
Slope represents change in function relative to age equivalent untreated comparator group; positive slope indicates improvement relative to comparator group; closer slope is to ±1, the stronger the relative improvement.
* Slope calculated on scores from visits before age 5y; ND: no data

Correlation analysis between age at HSCT and slope (age equivalent scores based on untreated controls), Spearman Rho (p-value)
Communication: -0.09 (NS)
Daily Living: -0.22 (NS)
Socialisation: -0.18 (NS)
Motor: -0.24 (NS)</td></tr>
</table>

	NS: significant
Comments	Adaptive functioning defined by authors as "the performance of the daily activities required for personal and social sufficiency." Adaptive function across all four domains declined in absolute terms over time following transplant, but the change in function was beneficial relative to age equivalent scores from untreated patients (slope). Correlation analysis suggests that there is a very weak to weak, non-significant inverse relationship between age at treatment initiation and the relative improvement in adaptive functioning compared to age equivalent untreated comparator group. No information provided on recruitment, selection, or loss to follow-up. Potential bias due to these factors is unknown. No information on lost to follow-up comparator group, or on differences at baseline between transplanted and untransplanted group.

Appendix number	17
Relevant criteria	10
Publication details	[29] Boelens JJ, Aldenhoven M, Purtill D, et al. Outcomes of transplantation using various hematopoietic cell sources in children with Hurler syndrome after myeloablative conditioning. Blood. 2013;121(19):3981-7.
Study details	Retrospective case series, various countries
Study objectives	To assess outcomes of HSCT transplantation from various sources in children with Hurlers syndrome following myeloablative conditioning.
Inclusions	Diagnosis of Hurlers syndrome confirmed by an increase in urinary GAG excretion, deficiency or absence of alpha-L-iduronidase in peripheral blood leukocytes, and clinical phenotype; transplantation with either a Human leukocyte antigen (HLA) matched sibling donor (MSD), a HLA-matched or mismatched unrelated donor (UD), or a non-expanded, single, unmanipulated UCB unit; complete clinical data with at least three months posttransplant follow-up; transplants using myeloablative conditioning performed between 1995 and 2007; transplant data reported to the Promise Database and/or the Eurocord Registry from European and non-European centers.
Exclusions	NR
Population	n=258 children (133 male, 121 female) with Hurler syndrome who underwent myeloablative conditioning and HSCT (using various cell sources) between 1995 and 2007. Median age at transplant: 16.7 months (range: 2.1 to 228 months); median follow-up: 59 months (range: 1.3 to 159 months); median diagnosis-treatment interval: 5.2 months (range: 1 to 63.6 months). 19% (n=48) received at least 4 infusions ERT prior to transplant.
Intervention	HSCT using various cell sources (HLA matched sibling donor, HLA matched or mismatched unrelated donor, unrelated cord blood) following myeloablative

	conditioning regimen.
Comparator	NA
Outcome	"The primary endpoints were: (1) event-free survival (EFS), defined as survival from transplantation to last contact: autologous reconstitution (defined by documentation of <10% donor-derived engraftment), graft failure (defined as a lack of neutrophil recovery or transient engraftment of donor cells after transplantation and/or a requirement for a second transplant), or death were considered as events; (2) overall survival (OS) was defined as time from transplantation to death. All surviving patients were censored at date of last contact. "
Results	5-year EFS, probability (SD) Overall: 63% (3%) <16.7 months (n=128): 71% (4%) >16.7 months (n=130): 55% (4%) p=0.02 for age group difference Multivariate predictors of 5y EFS after first HSCT, Hazard Ratio [HR] (95% CI) Age <16.7m HR: 1.6 (1.06 to 2.49) p=0.03
Comments	Hazard Ratio adjusted for year of transplant and previous ERT. Analysis censored at last contact; no information on variations in outcome according to attrition. Age analysis was binary in nature (less than vs. greater than16.7 months); likely most applicable to early vs. late treatment in clinically detected Hurlers population as opposed to early treatment following screen detection. No information provided on recruitment, selection, or loss to follow-up. Potential bias due to these factors is unknown.

Appendix number	18
Relevant criteria	10
Publication details	[30] Boelens JJ, Wynn RF, O'Meara A, et al. Outcomes of hematopoietic stem cell transplantation for Hurler's syndrome in Europe: a risk factor analysis for graft failure. Bone Marrow Transplant. 2007;40(3):225-33.
Study details	Retrospective cohort, various (Europe)
Study objectives	To determine risk factors for graft failure among Hurlers syndrome patients following hematopoietic stem cell transplantation.
Inclusions	Hurler patients who received HSCT and included in the EBMT registry between

	January 1997 and September 2004.
Exclusions	NR
Population	n=146 patients (82 male/64 female; n=54 [37.0%] transplanted in UK) entered in the European Blood and Marrow Transplantation database who received HSCT between 1997 and 2004. Median age at diagnosis: 10.5 months (range: 0 to 55 months); median age at transplant: 18 months (range: 1 to 96 months); median post-HSCT follow-up: 44 months (range: 6 to 120 months).
Intervention	HSCT using various cell sources (bone marrow, peripheral blood stem cells, cord blood)
Comparator	NA
Outcomes	Alive and engrafted rate (donor chimerism >10% and alpha-L-iduronidase level >4.5nmol/h/mg) and survival rate after first HSCT at the latest follow-up point (at least >6 months)
Results	<u>Alive and engrafted (overall rate and OR for predictors in univariate analysis)</u> Overall: 56% Older age and A&E: OR 0.98 (95% CI 0.96 to 1.01), p=0.23 <u>Alive (overall rate and OR for predictors in univariate analysis)</u> Overall: 85% Age: OR 1.02 (95% CI 0.99 to 1.05), p=0.23
Comments	Overall, age at transplant was not a significant predictor of either alive and engrafted status or survival in univariate analysis. Wide range of age at diagnosis and age at transplant in assessed Hurlers population, with the range of both encompassing that which would be expected in a screened population. No information provided on recruitment, selection, or loss to follow-up. Potential bias due to these factors is unknown.

Appendix number	19
Relevant criteria	10
Publication details	[2] Poe MD, Chagnon SL, Escolar ML. Early treatment is associated with improved cognition in Hurler syndrome. Ann Neurol. 2014;76(5):747-53.
Study details	Retrospective case series, USA
Study objectives	To determine whether age at umbilical cord blood transplantation can predict cognitive outcomes in patients with Hurlers syndrome.
Inclusions	Hurlers syndrome (confirmed by clinical phenotype) patients referred to the Program for the Study of Neurodevelopment in Rare Disorders who subsequently underwent HSCT using unrelated umbilical cord blood between June 1997 and February 2013.

Exclusions	NR
Population	n=31 Hurlers patients (15 male/16 female; 29 white/2 black) treated between 1997 and 2013. Median age at transplant: 13.8 months (range: 2.1 to 34.3). Three age groups assess by age at transplant: 2-8 months (n=6), 9-17 months (n=17), ≥18 months (n=8). Median follow-up: 7.3 years (range: 2 to 21.7 years). No patient underwent ERT prior to transplantation; all patients maintained stable donor engraftment.
Intervention	Umbilical cord blood transplantation following conditioning with busulfan, cyclophosphamide and horse antihymocyte globulin. Prophylaxis against GVHD using cyclosporine and methylprednisolone.
Comparator	NA
Outcomes	Cognitive development, receptive language, expressive language and adaptive behaviour reported as assessed using standardised and validated neurobehavioural tools (specific test not reported, scale not reported); audiological function (severity of hearing loss and use of hearing aids), corneal clouding (severity of clouding; rates of improvement, stabilisation, and worsening; corneal transplant and use of eyeglasses).
Results	<u>Effect of age (months) at transplantation on post-transplant development, β regression coefficient (SE)</u> Cognitive development: -0.024 (0.006), p<0.001 Receptive language: -0.022 (0.007), p=0.004 Expressive language: -0.023 (0.009), p=0.01 Adaptive behaviour: -0.013 (0.005), p=0.03 <u>Audiological and Visual function</u> Hearing loss and corneal clouding and other visual outcomes did not vary according to age at transplantation (data not reported).
Comments	Interaction between baseline cognitive score and age was not significant. Age entered as a continuous variable, but outcomes presented graphically according to age category. Children who underwent transplantation at younger age had better outcomes in terms of cognitive development, language skills and adaptive behaviour (β interpretation: each month increase in age at transplant associated with 0.013 to 0.024 reductions [units unknown] in development]). Data not reported for non-significant results in audiological and visual functions (descriptive only). Visual outcomes assessed for 28/31 patients. Test and scale not reported for cognitive, language and adaptive behaviour outcomes; impact of age at transplant reported as statistically significant, but clinical significance of β ranging between -0.013 and -0.024 is not clear.

	Modelled developmental trajectories by three age-at-transplantation groups presented graphically only; visual assessment suggests that developmental trajectory consistently higher for patients transplanted at younger age, and were lowest for patients in the oldest age at transplant group. Further outcomes not reported in this review. Authors reported that transplantation before 9 months is necessary for optimal long-term cognitive and language outcomes, which appears to be supported by the graphs. Given small number of participants in each age band, it is unclear how appropriate this interpretation is.

Appendix number	20
Relevant criteria	10
Publication details	[32] Tylki-Szymanska A, Rozdzynska A, Jurecka A, et al. Anthropometric data of 14 patients with mucopolysaccharidosis I: retrospective analysis and efficacy of recombinant human alpha-L-iduronidase (laronidase). Mol Genet Metab. 2010;99(1):10-7.
Study details	Retrospective case series, Poland
Study objectives	To evaluate growth patterns in MPS I patients without treatment and following ERT with laronidase.
Inclusions	Diagnoses of MPS I confirmed by alpha-L-iduronidase activity in leukocytes and molecular analysis (not further defined); born at term.
Exclusions	NR
Population	n=14 MPS I patients (11 male/3 female; 10 Hurler, 1 Hurler/Scheie, 3 Scheie). Median age at diagnosis: 1.25y (range: 5 months to 7 years); Median age at ERT initiation: 4y (range: 1 to 15 years). Patients were divided into two groups depending on age at treatment: Group 1 ERT initiated at age 1y (7 patients, all with Hurler syndrome) and Group 2 ERT initiated after age 3y (7 patients, 3 Hurler, 1 Hurler/Scheie, 3 Scheie). Differentiation between phenotype based on genotype (most common genotype in Hurler: homozygous Q70X and W402X, and heterozygous Q70X and W402X. All patients under age 2y were considered for HSCT, but 16/17* patients' parents refused HSCT.
Intervention	Weekly intravenous infusions with 100U/kg (0.58mg/kg) laronidase. All patients completed at least 52 weeks treatment (14.3% completed 260 weeks, 50% completed 208 weeks, 21% 104 weeks, and 7% 52 weeks). Compliance with weekly infusions was 100%.
Comparator	Pre-ERT outcomes compared to age-specific general population standards (using Polish body growth, weight, head and chest circumference reference charts); post-ERT outcomes compared to both age-specific general population standards and between study groups, not to changes in an observed group.
Outcomes	Anthropometric features (body height, weight, head and chest circumference). Assessed at baseline, after 52-260 weeks of treatment and periodically during

	treatment (weeks 24, 48, 72, 96 and annually thereafter).
Results	<u>Change in height during first 3 years of life, mean cm (SD), 95% CI</u> Group 1: 36.3 (3.59), 32.5 to 40.1 Group 2 : 36.7 (3.68), 33.3 to 40.1 Population standard: 43.1 Group 1 vs. Population: p=0.056 Group 2 vs. Population: p=0.037 Group 1 vs. Group 2: p=0.84 <u>Change in weight during first 3 years of life, mean kg (SD), 95% CI</u> Group 1: 10.9 (0.95), 9.9 to 11.8 Group 2: 11.8 (2.21), 9.1 to 14.6 Population standard: 11.5 Group 1 vs. Population: p=0.13 Group 2 vs. Population: p=0.78 Group 1 vs. Group 2: p=0.36 <u>Change in head circumference during first 3 years of life, mean cm (SD), 95% CI</u> Group 1: 19.6 (1.45), 18.1 to 21.2 Group 2: 17.2 (1.68), 15.7 to 18.8 Population standard:14.5 Group 1 vs. Population: p=0.003 Group 2 vs. Population: p=0.005 Group 1 vs. Group 2: p=0.018 <u>Change in chest circumference during first 3 years of life, mean cm (SD), 95% CI</u> Group 1: 19.4 (2.78), 16.5 to 22.3 Group 2: 17.9 (0.47), 17.4 to 18.3 Population standard: 17.6 Group 1 vs. Population: p=0.17 Group 2 vs. Population: p=0.14 Group 1 vs. Group 2: p=0.23
Comments	* No explanation of discrepancy between study population (n=14 included, n=17 under age 2y offered HSCT). No differences between Group 1 and Group 2 at birth for height or chest circumference; weight at birth was higher in Group 2 vs. Group 1 (difference 0.6kg, p=0.04), head circumference at birth was significantly higher in Group 2 vs. Group 1 (difference 2.2cm, p=0.02). Comparisons between Group 1 and 2 restricted to first three years of life; Group 1 values indicate effect of early treatment (by age 1) in Hurler patients, Group 2 values indicate effect of no treatment in mixed MPS I phenotype (Hurler, Hurler/Scheie, Scheie). Population averages reflect general population standards. Urinary GAG concentration change narrative results only; authors suggest GAG

	concentration did not approach the normal range for treated patients. 3 years chosen as cutoff for group 2 as these patients were born earlier and were 3 years of age when ERT became available. Small sample size in Groups 1 and 2 may have influence significant findings between groups, as mean and not median measurements were used, the influence of a single outlier may account for between group differences. Non-significant differences between treated and untreated patients could be due to: Lack of effectiveness of ERT in terms of joint and bone disease in Hurlers patients, regardless of treatment timing Small sample size resulting in underpowered analyses Phenotype heterogeneity between the compared groups

Appendix number	21
Relevant criteria	10
Publication details	[33] Wraith JE, Beck M, Lane R, et al. Enzyme replacement therapy in patients who have mucopolysaccharidosis I and are younger than 5 years: results of a multinational study of recombinant human alpha-L-iduronidase (laronidase). Pediatrics. 2007;120(1):e37-46.
Study details	Open label Phase II trial, various (UK, France, Germany, the Netherlands)
Study objectives	To evaluate the safety, pharmacokinetics and efficacy of laronidase in young, severely affected MPS I patients
Inclusions	MPS I patients naïve to laronidase; aged <5 years; MPS I diagnosis confirmed by fibroblast or leukocyte alpha-L-iduronidase enzyme activity (<10% of normal) and by genotyping.
Exclusions	Having undergone or being under consideration for HSCT; acute hydrocephalus; clinically significant organic disease unrelated to MPS I; administration of an investigative drug within 30 days prior to study enrolment; known hypersensitivity to laronidase solution.
Population	n=20 MPS I patients under the age of 5 years (16 Hurler, 4 Hurler/Scheie; 12 male/8 female; 18 white/2 unreported ethnicity). Mean age at diagnosis: 1.3 years (range: prenatal to 4.5 years); mean age at study enrolment: 2.9 years (range: 0.5 to 5.1 years). Most common mutations were W402X (45%) and Q70X (20%).
Intervention	Intravenous laronidase at 100U/kg (0.58mg/kg) weekly for 52 weeks. Four patients had dosage increases to 200U/kg for the last 26 weeks due to elevated urinary GAG levels (>200µg/mg creatinine) at week 22. Patients received antipyretic and antihistamine before each infusion.

Comparator	NA
Outcome	Adverse events (AE), urinary GAG excretion, liver size, cardiac status, upper airway obstruction during sleep, growth velocity, investigator's global assessment, mental development (assessed as chronological age [months] vs. Griffiths mental age equivalent [months]). Age/early treatment outcome data available for mental development only.
Results	<u>Mental Development</u> Hurler patients treated at <2.5y and Hurler/Scheie patients: showed steepest slope of development (chronological age vs. Griffiths mental age equivalent), similar to that of normal age-matched children. Hurlers patients treated at >2.5y: mental development had already started to plateau at start of study, and continued on a flat development trajectory (as chronological age increased, Griffiths mental age equivalent did not).
Comments	90% study completion rate (18/20). No statistical tests performed for open label study, all results descriptive (e.g. means, medians, ranges, frequencies, distributions) only. Study reported wide range of outcomes; only those related to age at treatment (i.e. mental development) are reported in the current review due to patient age range at treatment exceeding that expected in a UK screening population. Study suggests that 1 year of ERT treatment in Hurler/Scheie patients and younger (<2.5y) Hurlers patients may be associated with developmental gains similar to the non-MPS I population. However, further investigations on long term development and effect of longer treatment are needed. Authors' conclusions: "Exploratory mental development testing indicated that the patients with Hurler-Scheie syndrome had a normal to above-normal rate of cognitive growth during the 1-year study. Similarly, the younger (<2.5 years of age) patients with hurler syndrome showed an increase in cognitive function at a rate similar to that of healthy children. In contrast , the older patients with Hurler syndrome did not show any significant gains or loss in cognition."

Appendix number	22
Relevant criteria	14
Publication details	[34] de Ru MH, Bouwman MG, Wijburg FA, et al. Experiences of parents and patients with the timing of Mucopolysaccharidosis type I (MPS I) diagnoses and its relevance to the ethical debate on newborn screening. Mol Genet Metab. 2012;107(3):501-7.
Study details	Qualitative study, The Netherlands
Study objectives	To explore the experiences of MPS I patients and their parents with the timings of their diagnoses, specifically in regards to delayed diagnosis and potential earlier

	diagnosis.
Inclusions	NR
Exclusions	NR
Population	n=17 MPS I (6 Hurler, 4 Hurler-Scheie, 7 Scheie) patients and/or their parents (6 adolescent or adult patients, 13 parents). Median patient age 9 years (range 3 to 44y), 14 patients presented clinically, 2 following cascade-testing, and 1 after broad metabolic screening following failure to thrive. Median age of diagnosis for clinically presenting patients: 0.9y Hurler, 3.8y Hurler-Scheie, 9y Scheie. Semi-structured interviews conducted between July and October 2011.
Intervention/test	NA
Comparator	NA
Results	Five main themes emerged from the qualitative analysis with regards to disadvantages experienced due to delayed diagnosis and the advantages and possible disadvantages of a hypothetical earlier diagnosis: 1) delayed diagnosis causing parental frustration – especially regarding the uncertainty surrounding the period after symptom onset and before diagnosis, which arose due to the non-specific nature of symptoms. Prolonged diagnostic odyssey across the phenotypic spectrum often involved multiple specialists and hospitalisations, and a sense of powerlessness when faced with specialists who dismissed symptoms as typical or unexplained by an underlying cause, and in some cases, this involved misdiagnosis of other conditions. For some, however, the prolonged diagnostic odyssey was an advantaged in that it allowed for the gradual accumulation of knowledge and the final diagnosis was not a sudden, heavy burden that they were unprepared for. 2) delayed diagnosis causing patient frustration – two attenuated MPS I patients described similar frustrations relating to living with limiting symptoms but no diagnosis. 3) [hypothetical] early diagnosis enabling reproductive decision-making – three parents discussed late diagnosis leading to lack of opportunity to consider possibility of having another ill child when making reproductive decisions, including parents with two MPS I Scheie patients. 4) [hypothetical] early diagnosis enabling focusing on the diagnosis – hypothetical earlier diagnosis would have allowed parents to focus on caring for child instead of chasing down a diagnosis and moving from specialist to specialist, and would have helped them understand the child and his/her limitations, to focus on life choices such as schooling, and to avoid the strain the diagnostic odyssey places on a family. However, some parents said that an earlier diagnosis would have taken

	away a carefree period in their lives (both MPS I Scheie parents/patients). 5) [hypothetical] early diagnosis enabling timely initiation of treatment – parents felt that an earlier diagnosis would have enabled earlier treatment, preventing disease progression and significant harm, and have allowed the child to better bear the burden of treatment (due to lack of memory of treatment). A potential harm of early treatment, in both a Scheie and Hurler parent, described as losing the early good years to difficult courses of treatment that are not without risks or harms.
Comments	Includes MPS I patients detected clinically presenting or cascade testing; no screen detected patients represented. Patients recruited by a paediatrician involved in the clinical care of MPS I patients; no information provided on number of patients invited vs. number who agreed to participate, or any differences between the two groups. All results regarding feelings toward earlier diagnosis are regarding a hypothetical or potential earlier diagnosis only; no results compared differences in experience between screen and clinically detected patients.

References

1. Beck M, Arn P, Giugliani R, et al. The natural history of MPS I: global perspectives from the MPS I Registry. Genet Med. 2014;16(10):759-65.
2. Poe MD, Chagnon SL, Escolar ML. Early treatment is associated with improved cognition in Hurler syndrome. Ann Neurol. 2014;76(5):747-53.
3. Clarke LA HJ. Mucopolysaccharidosis Type I [Internet].2011 [updated 2011 July 21]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20301341.
4. Clarke LA, Wraith JE, Beck M, et al. Long-term efficacy and safety of laronidase in the treatment of mucopolysaccharidosis I. Pediatrics. 2009;123(1):229-40.
5. Seymour CA, Thomason MJ, Chalmers RA, et al. Newborn screening for inborn errors of metabolism: a systematic review. Health Technol Assess. 1997;1(11):i-iv, 1-95.
6. Bertola F, Filocamo M, Casati G, et al. IDUA mutational profiling of a cohort of 102 European patients with mucopolysaccharidosis type I: identification and characterization of 35 novel alpha-L-iduronidase (IDUA) alleles. Hum Mutat. 2011;32(6):E2189-210.
7. Vijay S, Wraith JE. Clinical presentation and follow-up of patients with the attenuated phenotype of mucopolysaccharidosis type I. Acta Paediatr. 2005;94(7):872-7.
8. Moore D, Connock MJ, Wraith E, et al. The prevalence of and survival in Mucopolysaccharidosis I: Hurler, Hurler-Scheie and Scheie syndromes in the UK. Orphanet J Rare Dis. 2008;3:24.
9. Murphy AM, Lambert D, Treacy EP, et al. Incidence and prevalence of mucopolysaccharidosis type 1 in the Irish republic. Arch Dis Child. 2009;94(1):52-4.
10. Baehner F, Schmiedeskamp C, Krummenauer F, et al. Cumulative incidence rates of the mucopolysaccharidoses in Germany. J Inherit Metab Dis. 2005;28(6):1011-7.

11. Lin HY, Lin SP, Chuang CK, et al. Incidence of the mucopolysaccharidoses in Taiwan, 1984-2004. Am J Med Genet A. 2009;149A(5):960-4.
12. Pastores GM, Arn P, Beck M, et al. The MPS I registry: design, methodology, and early findings of a global disease registry for monitoring patients with Mucopolysaccharidosis Type I. Mol Genet Metab. 2007;91(1):37-47.
13. D'Aco K, Underhill L, Rangachari L, et al. Diagnosis and treatment trends in mucopolysaccharidosis I: findings from the MPS I Registry. Eur J Pediatr. 2012;171(6):911-9.
14. Munoz-Rojas MV, Bay L, Sanchez L, et al. Clinical manifestations and treatment of mucopolysaccharidosis type I patients in Latin America as compared with the rest of the world. J Inherit Metab Dis. 2011;34(5):1029-37.
15. Thomas JA, Beck M, Clarke JT, et al. Childhood onset of Scheie syndrome, the attenuated form of mucopolysaccharidosis I. J Inherit Metab Dis. 2010;33(4):421-7.
16. Lin SP, Lin HY, Wang TJ, et al. A pilot newborn screening program for Mucopolysaccharidosis type I in Taiwan. Orphanet J Rare Dis. 2013;8:147.
17. Paciotti S, Persichetti E, Pagliardini S, et al. First pilot newborn screening for four lysosomal storage diseases in an Italian region: identification and analysis of a putative causative mutation in the GBA gene. Clin Chim Acta. 2012;413(23-24):1827-31.
18. Blanchard S, Sadilek M, Scott CR, et al. Tandem mass spectrometry for the direct assay of lysosomal enzymes in dried blood spots: application to screening newborns for mucopolysaccharidosis I. Clin Chem. 2008;54(12):2067-70.
19. Brand GD, Matos HC, Cruz GC, et al. Diagnosing lysosomal storage diseases in a Brazilian non-newborn population by tandem mass spectrometry. Clinics. 2013;68(11):1469-73.
20. Chennamaneni NK, Kumar AB, Barcenas M, et al. Improved reagents for newborn screening of mucopolysaccharidosis types I, II, and VI by tandem mass spectrometry. Anal Chem. 2014;86(9):4508-14.
21. Gelb MH, Turecek F, Scott CR, et al. Direct multiplex assay of enzymes in dried blood spots by tandem mass spectrometry for the newborn screening of lysosomal storage disorders. J Inherit Metab Dis. 2006;29(2-3):397-404.
22. Han M, Jun SH, Song SH, et al. Use of tandem mass spectrometry for newborn screening of 6 lysosomal storage disorders in a Korean population. Korean J Lab Med. 2011;31(4):250-6.
23. Campos D, Monaga M, Gonzalez EC, et al. Optimization of enzymatic diagnosis for mucopolysaccharidosis I in dried blood spots on filter paper. Clin Biochem. 2013;46(9):805-9.
24. de Ruijter J, de Ru MH, Wagemans T, et al. Heparan sulfate and dermatan sulfate derived disaccharides are sensitive markers for newborn screening for mucopolysaccharidoses types I, II and III. Mol Genet Metab. 2012;107(4):705-10.
25. Coppa GV, Galeotti F, Zampini L, et al. High-throughput determination of urinary hexosamines for diagnosis of mucopolysaccharidoses by capillary electrophoresis and high-performance liquid chromatography. Anal Biochem. 2011;411(1):32-42.
26. Scott CR, Elliott S, Buroker N, et al. Identification of infants at risk for developing Fabry, Pompe, or mucopolysaccharidosis-I from newborn blood spots by tandem mass spectrometry. J Pediatr. 2013;163(2):498-503.
27. Martins AM, Dualibi AP, Norato D, et al. Guidelines for the management of mucopolysaccharidosis type I. J Pediatr. 2009;155(4 Suppl):S32-46.

28. Giugliani R, Federhen A, Rojas MV, et al. Mucopolysaccharidosis I, II, and VI: Brief review and guidelines for treatment. Genet. 2010;33(4):589-604.
29. Boelens JJ, Aldenhoven M, Purtill D, et al. Outcomes of transplantation using various hematopoietic cell sources in children with Hurler syndrome after myeloablative conditioning. Blood. 2013;121(19):3981-7.
30. Boelens JJ, Wynn RF, O'Meara A, et al. Outcomes of hematopoietic stem cell transplantation for Hurler's syndrome in Europe: a risk factor analysis for graft failure. Bone Marrow Transplant. 2007;40(3):225-33.
31. Bjoraker KJ, Delaney K, Peters C, et al. Long-term outcomes of adaptive functions for children with mucopolysaccharidosis I (Hurler syndrome) treated with hematopoietic stem cell transplantation. J Dev Behav Pediatr. 2006;27(4):290-6.
32. Tylki-Szymanska A, Rozdzynska A, Jurecka A, et al. Anthropometric data of 14 patients with mucopolysaccharidosis I: retrospective analysis and efficacy of recombinant human alpha-L-iduronidase (laronidase). Mol Genet Metab. 2010;99(1):10-7.
33. Wraith JE, Beck M, Lane R, et al. Enzyme replacement therapy in patients who have mucopolysaccharidosis I and are younger than 5 years: results of a multinational study of recombinant human alpha-L-iduronidase (laronidase). Pediatrics. 2007;120(1):e37-46.
34. de Ru MH, Bouwman MG, Wijburg FA, et al. Experiences of parents and patients with the timing of Mucopolysaccharidosis type I (MPS I) diagnoses and its relevance to the ethical debate on newborn screening. Mol Genet Metab. 2012;107(3):501-7.
35. Boy R, Schwartz IV, Krug BC, et al. Ethical issues related to the access to orphan drugs in Brazil: the case of mucopolysaccharidosis type I. J Med Ethics. 2011;37(4):233-9.