JIMD Reports
DOI: 10.1007/8904_2011_9

Received: 30 August 2010; Revised: 26 October 2010;
Accepted: 30 December 2010; Published online: 22 June 2011
Communicated by: Frits Wijburg

Enzyme Replacement Therapy and Extended Newborn Screening for Mucopolysaccharidoses: Opinions of Treating Physicians

David J. Coman, Ian M. Hayes, Veronica Collins, Margaret Sahhar, J. Ed Wraith, and Martin B. Delatycki

Abstract We conducted a survey of physician opinions in relation to enzyme replacement therapy (ERT) and extended newborn screening (ENBS) for mucopolysaccharidoses (MPS). A questionnaire consisting of hypothetical clinical scenarios about ERT and ENBS for MPS was posted on metab-L, a list server for the metabolic community. The questionnaire included similar questions to those used in previous studies that sought the views of individuals and families affected by MPS. Our aim was to compare medical professionals' opinions with that of the individuals and families affected by MPS that they serve. The questionnaire was completed by 35 physicians, most of whom were metabolic physicians. Responses differed significantly between the physician and parent groups when the clinical scenario involved intellectual impairment. In this setting, physicians were significantly less inclined to advocate the use of ERT. Comparison of the responses to the ENBS scenarios revealed that compared to physicians, family of individuals with MPS were more inclined to desire diagnosis at birth, even if no treatment could alter the outcome of the condition. Compared to the family of individuals with MPS, physicians are more likely to advocate the use of ERT and ENBS where there is proven medical benefit to the affected individual.

Keywords Ethics · Lysosomal storage disorders · Questionnaire

D.J. Coman
Bruce Lefroy Centre for Genetic Health Research, Murdoch Childrens Research Institute, 10th Floor, Royal Children's Hospital, Flemington Road, Parkville 3052, Victoria, Australia
and
Department of Metabolic Medicine, The Royal Children's Hospital, Brisbane Queensland, Australia

I.M. Hayes
Bruce Lefroy Centre for Genetic Health Research, Murdoch Childrens Research Institute, 10th Floor, Royal Children's Hospital, Flemington Road, Parkville 3052, Victoria, Australia
and
Northern Regional Genetic Service, Auckland City Hospital, Auckland New Zealand

V. Collins
Bruce Lefroy Centre for Genetic Health Research, Murdoch Childrens Research Institute, 10th Floor, Royal Children's Hospital, Flemington Road, Parkville 3052, Victoria, Australia
and
Public Health Genetics Unit, Murdoch Childrens Research Institute, Parkville Victoria, Australia

M. Sahhar
Bruce Lefroy Centre for Genetic Health Research, Murdoch Childrens Research Institute, 10th Floor, Royal Children's Hospital, Flemington Road, Parkville 3052, Victoria, Australia
and
Genetic Health Services Victoria, Parkville Victoria Australia

J.E. Wraith
Department of Genetic Medicine, St. Mary's Hospital, Manchester UK

M.B. Delatycki (✉)
Bruce Lefroy Centre for Genetic Health Research, Murdoch Childrens Research Institute, 10th Floor, Royal Children's Hospital, Flemington Road, Parkville 3052, Victoria, Australia
and
Department of Clinical Genetics, Austin Health, Heidelberg Victoria, Australia
and
Department of Medicine, University of Melbourne, Austin Health, Heidelberg Victoria, Australia
e-mail: martin.delatycki@ghsv.org.au

Introduction

The mucopolysaccharidoses (MPS) are a group of related disorders of lysosomal storage that have an approximate prevalence of 1:22,500 live births (Meikle et al. 1999). Diminished levels of specific lysosomal enzymes result in progressive accumulation of glycosaminoglycans (GAGs) in the lysosomes of various organs. The resultant clinical manifestations can include intellectual disability, hydrocephalus, spinal cord compression, deafness, dysostosis multiplex, short stature, hepatosplenomegaly, sleep apnoea, cardiac

disease, corneal clouding, coarse facial features, and reduced life span in the majority (McKusick 2001).

Early bone marrow transplantation is effective in the severe form of MPSI (MPS-1H) (Pastores and Barnett 2005). Enzyme replacement therapy (ERT) can ameliorate some clinical features associated with select subtypes of MPS and is now available for MPSI (Laronidase), MPSII (Idursulfase), and MPSVI (Galsulfase) (Muenzer et al. 2006; Kakkis 2002; Harmatz et al. 2006). Significant limitations of ERT include that ERT will not cross the blood–brain barrier and thus do not impact the central nervous system manifestations of MPS and the very high cost, and resultant limited drug availability in some countries.

Newborn screening (NBS) methods have been developed for the identification of individuals at birth who have specific lysosomal storage disorders (Meikle et al. 2006; Wang et al. 2005, 2007). Glycosphingolipid and oligosaccharide markers (measured using tandem mass spectroscopy) have 100% sensitivity and specificity for the identification of MPSIIIA, MPSIVA, I-cell disease as well as a number of other lysosomal storage disorders (Janssen et al. 2005). Measurement of specific enzymes deficient in other types of MPS would enable these to be identified by NBS (Wang et al. 2007; De Jesus et al. 2009).

We have previously conducted questionnaire studies to assess the opinions of parents of individuals with MPS and adults with MPS in the USA and Australia regarding NBS and ERT for these conditions (Coman et al. 2008; Hayes et al. 2007). Eighty-six percent of respondents indicated that they would have wanted NBS for their own children, with the most common reason cited in support of NBS being the avoidance of a delay in diagnosis and the distress caused by a delayed diagnosis (Hayes et al. 2007). This study indicated strong support for the introduction of NBS from MPS families, in which the psychosocial benefits of screening may outweigh potential harms. Overall, 92% were in favor of ERT where MPS causes severe physical problems but does not affect intellect, and 69% were in favor of ERT where the physical limitations are mild and intellect is spared (Coman et al. 2008). The majority of respondents were in favor of ERT for MPS, even where it would not alter the intellectual deterioration, with perceived improvements in quality of life (QOL) produced by ERT, the most commonly cited factor (Coman et al. 2008).

In considering treatments such as ERT, the clinician must consider factors such as (1) the prospects for benefit, (2) parental wishes, (3) potential negative impacts on the patient and the wider family unit, and (4) the cost of treatment. We undertook a questionnaire study to elicit the views of physicians who treat MPS, on ERT and NBS for MPS. We hypothesized that clinicians would have differing views to the MPS families regarding the suitability of NBS and ERT in some MPS patient scenarios, especially where intellectual impairment is involved in the clinical phenotype.

Methods

The questionnaire used in this study was based on that used in our previous studies to elicit the views of individuals with MPS and parents (Coman et al. 2008; Hayes et al. 2007) but included some questions specifically designed for medical professionals. It included questions on the clinical role of the respondent, how many patients they have treated with each MPS subtype, and their responses to a number of hypothetical clinical scenarios regarding ERT and extended newborn screening (ENBS) for MPS. The questionnaire with details of these scenarios is available at http://www.mcri.edu.au/Downloads/Survey/ERT_expert_survey.pdf, and the scenarios are summarized in Tables 1 and 2. Questionnaires were distributed online via metab-L (http://www.daneel.franken.de/metab-l), a list server for the worldwide metabolic community with over 1,000 active members. The metab-L post-directed respondents to the MCRI website where the questionnaire was completed anonymously.

Statistical Analysis

Characteristics of the health professionals who responded to the survey are provided as frequency data. Physician responses are presented as the proportion of respondents agreeing with the use of ERT or ENBS for each scenario. The responses of the physicians were compared with those of the individuals affected by MPS and parents, elicited in earlier studies (Coman et al. 2008; Hayes et al. 2007), using chi-square statistics with one degree of freedom or Fisher's exact tests where an expected cell frequency was less than five. The level of evidence for an association between responses to scenarios and whether the respondent was a physician or an affected individual/parent is given as a p value. A p value of < 0.05 was considered statistically significant.

Results

Thirty-five physicians responded to the survey. Metabolic physicians were the highest represented specialty among the respondents (65.7%) followed by medical geneticists (11.4%), general pediatricians (8.5%), with three respondents not stating their specialty, and two indicating another specialty

Table 1 Outline of the six ERT scenarios presented in the questionnaire

	Scenario summary	Manifestations		Effect of ERT		
		Physical	Intellectual	Physical	Life expectancy	Intellectual
1a	11-year old with severe physical MPSVI and normal intellect, ERT will prolong life	Severe	Nil	Significant improvement	Increased	Nil improvement
2a	MPSI-S with minor health issues as an adult but normal intellect, ERT will only improve health issues a little	Mild	Nil	Minimal improvement	Unchanged	Nil improvement
3a	Severe physical and intellectual manifestations of MPSII. Death in 5 years without ERT	Severe	Severe	Minimal improvement	Increased 3 years	Nil improvement
4a	The 1-year-old younger brother of the MPSII patient in 3a. ERT will prolong his life but not halt the CNS manifestations	Moderate	Severe	Minimal improvement	Increased 15 years	Nil improvement
5a	Mild MPSII with early joint and mobility difficulties, and mild school performance issues	Mild	Mild	Moderate improvement	Not significant	Nil improvement
3b	–[a]	Severe	Severe	Minimal improvement	Increased 3 years	Significant improvement
4b	–[a]	Moderate	Severe	Minimal improvement	Increased 15 years	Significant improvement
5b	–[a]	Mild	Mild	Moderate improvement	Unchanged	Significant improvement

[a]3b, 4b, and 5b are identical to 3a, 4a, and 5a; however, the respondents were asked to consider whether they would use ERT for the patients in 3a, 4a, and 5a if it improved the CNS manifestations

Table 2 Outline of three NBS scenarios presented in the questionnaire

	MPS type	Manifestations	
		Physical	Intellectual
Scenario 1	MPSVI	Mild	Nil
Scenario 2	MPSIII	Mild	Severe
Scenario 3	MPSI	Severe	Severe

Table 3 Characteristics of the participating physicians (n = 35)

	Number	Proportion (%)
Specialty		
Metabolic physician	23	65.7
Medical geneticist	4	11.4
Pediatrician	3	8.6
Other	2	5.7
Not stated	3	8.6
Years in practice		
0–10	15	42.8
11–20	8	22.9
More than 20	8	22.9
Not stated	4	11.4

(Table 3). Under half (42.8%) of respondents had been practicing in the field for 10 years or less with 22.8% very experienced as evidenced by working in the field for over 20 years.

The numbers of past and present MPS I, II, and VI patients treated by the responding physicians are outlined in Table 4, indicating a broad range of experience with these conditions. Unsurprisingly, given its novelty and expense, there was relatively limited experience with the use of ERT (Table 5).

Enzyme Replacement Therapy

The hypothetical ERT scenarios are outlined in Table 1, and the physician responses are shown in Table 6 where they are compared to those of the individuals with MPS/families (Coman et al. 2008).

Responses of the physician and parent groups followed certain themes. Both groups were united in their opinions that ERT should be used in situations where intellect is normal with only mild physical problems (scenario 1a), mild decreases in IQ with mild joint restriction improved by ERT (scenario 5a), severe intellectual disability where ERT would prolong life by 15 years (scenario 4a), and in hypothetical scenarios where ERT can avert the evolving CNS manifestations (scenarios 4b and 5b).

However, differences were observed in other scenarios. Physicians were significantly less inclined to support the use of ERT in scenarios where severe intellectual impairment is prominent (scenario 3a: 8.8% physicians in favor vs. 46.9% families in favor, $p < 0.001$; scenario 3b: 38.2% physicians in favor vs. 82.6% families in favor, $p < 0.001$) or when the child displays only mild physical manifestations (scenario 2a: 38.2% physicians in favor vs. 69.2% families in favor, $p < 0.001$).

Forty percent (14/35) of the physician group made additional comments. The most common themes among the comments included the need to involve the affected individual/families in the ERT decision process (4/14, 28.5%), concerns that ERT may prolong suffering rather than prolong

Table 4 Number and type of MPS patients treated by physicians in the study (current and past)

MPS type	Current care			Past care		
	Number responded	Median number of patients	Total number of patients	Number responded	Median number of patients	Total number of patients
MPSI	30	5.7	171	26	8.5	220
MPSII	26	5.7	150	23	6	139
MPSIII	22	8.7	193	21	8.6	180
MPSIV	21	4.2	90	18	5.2	94
MPSVI	20	3.3	67	16	4.3	69
MPSVII	9	0.8	8	6	0.66	4

Table 5 Number and type of MPS patients treated by ERT

MPS type	ERT patient numbers				
	Nil	1–10	11–20	21–30	No response
MPSI	9 (25.7%)	20 (57%)	0 (0%)	1 (2.8%)	5 (14.3%)
MPSII	7 (20%)	21 (60%)	0 (0%)	1 (2.8%)	6 (17%)
MPSVI	6 (17%)	18 (51.4%)			11 (31.4%)

MPSIII, MPSIV, and MPSVII not applicable as no ERT is currently available for these subtypes of MPS

Table 6 Comparison of proportions of respondents who agreed with the use of ERT in each scenario between physicians and patients/parents

Scenario	Physicians		Patients/parents[a]		*p* value
	No. responded	% agree with ERT	No. responded	% agree with ERT	
1a	34	91.2	245	91.8	0.896
2a	34	38.2	247	69.2	<**0.001**
3a	34	8.8	245	46.9	<**0.001**
4a	34	67.6	241	76.8	0.246
5a	33	90.9	247	92.7	0.712
3b	34	38.2	242	82.6	<**0.001**
4b	34	100	243	97.1	0.603[b]
5b	34	97.1	241	98.3	0.486[b]

[a]Affected individual/parent responses from previous study (Coman et al. 2008)
[b]Fisher's exact test

QOL in some MPS scenarios (4/14, 28.5%), and that the use of ERT is not ideal in situations of intellectual impairment (4/14, 28.5%). The most common additional comments cited in favor of ERT in the family study included improved QOL (26% of those who made additional comments), that ERT should be available to all regardless of intellectual status (18%), with 4% of parents of children with MPS stating that ERT should not be used where it would prolong suffering (Coman et al. 2008).

Expanded Newborn Screening

The hypothetical NBS scenarios are outlined in Table 2, and the physician responses are listed in Table 7 where they are compared to those of the individuals with MPS/families (Hayes et al. 2007).

Table 7 Comparison of proportions of respondents who agreed with having NBS in each scenario between physicians and patients/parents

Scenario	Physicians		Patients/parents[a]		*p* value
	No. responded	% agree with ENBS	No. responded	% agree with ENBS	
1	34	64.7	242	83.9	<**0.01**
2	34	64.7	247	87.4	<**0.001**
3	35	100	245	97.1	0.60[b]

[a]Affected individual/parent responses from previous study (Hayes et al. 2007)
[b]Fisher's exact test

There was no significant difference between the groups in relation to the response to scenario 3 where NBS would allow early diagnosis of MPSI such that bone marrow transplantation can be offered (100% of physicians in favor and 97.1% of families in favor, $p = 0.60$). There was a significantly lower positive response by the physicians compared to individuals with MPS/families for scenario 1 (mild case of MPSVI where ERT would not be required), where NBS was advocated by 64.7% of the physicians and 83.9% of the affected individuals/families ($p = 0.007$); and scenario 2 (MPSIII) where NBS was advocated by 64.7% of physicians and 87.4% of the affected individuals/families ($p < 0.001$).

Overall, 42.8% (15/35) of physician respondents made additional comments. The most frequently cited reasons in favor of NBS were the ability to provide genetic counseling to affected families to allow the option of preventing the birth of further children with the condition (7/15 of those who made comments, 46.6%), and health benefits and treatments potentially made available by early diagnosis (7/15, 46.6%). The most frequent comments in favor of NBS in the family study were increased stress associated with not having a diagnosis (25%), improved medical care (24%), and genetic counseling (19%) (Hayes et al. 2007). The most commonly cited arguments against NBS cited by physicians in this study were the inability to judge phenotype from the NBS results and thus predict those in need of treatment where available (4/14, 26.6%). Only one clinician made comments about the possible impact on families from

false-negative and false-positive NBS results. Themes of potential harm were cited in the family study, with NBS removing a period of perceived good health (7%) and creating an altered and negative perception of their child (2%).

Discussion

MPS presents with a wide range of clinical manifestations which can create significant morbidity and mortality. The emergence of ERT has been welcomed by clinicians and families; however, it carries significant limitations. Clinical trials of ERT in MPS I, II, and VI have demonstrated reduced disease burden for many non-CNS manifestations, but ERT does not impact on CNS morbidity (Muenzer et al. 2006; Harmatz et al. 2006; Wraith et al. 2004; Kakkis et al. 2001).

We previously found that MPS families have a sound understanding of the uses and limitations of ERT for MPS (Coman et al. 2008). Nevertheless, we hypothesized that variation would exist in how medical professionals and families judge burden of disease, especially where intellectual impairment is involved, and thus the appropriateness of ERT in these situations. Physicians were significantly less inclined than parents to think that ERT was an appropriate therapeutic option in scenarios where severe intellectual impairment is prominent (scenario 3a and 3b) or when the child displays only mild physical manifestations (scenario 2a). Further evidence for differing views on the appropriateness of ERT in these situations came from the additional comments. A commonly cited theme from the physicians was concern regarding the use of ERT where life might be prolonged without associated improvement in QOL, where intellectual impairment was involved.

MPS creates a significant burden of disease for the individual, the family, and health care systems, which can be judged in terms of the clinical manifestations (intellectual and physical), functional limitations, familial dysfunction and dislocation, invasive medical intervention (especially weekly ERT), impacts on hospital resources, and monetary cost to society (again exacerbated by ERT). QOL is defined as the individual's perception of their physical and psychological health, level of independence, and social and personal relationships that are tempered by the environment and culture in which the individual lives (Saxena and Orley 1997). Our study demonstrates affected individual/family-physician discordance regarding the use of ERT when the disease burden involves intellectual impairment. Physicians have been shown to misjudge the perceived QOL in patients with intellectual disability (Janssen et al. 2005), and underestimate the patient's positive view of their own QOL (Nursey et al. 1990). Similar discordance in assessing disease severity, management decisions, and perceived QOL has been observed in rheumatoid disorders (Consolaro et al. 2007; Spoorenberg et al. 2005; Yen et al. 2003), planning gastroenterological procedures (Sonnenberg 2004), inflammatory bowel disease (Sewitch et al. 2002), schizophrenia (Fitzgerald et al. 2001), and malignancy (Wilson et al. 2000). ERT is very expensive in its own right, but its administration also creates collateral costs on health professional's time and resources beyond the time pressures on the individual and family.

Affected individual/families may well be able to make a valid argument that the child's non-CNS health and QOL would be improved with ERT, and not providing ERT to their child is discrimination on the basis of symptoms. Ultimate decisions regarding the appropriateness of ERT for individuals with progressive intellectual deterioration need to be made in conjunction with government bodies, treating physicians and other health professionals and families. An example of this process is the UK guidelines for investigations and management of MPSI (http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4118402).

Both physicians and family groups were supportive of NBS where the early diagnosis would lead to a proven therapeutic option, e.g., BMT for MPSI (scenario 3). Highly statistically significant variation was observed, however, for the use of NBS in a scenario where it would diagnose mild MPSVI that would not qualify for ERT (scenario 1) and for MPSIII (scenario 2), where no treatment can prevent the inexorable decline of this condition. MPSIII has a severe CNS phenotype including intellectual impairment and regression but far fewer non-CNS manifestations than other MPSs. The extra comments from families suggest that it is psychosocial rather than medical benefits that underlie this difference. The themes emerging from additional comments support this contention, especially revolving around the stress of a delayed diagnosis (Hayes et al. 2007).

A significant limitation of NBS at present is the inability to accurately predict phenotype and projected treatment requirements, something noted by the physician group, highlighting the need for ongoing education of affected individuals and their families. False-positive results would undoubtedly cause significant stress to families, and proven diagnoses may "rob" the family of a period of normality when no treatment options are available to alter later onset disease progression, and may even create a negative impact on parent–child bonding. However, the latter concern has not been the reported experience in Duchene muscular dystrophy newborn screening in Wales, which uses detailed parent–physician communication strategies (Parsons et al. 2002). These are issues that were raised by the affected individual/family group but not the physicians (Hayes et al. 2007). Guidelines state that NBS should only be introduced if a disorder is severe, and early diagnosis results in a better outcome for the affected individual (Wilcken 2008). Early

diagnosis afforded by NBS might allow timely genetic counseling and family planning, and was raised as a positive outcome by both physicians and affected individuals/families as an important potential benefit of NBS.

This study has some limitations. Ascertainment bias may exist by virtue of the small sample of clinicians who responded to the survey, with varying degrees of experience with the use of ERT, and therefore the range of responses to the hypothetical scenarios may be biased in those motivated to complete the online survey. Thus, the views of the physicians who responded to the survey may not reflect those of the wider medical community involved in treating MPS. Continental or cultural variances and the impacts of the respondent's area of medical specialization on physician's opinions were not explored due to the small sample size. The results of the current study were compared to the results of previous studies that assessed the responses of patients/parents to the same scenarios (Coman et al. 2008; Hayes et al. 2007). The time interval between the two studies may have resulted in bias as the patients/parents may have responded differently now, since experience with ERT has considerably increased during the time since the initial survey was conducted.

The advent of ERT and the evolution of NBS create many ethical and sociological issues that impinge on the physician–family interface. Clinicians face the difficult dual task of advocating for their patients and developing guidelines for the use of expensive medications that impact on already stretched health budgets and systems. Involvement of advocacy groups in formulating these policies offers an opportunity for informing both parties as to the range of opinions about appropriateness for treatment, as indicated in this study. Failure to involve families in such important matters may alienate the treating clinicians and funding bodies from those that they advocate for and may even be construed as paternalistic.

Acknowledgments We thank the MPS societies of Australia and the USA for distributing the questionnaires and those who took the time to complete the surveys. We thank Drs. Heidi Peters and Joy Lee for their helpful comments in relation to the manuscript. We also thank the Information Technology Department at Murdoch Childrens Research Institute for their assistance in developing the web-based questionnaire. MBD is an NHMRC Practitioner Fellow. All authors have contributed to the planning, data interpretation, and manuscript production, and have reviewed the material, agreed to its content, and declared no conflict of interests. Ethics approval and funding were not required for this survey-based study. Prof. Martin B Delatycki is the guarantor for the manuscript.

Take Home Message

Compared to the family of individuals with MPS, physicians are more likely to advocate the use of enzyme replacement therapy and extended newborn screening where there is proven medical benefit to the affected individual.

References

Coman DJ, Hayes IM, Collins V, Sahhar M, Wraith JE, Delatycki MB (2008) Enzyme replacement therapy for mucopolysaccharidoses: opinions of patients and families. J Pediatr 152:723–727

Consolaro A, Vitale R, Pistorio A, Lattanzi B, Ruperto N, Malattia C et al (2007) Physicians' and parents' ratings of inactive disease are frequently discordant in juvenile idiopathic arthritis. J Rheumatol 34:1773–1776

De Jesus VR, Zhang XK, Keutzer J, Bodamer OA, Muhl A, Orsini JJ et al (2009) Development and evaluation of quality control dried blood spot materials in newborn screening for lysosomal storage disorders. Clin Chem 55:158–164

Fitzgerald PB, Williams CL, Corteling N, Filia SL, Brewer K, Adams A et al (2001) Subject and observer-rated quality of life in schizophrenia. Acta Psychiatr Scand 103:387–392

Harmatz P, Giugliani R, Schwartz I, Guffon N, Teles EL, Miranda MC et al (2006) Enzyme replacement therapy for mucopolysaccharidosis VI: a phase 3, randomized, double-blind, placebo-controlled, multinational study of recombinant human N-acetylgalactosamine 4-sulfatase (recombinant human arylsulfatase B or rhASB) and follow-on, open-label extension study. J Pediatr 148:533–539

Hayes IM, Collins V, Sahhar M, Wraith JE, Delatycki MB (2007) Newborn screening for mucopolysaccharidoses: opinions of patients and their families. Clin Genet 71:446–450

Janssen CG, Schuengel C, Stolk J (2005) Perspectives on quality of life of people with intellectual disabilities: the interpretation of discrepancies between clients and caregivers. Qual Life Res 14:57–69

Kakkis ED (2002) Enzyme replacement therapy for the mucopolysaccharide storage disorders. Expert Opin Investig Drugs 11:675–685

Kakkis ED, Muenzer J, Tiller GE, Waber L, Belmont J, Passage M et al (2001) Enzyme-replacement therapy in mucopolysaccharidosis I. N Engl J Med 344:182–188

McKusick VA (2001) The mucopolysaccharidoses, 8th edn. McGraw-Hill, New York. J Inherit Metab Dis 31:173–177

Meikle PJ, Hopwood JJ, Clague AE, Carey WF (1999) Prevalence of lysosomal storage disorders. JAMA 281:249–254

Meikle PJ, Grasby DJ, Dean CJ, Lang DL, Bockmann M, Whittle AM et al (2006) Newborn screening for lysosomal storage disorders. Mol Genet Metab 88:307–314

Muenzer J, Wraith JE, Beck M, Giugliani R, Harmatz P, Eng CM et al (2006) A phase II/III clinical study of enzyme replacement therapy with idursulfase in mucopolysaccharidosis II (Hunter syndrome). Genet Med 8:465–473

Nursey AD, Rohde JR, Farmer RD (1990) A study of doctors' and parents' attitudes to people with mental handicaps. J Ment Defic Res 34(Pt 2):143–155

Parsons EP, Clarke AJ, Hood K, Lycett E, Bradley DM (2002) Newborn screening for Duchenne muscular dystrophy: a psychosocial study. Arch Dis Child Fetal Neonatal Ed 86:F91–F95

Pastores GM, Barnett NL (2005) Current and emerging therapies for the lysosomal storage disorders. Expert Opin Emerg Drugs 10:891–902

Saxena S, Orley J (1997) Quality of life assessment: the world health organization perspective. Eur Psychiatry 12(Suppl 3):263s–266s

Sewitch MJ, Abrahamowicz M, Bitton A, Daly D, Wild GE, Cohen A et al (2002) Psychosocial correlates of patient-physician discordance in inflammatory bowel disease. Am J Gastroenterol 97:2174–2183

Sonnenberg A (2004) Patient-physician discordance about benefits and risks in gastroenterology decision-making. Aliment Pharmacol Ther 19:1247–1253

Spoorenberg A, van Tubergen A, Landewe R, Dougados M, van der Linden S, Mielants H et al (2005) Measuring disease activity in ankylosing spondylitis: patient and physician have different perspectives. Rheumatology (Oxford) 44:789–795

Wang D, Eadala B, Sadilek M, Chamoles NA, Turecek F, Scott CR et al (2005) Tandem mass spectrometric analysis of dried blood spots for screening of mucopolysaccharidosis I in newborns. Clin Chem 51:898–900

Wang D, Wood T, Sadilek M, Scott CR, Turecek F, Gelb MH (2007) Tandem mass spectrometry for the direct assay of enzymes in dried blood spots: application to newborn screening for mucopolysaccharidosis II (Hunter disease). Clin Chem 53: 137–140

Wilcken B (2008) The consequences of extended newborn screening programmes: do we know who needs treatment? J Inherit Metab Dis 2008

Wilson KA, Dowling AJ, Abdolell M, Tannock IF (2000) Perception of quality of life by patients, partners and treating physicians. Qual Life Res 9:1041–1052

Wraith JE, Clarke LA, Beck M, Kolodny EH, Pastores GM, Muenzer J et al (2004) Enzyme replacement therapy for mucopolysaccharidosis I: a randomized, double-blinded, placebo-controlled, multinational study of recombinant human alpha-L-iduronidase (laronidase). J Pediatr 144:581–588

Yen JC, Abrahamowicz M, Dobkin PL, Clarke AE, Battista RN, Fortin PR (2003) Determinants of discordance between patients and physicians in their assessment of lupus disease activity. J Rheumatol 30:1967–1976