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Treatment of mucopolysaccharidosis type II (Hunter syndrome): a Delphi derived practice resource of the American College of Medical Genetics and Genomics (ACMG)

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Mucopolysaccharidosis, type II (MPS II, MIM 309900) is a severe lysosomal storage disease with multisystem involvement. There is one product approved by the FDA, an enzyme replacement therapy, based on a phase III trial in older, attenuated MPS II individuals. Guidance on treatment of MPS II is lacking, not only in general, but for specific clinical situations. A previous systematic evidence-based review of treatment for MPS II demonstrated insufficient strength in all data analyzed to create a definitive practice guideline based solely on published evidence. The American College of Medical Genetics and Genomics (ACMG) Therapeutics Committee conducted a Delphi study to generate an MPS II clinical practice resource of the treatment for these individuals for the genetics community, based on the evidence-based review and subsequent literature. This report describes the process, including consensus development and areas where consensus could not be obtained due to lack of quality evidence. Recommendations from the Delphi process were generated, and areas were highlighted that need further study to help guide clinical care of these individuals.

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INTRODUCTION

The typical, severe form of mucopolysaccharidosis, type II (MPS II, MIM 309900) was first described in two brothers by the Canadian physician Charles Hunter in 1917.[1] The estimated incidence varies from 1/60,000 to 1/150,000, with reports of higher rates among Ashkenazi Jews.[2] It is X-linked and predominately a disease of males, although in rare cases affected females occur through skewing of X-chromosome inactivation.[3] Iduronate-2-sulfatase (IDS), the enzyme deficient in MPS II, catalyzes the removal of sulfate groups from glycosaminoglycans (GAGs). It is targeted to the lysosome by the mannose-6-phosphate system. Loss of enzyme activity causes accumulation of GAGs in tissues and increased excretion of their breakdown products dermatan and heparan sulfate in urine. Enzyme deficiency may be due to total lack of enzyme, but is more often from decreased production, decreased catalytic activity, or protein misfolding.[4]

The signs of MPS II become apparent between the ages of 2 and 4 years with coarsening facial features, short stature, skeletal deformities (dysostosis multiplex), joint stiffness, hepatosplenomegaly, and progressive cognitive deterioration. Multiple organs may be affected as GAGs accumulate over time. Delays in developmental skills are typically evident by age 2 years, with plateauing and decline by age 4 to 6 years.

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Chronic otitis media and conductive hearing loss is present in most and many patients require hearing aids. Umbilical and inguinal hernias are also common, often at initial presentation. Upper airway obstruction manifests with snoring and sleep apnea, and wheezing is noted due to obstructive pulmonary disease. Cardiac disease leading to congestive heart failure occurs from both valve thickening leading to regurgitation and stenosis, and myocardial dysfunction secondary to infiltration with GAGs. Death occurs from the cardiac or pulmonary disease in most by 10 to 15 years of age.[5] There is a broad spectrum of MPS II from the typical severe form to an attenuated or very mild form, with significant heterogeneity between the extremes. Individuals with attenuated disease have minimal if any neurological deficit and live into adulthood but still exhibit skeletal, joint, airway, and cardiac disease. Roughly two thirds of individuals with MPS II have the severe form of the condition, with some genotype–phenotype correlation[6–8] and general consistency of phenotype between siblings in families.[9]

Treatment for MPS II has generally been directed at treating symptoms. Only one product specifically for MPS II treatment has been approved by the US Food and Drug Administration (FDA). Idursulfase (Elaprase®) is an intravenous enzyme replacement therapy (ERT) for MPS II that has been licensed in the United States by the FDA since 2006. A phase II/III trial of this product in individuals with attenuated MPS II over the age of 8 who were cognitively intact demonstrated improvement in some somatic manifestations. Clinical trial endpoint improvements were noted on the six-minute walk test (6MWT) distance and forced vital capacity on pulmonary function tests (PFT).[10,11] Early evidence from the Hunter Outcome Survey suggest life span may be increased by ERT.[12]

Controlled trials of idursulfase have not been conducted on individuals with severe MPS II. Despite the lack of known therapeutic efficacy, individuals with severe MPS II have been treated with ERT. Small case series reporting ERT for the severe form of the disease seem to confirm benefits for reduction in liver and spleen volumes, joint range of motion, and possibly improved growth velocities.[13] It could be anticipated that some somatic manifestations will improve in this group but that cognitive manifestations would not be improved due to the inability of the enzyme product to cross the blood–brain barrier. A phase I/II trial on the use of intrathecal enzyme replacement in severe MPS to overcome this obstacle has recently been reported, demonstrating preliminary safety data, but unfortunately no conclusive improvement in cognition.[14] Hematopoietic stem cell transplant (HSCT) has also been used in MPS II. Earlier studies did not show benefit and demonstrated poor safety, but later case series suggest it may be effective.[15] However, no HSCT clinical trial has been performed for any form of the disorder. Few long-term studies have been published, either in attenuated or severe forms, for any intervention.

Guidance on how to treat MPS II is lacking, not only in general, but for specific clinical situations. Previous guidelines for management of MPS II have been based on informal expert opinion without systematic evidence-based review[16–18] with one previous Delphi method review[19] and one Cochrane review.[20] A guideline on treatment of severe MPS II specifically has also been published, based on clinical experience alone.[21] Recommendations have varied, with statements to "consider" ERT in all patients with MPS II, usually with several caveats.

ERT is expensive and its precise benefits are uncertain. Guidance on many aspects of therapeutic management are needed by the community, including when to initiate ERT, how early in life to start for maximal benefit, when home therapy should be initiated, when to stop therapy, what benefits are expected, how to assess if therapy is working, and what to do if it is not, among many other questions that remain unaddressed by extant studies or current guidelines. To address the lack of guidance, the American College of Medical Genetics and Genomics (ACMG) Therapeutics Committee attempted to examine these issues through a commissioned, independent, systematic evidence-based review of all available data on the treatment of MPS II. Importantly, this review demonstrated insufficient strength in all data analyzed to create a definitive practice guideline based solely on published evidence.[22] The purpose of this project was to use the evidence-based review as a basis to undertake a Delphi process using experts from a variety of disciplines that care for patients with MPS II to develop a practice resource for the community, providing consensus-based recommendations where possible.

MATERIALS AND METHODS

We applied study design and methodologic criteria as specified previously for Delphi studies,[23,24] including definition of an expert, panel size, number of rounds, and a priori definition of consensus. We chose to use number of rounds as our strategy rather than attempting to reach consensus on items given that the quality of the evidence available might not encourage consensus based specifically on the evidence available.

Creating the working group

The ACMG Therapeutics Committee engaged a subcommittee of three members. An initial set of clinical questions was created according to patient, interventions, comparator, and outcome (PICO) methodology, using the initial systematic evidence-based review as the source for statement derivation. This group solicited members of a workgroup that would form the Delphi members, a writing group, and two chairs, and included a Delphi content expert. Individuals who treat MPS II patients were approached to join the workgroup, selected to be a heterogeneous mix of specialties. Conflict of interests were assessed, and the proposal and members were approved by the ACMG Board of Directors.

Systematic evidence-based review methodology

We utilized the previous review,[22] and further added literature published since up to the time of Delphi study initiation (December 2018) using the terms and headings from Bradley supplemental table S2, with dates added to include articles after their search date (ended 31 December 2015) to 1 December 2018:

(((((Mucopolysaccharidosis II[mh] OR Mucopolysaccharidos*[tw]) AND (enzyme replacement therap*[mh] OR ERT [tw] OR idursulfase[tw] OR Elaprase[tw] OR idursulfase beta [tw] OR Hunterase[tw] OR hematopoietic stem cell transplantation[mh] OR bone marrow transplantation[mh] OR cord blood stem cell transplantation[mh])) AND English [lang])) AND ("2016/01/01"[Date—Publication]: "2018/12/01"[Date—Publication]))

A total of 183 additional articles beyond those reviewed by Bradley et al. were retrieved in PubMed. Articles excluded from further review were (1) not MPS II patients, (2) case studies of 1–3 patients, (3) animal studies, or (4) review articles. The remaining articles ($n = 29$) were extracted to a collection and made available to the Delphi members through a shared online drive (Supplementary Material).

Delphi process

The Delphi group consisted of ten members. Two rounds were planned, with an optional third round if it was thought an additional round would generate additional consensus of statements. The Delphi members were provided access to the Bradley review and the subsequent articles that met their original inclusion criteria via an online shared drive, and members were specifically asked to use this information when rating the statements. Statements for the consensus process were created by the writing group from the initial evidence-based review. Surveys with these statements were created in REDCap and invitations sent to the Delphi group. Four weeks were allowed for completion of the survey, with two reminder emails sent prior to closing. A nine-point Likert scale was used to rate agreement or disagreement with the statement. A rating of 7 or more was defined as definite agreement, and a score of 3 or less as definite disagreement with the statement. A predefined threshold of 75% agreement or disagreement to a statement was used to indicate consensus. Participants were required to provide a comment if they did not agree with the statement, or if they wanted to provide feedback. Statements that did not reach consensus in round 1 were reviewed by the chairs. Based on respondent critiques and feedback, those statements needing clarification or division into separate statements were amended and sent out for round 2. Those that would not reach consensus due to lack of guiding data were not carried forward. Responses to round 1 were anonymized and shared with the Delphi members when the round 2 survey invitation was sent out.

Following data analysis and manuscript preparation, this document was reviewed and approved by the ACMG Board of Directors.

RESULTS

A total of eight Delphi members responded in round 1 and nine in round 2, with one person not completing either round. Statements and responses have been grouped together by theme below. A summary of statement consensus results is in Table 1. The full set of 37 statements in round 1 and 24 statements in round 2, with detailed results and Delphi member comments to the statements are included in the Supplementary Material.

Considerations regarding treatment initiation

We first attempted to define in which circumstances therapy should be initiated. There was broad consensus for initiating ERT across a range of considerations. Consensus was achieved for starting ERT for any age with signs or symptoms of severe phenotype or predicted to have severe disease by genotype of any age. Those individuals with a genotype predicted to be attenuated or with a genotype that could not predict phenotype had consensus for starting ERT if they were symptomatic or had signs of disease, but not if they did not have signs or symptoms of disease. Comments from the Delphi members debated what would constitute signs and symptoms, but broad consensus for initiating ERT was achieved using the unqualified statement. Consensus was also reached for the use of pressure equalizing (PE) tubes and hearing aids. No consensus for use of HSCT or intrathecal ERT (IT-ERT) could be reached, regardless of clinical circumstances considered.

A focused consensus emerged regarding use of ERT home therapy. Although the Delphi members provided comments on the importance of moving ERT infusions to the home, the comments were tempered with caution. This guided us to the creation of the statement "I would transition individuals to home therapy with early disease, minimal or easily controlled infusion reactions, and stable home" for which consensus could be reached.

Considerations regarding discontinuing therapy

We next attempted to define stopping points for ERT. We explored if no response to therapy should lead to discontinuation or if adverse reactions to therapy should require stopping. Various factors were explored, including length of time before deciding nonresponse (out to 18 months), presence of antibodies to idursulfase, or allergic reactions (including ability to ameliorate the reactions). No consensus could be obtained for any stopping rule explored, with the exception regarding ERT for an individual with severe MPS II and allergic reaction to ERT that could not be controlled by treatment. Comments from the Delphi members expressed reluctance to stop, even if there was no response. Many also felt that any reaction could be managed by simple measures (antihistamines, steroids, antipyretics) or even use of immunomodulation, thus stopping for adverse reactions was considered to be a rare circumstance.

Table 1 Summary of statement rating results for Delphi rounds 1 and 2, divided by statement reaching consensus and not reaching consensus.

	Average score	Number for	Number against	Number indeterminate
Statements reaching consensus in round 1 ($n = 8$ reviewers)				
S1. I would start enzyme replacement therapy on any infant diagnosed with MPS II	7.29	7	0	1
S2. I would start enzyme replacement therapy on any infant diagnosed with attenuated MPS II	7.43	6	0	2
S4. I would start enzyme replacement therapy on any child (age 1–10) with attenuated MPS II	7.14	6	1	1
S6. I would start enzyme replacement therapy on any adolescent or adult (age 11 and older) with attenuated MPS II[b]	7.00	6	0	1
S15. I would transition individuals to home infusions after 6 months of infusions in a hospital/clinic monitored setting	6.57	7	0	1
S18. If it were available all individuals with attenuated MPS II should have intrathecal treatment[a]	3.14	1	6	1
S29. PE tubes provide a benefit to the patient with MPS II	6.57	7	1	0
S30. PE tubes do not provide a benefit to the patient with MPS II	3.29	1	6	1
S31. Hearing aids provide a benefit to patients with MPS II[b]	7.00	5	1	1
S32. Hearing aids do not provide a benefit to patients with MPS II	2.86	1	6	1
S33. Urine GAG measurements are an important part of the follow up	6.57	6	1	1
S36. Neuropsychology testing is an important part of the follow up	6.57	6	0	2
Statements reaching consensus in round 2 ($n = 9$ reviewers)				
S2A. I would start enzyme replacement therapy on any infant diagnosed with attenuated MPS II predicted by genotype who has clinical signs or symptoms	8.89	9	0	0
S3A. I would start enzyme replacement therapy on any infant diagnosed with MPS II predicted to be severe by known genotype, who has not yet shown signs of neurologic decline	8.11	8	0	1
S3B. I would start enzyme replacement therapy on any infant diagnosed with MPS II predicted to be severe by known genotype, who is already showing signs of neurologic decline	8.22	8	0	1
S3C. I would start enzyme replacement therapy on any infant diagnosed with MPS II and phenotype could not be predicted by genotype who has somatic clinical signs or symptoms	9.00	9	0	0
S5A. I would start enzyme replacement therapy on any child (age 1–5) with severe MPS II	8.22	8	0	1
S5B. I would start enzyme replacement therapy on any child (age 6–10) with severe MPS II	7.67	7	0	2
S5C. I would start enzyme replacement therapy on a child (age 1–5) with severe MPS II only to attempt to improve somatic symptoms	7.33	8	0	1
S5D. I would start enzyme replacement therapy on a child (age 6–11) with severe MPS II only to attempt to improve somatic symptoms	7.33	8	0	1
S10A. I would discontinue ERT for a patient with severe MPS II if the patient had an allergic reaction if the reaction could not be controlled by treatment	7.67	7	0	2
S14B. I would transition individuals to home therapy with early disease, minimal or easily controlled infusion reactions, and stable home	8.56	9	0	0
S27A. Pulmonary function tests are an important part of MPS II evaluation and follow up if the patient is able to perform them	7.67	7	0	2
S34C. Six-minute walk tests are an important part of the follow up in patients who are unable to complete reliably	2.22	1	8	0
S35A. Antibody testing against idursulfase is important for management for those with infusion reactions	7.56	8	0	1
S37A. Liver volume measurements by physical exam are an important part of the follow up	7.78	8	0	1

Table 1 continued

	Average score	Number for	Number against	Number indeterminate
Statements that did not reach consensus				
S8. Age of the patient has no bearing on if I would start enzyme replacement therapy	6.14	4	1	3
S9. The apparent benefits of ERT outweigh the costs under any circumstance	5.43	2	5	1
S13. I would not discontinue ERT under any circumstance	3.29	1	2	5
S16. I would transition individuals to home infusions after 3 months of infusions in a hospital/clinic monitored setting	5.29	3	2	3
S17. If it were available all individuals with MPS II should have intrathecal treatment	4.43	1	2	5
S19. If it were available all individuals with severe MPS II should have intrathecal treatment	4.71	2	2	4
S20. The risks to intrathecal treatment with ERT outweigh the possible benefits	5.43	2	2	4
S21. The benefits to intrathecal treatment with ERT outweigh the possible risks	4.71	1	2	5
S22. Bone marrow transplantation should be considered a viable treatment option for patients with attenuated MPS II	4.71	2	2	4
S23. Bone marrow transplantation should be considered a viable treatment option in patients with severe MPS II	5.43	4	2	2
S24. Bone marrow transplantation is unlikely to provide benefit to patients with MPS II	5.43	2	2	4
S25. Bone marrow transplantation is likely to provide benefit to patients with MPS II[b]	5.14	3	2	2
S26. Annual MRI of the neck should be standard of care for patients with MPS II	4.86	3	3	2
S28. I do not recommend annual otolaryngologic follow up	3.86	2	5	1
S2B. I would start enzyme replacement therapy on any infant diagnosed with attenuated MPS II predicted by genotype who is asymptomatic	6.33	5	0	4
S3D. I would start enzyme replacement therapy on any infant diagnosed with MPS II and phenotype could not be predicted by genotype who is asymptomatic	6.11	4	2	3
S11A. I would discontinue ERT for a patient with attenuated MPS II if the patient had an allergic reaction if the reaction could not be controlled by treatment	6.67	4	1	4
S12A. I would discontinue ERT for a patient with severe MPS II if no measurable effect was appreciated after 12–18 months of treatment and no neutralizing antibodies were present	5.89	5	2	2
S12B. I would discontinue ERT for a patient with severe MPS II if no measurable effect was appreciated after 12–18 months of treatment and neutralizing antibodies were present	6.11	4	1	4
S14A. I would transition all individuals to home therapy	6.89	6	0	3
S34A. Six-minute walk tests are an important part of the follow up in all patients[b]	4.22	1	2	5
S34B. Six-minute walk tests are an important part of the follow up in patients who can complete reliably	6.00	4	1	4
S37B. Liver volume measurements by ultrasound are an important part of the follow up[b]	4.89	2	2	4
S37C. Liver volume measurements by MRI are an important part of the follow up	3.67	2	6	1

ERT enzyme replacement therapy, *GAG* glycosaminoglycan, *MPS* mucopolysaccharidosis, *MRI* magnetic resonance image, *PE* pressure equalizing.
[a]Statements in bold and italic reached consensus on disagreeing with statement. Rating of 7, 8, 9 are *for*; 1, 2, 3 are *against*; and 4, 5, 6 are *indeterminate*.
[b]One member did not submit a reply to this item.

Considerations regarding follow up and monitoring of therapy

Finally, we explored what types of follow up are useful for those on therapy. Consensus was reached for use of clinical exam for liver size, PFTs if they could be performed reliably, antibody testing for evaluating allergic reactions to ERT, urine GAGs, and neuropsychology testing. Consensus was not reached for use of the 6MWT (other than to exclude use if reliability was a concern), diagnostic imaging of liver or spleen size, and routine annual magnetic resonance image (MRI) of the neck.

DISCUSSION

Most rare diseases, even those with approved therapies, lack enough high-quality data to be able to create an evidence-based guideline to assist clinicians in the care of these individuals. MPS II is no exception. Our attempts to gather all available data from multiple sources, including gray sources (material produced by organizations or government outside of academic publishing), via a systematic evidence-based review failed to yield enough information to create a formal clinical guideline based on evidence alone. We attempted to provide an alternative means for guidance through an unbiased expert consensus statement using a Delphi approach.

The process demonstrated the difficulty of establishing guidance when few data are available. The Delphi members were able to reach consensus on statements for which there were good clinical data; however, for clinical questions that had minimal or conflicting published information, expert opinions reflected the uncertainty. One example is the key clinical question of not only when and on whom to initiate ERT, but also when it should be discontinued. Consensus was reached regarding initiation for those with the severe form of MPS II and those with attenuated MPS II who showed signs or symptoms of disease. Our expert panel was unable to establish a consensus on the critical clinical decision to stop therapy outside of allergic reaction that could not be controlled, as no information exists on discontinuation in the literature. Either evidence-based or consensus-based decisions about termination of therapy would depend on a better definition of treatment utility. Some therapies were also difficult to evaluate with no consensus developed for use of IT-ERT and HSCT. Although consensus could not be reached, these additional therapies could still be appropriate interventions if more information accumulates, particularly on HSCT and IT-ERT. Of note, although PFTs and 6MWT were used as defining endpoints in the only phase III trial for ERT, most of our Delphi members did not feel these were very useful measures for following patients, with comments in particular about futility in using them for severe MPS II. It is thus important that better measures be established for defining success in outcomes, particularly as further analysis and additional clinical trials are undertaken.

Our Delphi study yields the following recommendations:

1. All individuals with severe MPS II or predicted to have severe MPS II based on genotype warrant starting ERT, prior to showing signs or symptoms.
2. Individuals with signs or symptoms with either attenuated or severe MPS II warrant ERT.
3. Individuals with attenuated MPS II who are not showing signs or symptoms of disease do not warrant ERT.
4. Home infusions may be considered for those with early disease, easily managed ERT infusion reactions, and a stable home environment.
5. Individuals receiving ERT who have developed allergic reactions that cannot be controlled by standard therapies or immunomodulation should have ERT discontinued.
6. PE tubes and hearing aids are useful therapies.
7. Clinical evaluation of liver and spleen size are recommended for judging clinical effectiveness of treatment, with optional use of imaging modalities (ultrasound or MRI of the abdomen) to follow organ size. PFTs are recommended if the individual can reliably perform them, but there are concerns on the utility of the 6MWT. Lab studies of GAGs are recommended, as well as antibodies to ERT to assess infusion reactions. Finally, neuropsychology testing is recommended for following disease progress.

The statements reaching and not reaching consensus differ from previous expert opinion guidelines.[16,17,19,21] There is broad agreement across studies with ours on considering treatment for symptomatic individuals with ERT. We differ for those predicted to be severe prior to onset of signs and symptoms, recommending ERT. Compared with Latin America guidelines[16] that do not suggest use under age 6, we consider all ages eligible. Guidelines differ regarding discontinuation of therapy. Our study was not able to define a set of stopping rules, whereas previous guidelines have recommended stopping if no effect is noted after 6–12 months of ERT and stopping ERT near the end of life.[21] Our study and previous expert opinions are similar regarding evaluation and follow-up recommendations, reflecting pragmatism, as instruments used in the phase III trial are not easily transferred to the clinical setting for use in younger and more severely affected MPS II individuals.

Our study highlights the difficulties in the field of rare disease therapeutics to assemble evidence and create guidance documents for clinicians. Numerous rare diseases have not had any phase III trials to evaluate therapies, nor may they be possible in many circumstances. Narrow scopes of phase III clinical trials, while establishing short term efficacy and safety in small select populations, will not provide sufficient information to guide all aspects of clinical care. Postmarketing follow-up studies (phase IV patient registries such as the Hunter Outcome Survey[25]) may fill in some gaps, but still leave many questions. The balance between bringing needed therapies to market for individuals and families with these severe and lethal conditions and generating enough evidence in a limited number of affected individuals to fully inform

clinicians will continue to pose problems. In addition, evidence-based reviews are unlikely to find enough data for clinical practice guidelines that meet minimal criteria laid out by the Institute of Medicine,[26] leaving imperfect expert consensus methods as the best approach to create guidance for clinicians.

We attempted to make our process as transparent as possible and to use an expert group as heterogeneous as ACMG policies would allow. This did create limitations to our process, with a smaller Delphi group size that is limited in the number of non-ACMG members permitted and did not allow us to include patient advocates.

Future research should address the major deficiencies identified here: When is initiation of ERT not warranted? What should guide the clinician to stop ERT? Given recent literature on the use of immune modulating therapy in Pompe syndrome,[27,28] should immune tolerance induction also be considered for ERT in Hunter syndrome? What regimen should be used, and in which setting—prophylactic, after development of neutralizing antibodies, only for certain genetic variants? How does HSCT compare with ERT in a clinical trial? In addition, what do new therapies under study (IT-ERT, gene therapies) offer and when should they be considered? What is the best way to assess success of therapy—do we need new clinical evaluations, patient and family important endpoints, or better biomarkers? As more information becomes available, we hope to repeat our process to give better resources to the genetics community.

SUPPLEMENTARY INFORMATION

The online version of this article (https://doi.org/10.1038/s41436-020-0909-z) contains supplementary material, which is available to authorized users.

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DISCLOSURE

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Individual reviewer comments to statements for Delphi Round 1

STATEMENT	REVIEWER	COMMENTS
S1. I would start enzyme replacement therapy on any infant diagnosed with MPS II		
	1	
	2	
	3	
	4	
	5	Would depend on whether likely a severe or more attenuated form and whether symptomatic or asymptomatic
	6	Phenotypic severity at the time of the diagnosis is an important factor for decision making to start enzyme replacement therapy in an infant with MPSII. If the infant has severe neurological features, clinical skeletal features (e.g. scoliosis, kyphosis) and cardiac features (e.g. valvulopathy), there will be no use of enzyme replacement therapy to start, as the enzyme replacement therapy will not change or improve outcome in any of those organ system involvements. If the infant has normal development, normal cardiac anatomy and no severe skeletal system changes (only radiological evidence of bone disease) and hepatomegaly , it will not be known when to start, as the phenotype can be attenuated and enzyme replacement therapy can be delayed until clinical signs of MPSII in an infant with MPSII.
	7	
	8	
S2. I would start enzyme replacement therapy on any infant diagnosed with attenuated MPS II		
	1	
	2	I believe that starting therapy early is important
	3	
	4	
	5	Depending upon whether symptomatic
	6	If there are no or minimal symptoms (e.g. mild hepatomegaly) at the time of the diagnosis other than biochemical and radiological features of MPSII, I would not start enzyme replacement therapy as the treatment is applied weekly. The enzyme replacement therapy will decrease quality of life for individuals as well as increase risk of adverse events and development of antibodies which will likely cause ineffectiveness of enzyme replacement therapy.
	7	
	8	
S3. I would start enzyme replacement therapy on any infant diagnosed with severe MPS II		
	1	
	2	Same answer as earlier. The option would be discussed in detail with the family about benefits to peripheral system
	3	This is probably the right thing to do, and will likely improve QOL over the first 5-6 years. But no evidence it will improve the neurocognitive outcome and some families will find it very burdensome.
	4	
	5	
	6	If the infant has severe neurological features, there will be no use of enzyme replacement therapy, as the enzyme replacement therapy will not change or improve neurodevelopmental outcome. It will decrease quality of life for the patient. If there are clinical skeletal features (e.g. scoliosis, kyphosis) and cardiac features (e.g. valvulopathy) in the absence of neurological features, even I know that those organ damages, occurred prior to enzyme replacement therapy, will not improve, but enzyme replacement therapy might stop progression of organ damage.
	7	define infant - certainly not neonate
	8	
S4. I would start enzyme replacement therapy on any child (age 1-10) with attenuated MPS II		
	1	
	2	
	3	
	4	
	5	
	6	If there are no clinical features, I will not start enzyme replacement therapy to due to risk of neutralizing antibody development and decrease in enzyme effectiveness and not to decrease quality of life.
	7	that's a pretty wide age range
	8	
S5. I would start enzyme replacement therapy on any child (age 1-10) with severe MPS II		
	1	
	2	Dependent on degree of neurological involvement and parental thoughts
	3	I rated this one lower than the similar question for infants, as the evidence is less compelling for QOL improvement, particularly in a 1 year old.
	4	
	5	

	6	If neurological features present, I would not start. If marked hepatomegaly, I will consider. If airway problems and obstructive apnea, it will likely not improve outcome too.
	7	unless there are prevailing reasons not to
	8	
S6. I would start enzyme replacement therapy on any adolescent or adult (age 11 and older) with attenuated MPS II		
	1	
	2	
	3	
	4	
	5	
	6	If mild symptoms such as mild hepatomegaly and mild restricted joint range of motion, I would not start.
	7	probably
	8	I suppose that depends exactly how attenuated they are... perhaps it could be that they are so mildly affected it is not indicated.
S7. I would start enzyme replacement therapy on any adolescent or adult (age 11 and older) with severe MPS II		
	1	
	2	Would discuss risks and low possibility of benefits.
	3	Data do not support this as beneficial except to make the liver smaller.
	4	may not in those with short remaining life expectancy from advanced disease
	5	Depends on how affected and what treatment goals would be
	6	Severe disease outcome will not improve with enzyme replacement therapy, I would not start.
	7	
	8	depending upon wishes of the family. If end stage, probably not...
S8. Age of the patient has no bearing on if I would start enzyme replacement therapy		
	1	
	2	Later treatment is less beneficial. If patient has specific complaint that may benefit from ERT even in the face of neurological involvement, may consider
	3	Disagree because of lack of data supporting the use of ERT in older boys with severe MPS II
	4	
	5	
	6	
	7	
	8	Age, severity and goals of treatment definitely important
S9. The apparent benefits of ERT outweigh the costs under any circumstance		
	1	This may not be true for a very end stage patient
	2	Cost should not be limiting factor
	3	Obviously, many health systems outside the US disagree with this statement. Under any circumstance is very strong.
	4	family/parent choice will override other factors; advanced/end-stage disease may outweigh ERT
	5	
	6	The benefits are very limited that the cost is so high for the limited benefit.
	7	ANY circumstance? no.
	8	ANY is probably too strong a word
S10. I would discontinue ERT for a patient with severe MPS II if the patient had an allergic reaction		
	1	
	2	Would try to deal with reactions
	3	Depends on the severity of the IAR, but weighing potential long term benefits vs short term morbidity (which could be lethal) is difficult
	4	would only discontinue after having failed to treat/prevent allergic reaction successfully or repeated allergic reaction would be life-threatening due to advance disease
	5	Would first attempt management of symptoms
	6	Severity of allergic reaction is important, if not severe, I would not discontinue.
	7	not without trying immune modulation first
	8	treat and desensitize
S11. I would discontinue ERT for a patient with attenuated MPS II if the patient had an allergic reaction		
	1	
	2	Would attempt to deal with allergic reaction with premeds
	3	Here there is likely to be more benefit. Would try to find a solution to the IARs.
	4	would only discontinue after having repeatedly failed to treat/prevent allergic reaction successfully
	5	Would first attempt management of symptoms
	6	Severity of allergic reaction is important, if not severe, I would not discontinue.
	7	not without trying immune modulation
	8	treat and desensitize

S12. I would discontinue ERT for a patient with severe MPS II if no measurable effect was appreciated after 12-18 months of treatment

1	
2	
3	I would definitely consider this and engage the family is discussing discontinuation.
4	
5	Would discuss goals with parents and whether to continue
6	
7	case dependent
8	if nothing i.e. GAGs or liver size, etc... is measurement there is likely an additional issue which needs resolving e.g. neutralizing Ab.

S13. I would not discontinue ERT under any circumstance

1	I would discontinue in a late stage patient if parents and I agreed that the burden of therapy outweighed any possible benefit in terms of maintaining health
2	This is too broad a statement. neutralizing antibodies, severe allergy and questionable efficacy may be reasons to discontinue
3	Any is a strong statement.
4	if life-threatening effects, if there is no evidence of benefit, if had HSCT
5	
6	Depending on neurological features and no response to therapy, I would discontinue.
7	
8	Again, ANY is too strong a word.

S14. I would transition all individuals to home infusions

1	There might be rare exceptions if a very dysfunctional household
2	Depends on age, frequency/type of reaction
3	Try to do this if possible.
4	may not transition if has advanced/severe disease that requires close monitoring, if has prior evidence of repeated infusion reactions, if home/social circumstances are not beneficial to home infusions
5	If family wished and infusions without side effects
6	
7	not ALL, but certainly as many as possible
8	if the family is willing

S15. I would transition individuals to home infusions after 6 months of infusions in a hospital/clinic monitored setting

1	
2	
3	This is my usual timeline for transition.
4	if appropriate based on home/social circumstance, if no recurrent infusion reactions, if MPS severity not too severe so that clinical status not ideal or unsafe
5	If parents wish
6	
7	
8	6 months at earliest... usually a year

S16. I would transition individuals to home infusions after 3 months of infusions in a hospital/clinic monitored setting

1	Occasionally I might do this but usually wait 4-6 months
2	
3	
4	longer monitoring time period seems reasonable of about 6 months based on manuscript by Giugliani 217
5	If parents wish
6	Antibody production would be around 3 months and they are at risk for allergic reactions. I would wait longer than 3 months.
7	I'd give it longer than 3 mos
8	6 months at earliest... usually a year

S17. If it were available all individuals with MPS II should have intrathecal treatment

1	
2	Not proven. Early onset maybe
3	Data do not support and delivery is very difficult
4	minimal evidence of benefit with high risk of AEs
5	Unclear benefits:risks
6	If no neurological features, it is an invasive treatment to apply to all MPSII individuals.
7	SHOULD? I'd agree to should be considered with the patient/family
8	Agree we need CNS treatment for everyone... is IT effective? Perhaps statement should read "If an effective IT treatment was available...

S18. If it were available all individuals with attenuated MPS II should have intrathecal treatment

1	
2	No evidence based medicine
3	Data do not support, delivery is difficult.

4	minimal evidence of benefit
5	I think benefits are presently unclear
6	it is an invasive treatment to apply to attenuated MPSII individuals.
7	SHOULD? I'd agree to should be considered with the patient/family
8	as above

S19. If it were available all individuals with severe MPS II should have intrathecal treatment

1	It is likely not beneficial for severe patients with very late stage disease
2	data not clear
3	If delivery problem is solved, this would be a better option.
4	minimal evidence of benefit
5	
6	
7	SHOULD? I'd agree to should be considered with the patient/family
8	

S20. The risks to intrathecal treatment with ERT outweigh the possible benefits

1	This is probably true only for late stage patients who are unlikely to benefit and have high anesthetic risks
2	Not for all cases. Perhaps early severe may benefit
3	Currently this is true
4	risks appear manageable, but are present
5	
6	If neurological features present, IT-ERT will likely improve those and will be beneficial and should be applied.
7	who knows?
8	Is this generic or referring to Elaprase?

S21. The benefits to intrathecal treatment with ERT outweigh the possible risks

1	
2	Not clear to me
3	Little data on benefit since the number of individuals in trials was small and delivery was an issue.
4	minimal benefits are present
5	
6	In individuals with neurological features, but not in attenuated MPSII individuals.
7	who knows?
8	Is this generic or referring to Elaprase?

S22. Bone marrow transplantation should be considered a viable treatment option for patients with attenuated MPS II

1	Mortality is too high
2	
3	This is a really good question. It would depend on age of transplant and whether risks could be reduced. Costs are less than for ERT.
4	evidence of effective treatment of MRI findings, ADLs, and survival
5	
6	BMT is important treatment to treat neurological features and to prevent progressive neurodegeneration. BMT should not be applied to attenuated MPSII individuals.
7	worth discussing with patient/family
8	Could have just as easily checked 7, but this needs a little more discussion. What does viable mean? for non CNS... higher risk for perhaps similar gain as ERT. For me, CNS effects are less clear. Would a BMT perhaps preclude the use of an AAV gene therapy in the future?

S23. Bone marrow transplantation should be considered a viable treatment option in patients with severe MPS II

1	If the patient is diagnosed at a young age- the benefits are not totally clear but there may be some cognitive benefit
2	
3	Needs to be a clinical trial in boys identified by Family history or NBS. Transplant after age 3 seems to have poor neurocognitive outcomes in adolescents.
4	evidence of effective treatment of MRI findings, ADLs, and survival, but need to consider age of HSCT
5	If able to be done prior to development of neurologic symptoms
6	There is no proven effect of BMT in MPSII individuals.
7	
8	as above

S24. Bone marrow transplantation is unlikely to provide benefit to patients with MPS II

1	It has somatic benefits but the cognitive benefit are unclear
2	Undecided at this point
3	Data is still uncertain and there is very little experience in the US.
4	good evidence from studies in Japan and China on improved survival, engraftment. With newer transplant techniques available older data now seem less pertinent.
5	
6	
7	

	8	as above
S25. Bone marrow transplantation is likely to provide benefit to patients with MPS II		
	1	Same comment as above
	2	
	3	Same answer as above- not enough data.
	4	
	5	
	6	It is not proven to be beneficial so far. There are single case reports.
	7	if it doesn't kill them
	8	if it doesn't kill them...
S26. Annual MRI of the neck should be standard of care for patients with MPS II		
	1	Many older patients who have had stable MRI may only need imaging every 2-3 years. In the case of severe patients with advanced disease who require anesthesia for MRI, the benefits may be outweighed by the risks
	2	For childhood yes but ?adulthood
	3	Given airway and anesthesia issues, I need to see a BIG benefit to doing this.
	4	but with limited discussion in current literature review
	5	
	6	Anesthesia and positioning presents risks of cervical spine injury and should not performed as routine investigation for monitoring.
	7	I didn't see any data on this in the review
	8	
S27. Pulmonary function tests are an important part of MPS II evaluation and follow up		
	1	Although not possible for all patients
	2	
	3	Yes if you can get the boys to do it.
	4	but with limited discussion in current literature review
	5	
	6	Difficult to apply in children.
	7	
	8	cooperation is too important
S28. I do not recommend annual otolaryngologic follow up		
	1	I recommend it as needed depending on the patient
	2	Disagree but dependent on age
	3	They all need it, for hearing as well as airway issues.
	4	ongoing ENT management is necessary as disease related progression of symptoms is (ie, risk for recurrent infections are still present even after ERT
	5	
	6	I recommend to see the degree of hearing loss or middle ear effusions, if there is any need for hearing aid or middle ear tubes to drain effusions.
	7	
	8	I do
S29. PE tubes provide a benefit to the patient with MPS II		
	1	Most patients
	2	
	3	Many need hearing aids too.
	4	
	5	
	6	
	7	
	8	If there is middle ear dysfuction
S30. PE tubes do not provide a benefit to the patient with MPS II		
	1	
	2	
	3	Some have a definite conductive component.
	4	ongoing ENT management is necessary as disease related progression of symptoms is (ie, risk for recurrent infections are still present even after ERT
	5	
	6	Important to drain effusions to improve hearing.
	7	
	8	If there is middle ear dysfuction, this is false
S31. Hearing aids provide a benefit to patients with MPS II		
	1	
	2	
	3	Not all will wear them.
	4	limited evidence in literature review
	5	
	6	

7	
8	If hearing loss is present

S32. Hearing aids do not provide a benefit to patients with MPS II

1	
2	
3	Disagree.
4	limited evidence in current literature review
5	
6	Hearing aids are important to improve hearing and during regular ENT follow-up, all patients should be provided with hearing difficulties.
7	
8	If hearing loss not present

S33. Urine GAG measurements are an important part of the follow up

1	
2	
3	I do this, but not convinced they inform my management.
4	indicator of pharmacodynamic activity of ERT/HSCT
5	
6	If patient is on treatment/, is an important part of follow-up to monitor treatment outcome.
7	
8	

S34. Six minute walk tests are an important part of the follow up

1	For patients who are able to do it
2	
3	They are more important for clinical trials than for informing management. If they were easier to get done, I would do them more often.
4	important due to FDA, but limited due to nature of testing unable to differentiate between "incomplete" testing due to cognitive vs somatic/joint/muscle/bone limitations
5	
6	It might be in individuals on enzyme replacement therapy.
7	I'm lukewarm about this as a clinical tool
8	to much effort/orthopedic/CNS dependance

S35. Antibody testing against idursulfase (total and neutralizing) are important for management

1	
2	
3	
4	Ab testing is helpful for interpretation of patient response (ie, high GAG levels) but unclear for associations with AEs
5	Only if not meeting treatment goals or having allergic symptoms
6	
7	
8	

S36. Neuropsychology testing is an important part of the follow up

1	May be important if we have an approved therapy for the CNS. Right now not particularly useful
2	
3	
4	especially in attenuated patients; limited importance in severe patients
5	
6	
7	if you can get it done
8	If treating CNS disease

S37. Liver volume measurements are an important part of the follow up

1	By PE only, not imaging
2	
3	Not if you need a sedated MRI to do it. Clinical exam is helpful and without risk or cost.
4	
5	
6	
7	
8	

Individual reviewer comments to statements for Delphi Round 2

STATEMENT	REVIEWER	COMMENTS
S2A. I would start enzyme replacement therapy on any infant diagnosed with attenuated MPS II predicted by genotype who has clincal signs or symptoms		
	1	If there are signs and symptoms, disease burden is clearly significant enough to warrant therapy
	2	
	3	
	4	
	5	
	6	
	7	
	8	
	9	infant means<12 months?
S2B. I would start enzyme replacement therapy on any infant diagnosed with attenuated MPS II predicted by genotype who is asymptomatic		
	1	I think prevention of symptoms is more likely to be successful than reversal
	2	
	3	
	4	
	5	
	6	The asymptomatic infants should not be treated until they show first sign of the disease such as hepatosplenomegaly.
	7	data is limited/unclear on when therapy indicated in asymptomatic infant with predicted attenuated MPSII
	8	
	9	infant means <12 months
S3A. I would start enzyme replacement therapy on any infant diagnosed MPS II predicted to be severe by known genotype, who has not yet shown signs of neurologic decline		
	1	
	2	
	3	
	4	
	5	
	6	
	7	
	8	
	9	
S3B. I would start enzyme replacement therapy on any infant diagnosed MPS II predicted to be severe by known genotype, who is already showing signs of neurologic decline		
	1	Beneficial for somatic disease, will improve quality of life
	2	
	3	
	4	
	5	This one depends on the level of decline.
	6	
	7	
	8	
	9	
S3C. I would start enzyme replacement therapy on any infant diagnosed with MPS II and phenotype could not be predicted by genotype who has somatic clincal signs or symptoms		
	1	
	2	
	3	
	4	
	5	
	6	
	7	
	8	
	9	
S3D. I would start enzyme replacement therapy on any infant diagnosed with MPS II and phenotype could not be predicted by genotype who is asymptomatic		
	1	
	2	
	3	
	4	

	5
	6 The asymptomatic infants should not be treated until they show first sign of the disease such as hepatosplenomegaly.
	7 unclear indication for treatment of asymptomatic infant with unclear genotype
	8 hard to understand the scenario
	9
S5A. I would start enzyme replacement therapy on any child (age 1-5) with severe MPS II	
	1
	2
	3 Depends on behavior, ease of administration and parental wishes
	4
	5 At this age, there is likely to be some benefit to somatic features.
	6
	7
	8
	9
S5B. I would start enzyme replacement therapy on any child (age 6-10) with severe MPS II	
	1
	2
	3 Would have to predefine what symptoms I am interested in helping
	4
	5 Depends on level of function and what the burden of infusions is to family.
	6
	7
	8
	9
S5C. I would start enzyme replacement therapy on a child (age 1-5) with severe MPS II only to attempt to improve somatic symptoms	
	1 Don't like wording- would be interested not only in improvement but also in prevention of worsening
	2
	3
	4
	5
	6
	7
	8 signs and symptoms
	9
S5D. I would start enzyme replacement therapy on a child (age 6-11) with severe MPS II only to attempt to improve somatic symptoms	
	1 Same comment as above
	2
	3
	4
	5
	6
	7
	8 I really think changing to signs and symptoms is important. A 6 year old severe child is not likely to be able to describe symptoms... they would need to be deduced.
	9
S10A. I would discontinue ERT for a patient with severe MPS II if the patient had an allergic reaction if the reaction could not be controlled by treatment	
	1 If reaction severe and parents agree, would discontinue but would evaluate on a case by case basis. I think it is very rare that allergic reactions cannot be controlled.
	2
	3 Would have to weigh risk benefit
	4
	5
	6
	7
	8 my confusion about this is a single reaction or recurrent uncontrolled reactions.... I am answering for recurrent
	9 if treatment means an immune modulation or anti-anaphylaxis protocol
S11A. I would discontinue ERT for a patient with attenuated MPS II if the patient had an allergic reaction if the reaction could not be controlled by treatment	
	1 Same comment as above
	2

	3 Would depend on severity of reaction
	4
	5 I would try to find a way to attenuate the allergic response
	6
	7
	8 my confusion about this is a single reaction or recurrent uncontrolled reactions.... I am answering for recurrent
	9 same
S12A. I would discontinue ERT for a patient with severe MPS II if no measurable effect was appreciated after 12-18 months of treatment and no neutralizing antibodies were present	
	1 May not see a significant change and could still be of benefit in preventing worsening
	2 I have never encountered this situations when there are no neutralizing antibodies
	3 Likley yes but would discuss with family
	4
	5 depends on the age
	6 12-18 months to decide for discontinuation is not sufficient for me to stop the treatment, especially if tolerated well.
	7
	8
	9
S12B. I would discontinue ERT for a patient with severe MPS II if no measurable effect was appreciated after 12-18 months of treatment and neutralizing antibodies were present	
	1 I would discuss with family and consider immune modulation if family on board.
	2 I would try to desensitize first
	3
	4
	5
	6
	7 may consider more "aggressive" immunosuppressive therapies
	8
	9 if an immune modulation protocol doesn't work
S14A. I would transition all individuals to home therapy	
	1 I would aim to transition all patients but there will be exceptions where families do not want this or patient is having ongoing reactions
	2 unless they need monitoring because of reactions
	3 Not if having infusion reactions, airway issues
	4 After a period of months of uneventful infusions in our local infusion center
	5 some families can't manage this, but I try
	6
	7 this is dependent upon patient/family/social/insurance circumstances, but would prefer if patient stable/responding
	8 As long as the family is willing
	9 unless they have reactions
S14B. I would transition individuals to home therapy with early disease, minimal or easily controlled infusion reactions, and stable home	
	1
	2
	3
	4
	5
	6
	7
	8
	9
S27A. Pulmonary function tests are an important part of MPS II evaluation and follow up if the patient is able to perform them	
	1
	2
	3
	4
	5
	6
	7
	8
	9
S34A. Six minute tests are an important part of the follow up in all patients	
	1
	2

3	only if age appropriate and able to comply with directions
4	
5	
6	Only in treated patients.
7	the 6MWT testing is too challenging for routine care in young patients
8	
9	

S34B. Six minute tests are an important part of the follow up in patients who can complete reliably

1	
2	
3	
4	
5	
6	
7	may not correlate with clinical status/improvements
8	I'm meh about this. Very, very difficult to interpret and achieve reliability
9	

S34C. Six minute tests are an important part of the follow up in patients who are unable to complete reliably

1	If unable to perform reliably, it is pointless
2	this test is not important
3	
4	
5	
6	
7	6MWT is limited in its utility in this situation
8	
9	

S35A. Antibody testing against idursulfase is important for management for those with infusion reactions

1	
2	
3	Yes but the results take too long to come back to be clinically relevant
4	
5	IARs don't always correlate with measurable Abs
6	
7	
8	
9	

S37A. Liver volume measurements by physical exam are an important part of the follow up

1	
2	
3	
4	
5	
6	
7	
8	
9	

S37B. Liver volume measurements by ultrasound are an important part of the follow up

1	
2	
3	
4	
5	
6	
7	US is not as reliable/reproducible in this measurement often
8	
9	

S37C. Liver volume measurements by MRI are an important part of the follow up

1	
2	
3	
4	
5	additional information is not worth the risk of anesthesia and/or expense
6	Anesthesia will be invasive to perform MRI liver volume measurement in MPSII.
7	
8	
9	how often?

ADDITIONAL REFERENCES

The following is the list of articles published since the initial systematic evidence-based review that were made available to the Delphi members. Articles were selected per the description in the methods and materials.

1. Bodamer, O., Scarpa, M., Hung, C., Pulles, T. & Giugliani, R. Birth weight in patients with mucopolysaccharidosis type II: Data from the Hunter Outcome Survey (HOS). *Mol Genet Metab Rep* **11**, 62-64 (2017).
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