Unmet Needs in the Treatment and Care of Somatic Manifestations in People with Mucopolysaccharidosis Type II (Hunter Syndrome): a Targeted Literature Review

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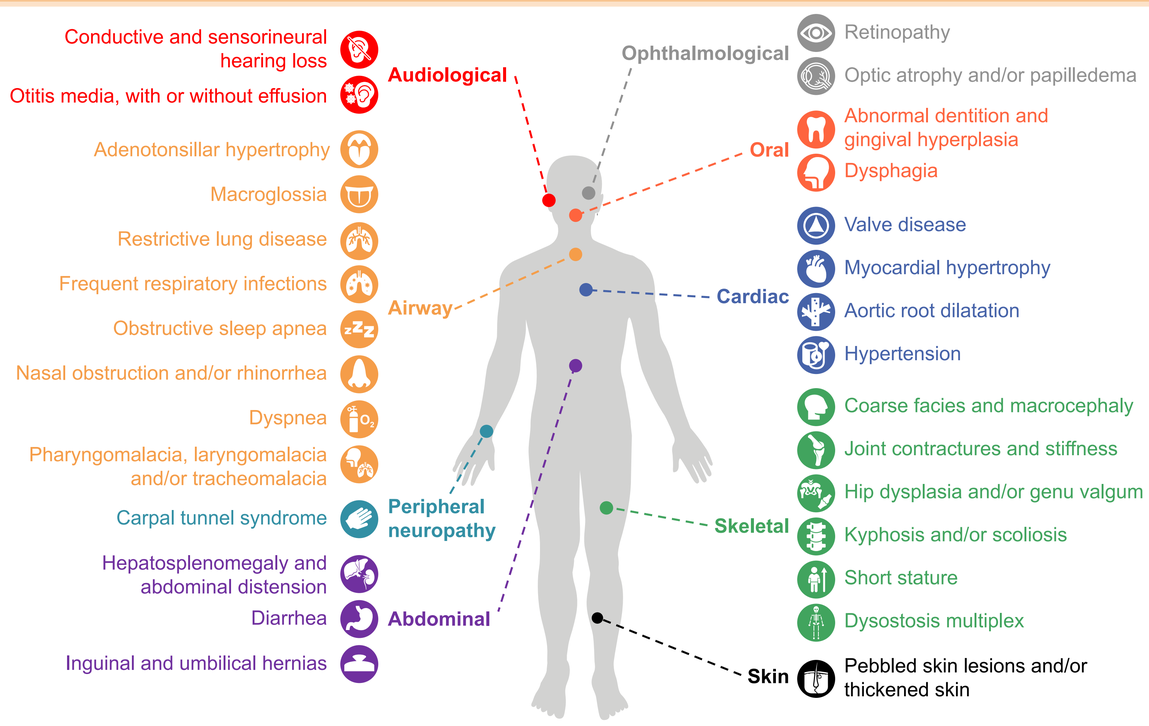
Introduction

- Mucopolysaccharidosis type II (MPS II) causes pathogenic accumulation of glycosaminoglycan (GAG) substrates throughout the bodies of affected individuals.[1,2]
- The neurological and somatic manifestations of MPS II are not fully addressed by approved treatments, including standard-of-care enzyme replacement therapy (ERT), which has been available since 2006.[2,3]
- While neurological manifestations have the greatest unmet need for novel therapeutic strategies, somatic manifestations (**Figure 1**) also substantially affect quality of life, morbidity and life expectancy.[3–8] Therefore, we conducted a targeted literature review (TLR) to characterize and gain insights into the unmet needs in the treatment and care of somatic manifestations of MPS II.

Figure 1. Somatic manifestations of MPS II



Methods

- This TLR was conducted between July and September 2024 in accordance with the PRISMA-S checklist (**Figure 2**).[9,10]
- Peer-reviewed publications, abstracts, reports and posters published between 2006 and 2024 were included.
- Records were identified from Embase, MEDLINE and expert sources. Following initial searches, an abstract screen, full-text review, citation cross-check and data extraction were performed.

Results

Literature searches

- Of 1289 records identified, 361 were included for data extraction (**Figure 2**).
- Four major unmet needs were identified:

1	Guidelines and recommendations are needed to enable **early diagnosis and early initiation of treatment of MPS II**, both of which have been shown to result in improved long-term somatic outcomes. Clarity is needed on how to best **monitor somatic disease progression and treatment effectiveness** for current treatments and in anticipation of next-generation therapeutic medicines in development.
2	Current treatments do not fully address **cardiovascular and respiratory disease manifestations** of MPS II that frequently lead to early-age death. In addition, current treatments do not fully address **audiological, ophthalmological and musculoskeletal manifestations** of MPS II, which lead to significant morbidity and impacts on health-related quality of life (HRQoL).
3	Strategies, recommendations and guidelines are needed for the **transition from pediatric to adult care** for those living with MPS II.
4	People living with MPS II experience **significant treatment and disease burden**. Caregivers also experience significant burden.

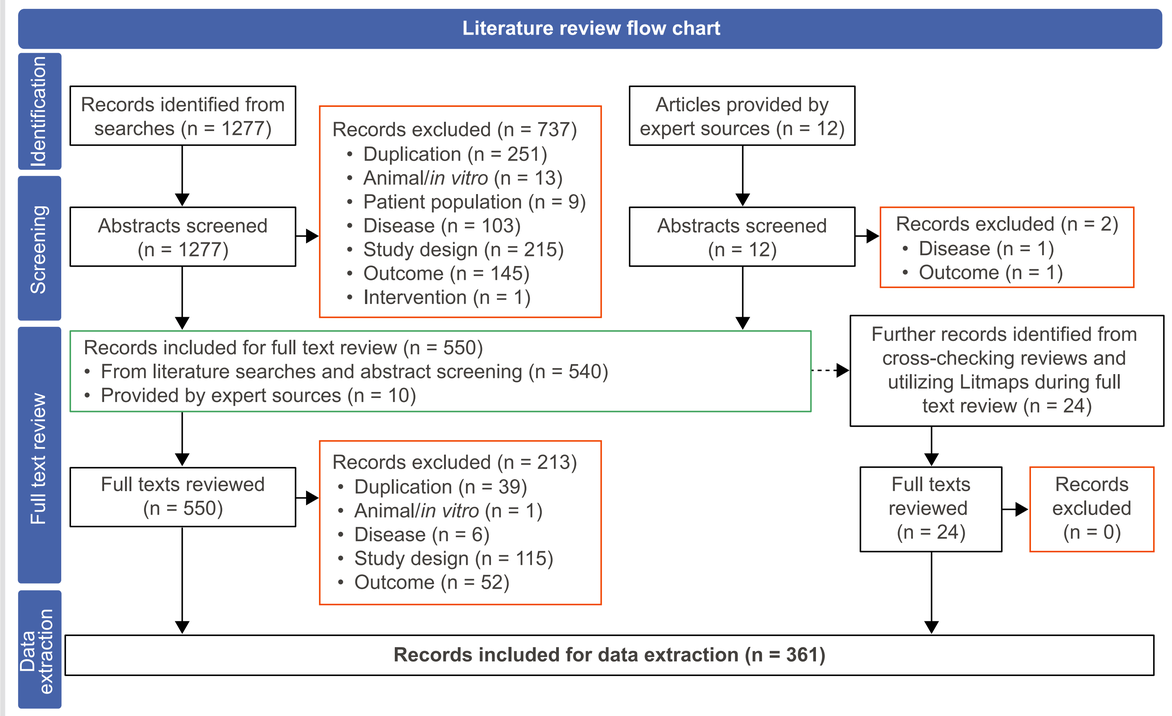
Unmet need 1 – diagnosis, treatment initiation, dosing and monitoring

- Early treatment initiation can improve patient outcomes, as evidenced by trials in patients under 5 years of age and sibling pair studies. Presymptomatic treatment initiation has been recommended to optimize patient outcomes and to prevent or slow the development of irreversible damage.[11–13]
- However, presymptomatic treatment initiation requires early diagnosis before observable symptoms. Proposed strategies to achieve early diagnosis include the wider adoption of newborn screening and increased awareness of early signs and symptoms that should raise MPS II clinical suspicion.[14–16]
- Because GAGs are the primary treatment target for MPS II, the initial marker of efficacy should be the rapid normalization of urinary GAGs. In the absence of established MPS II treatment goals, targeting the normalization of urinary GAGs could be an important strategy to increase the likelihood of clinical benefit.[3,17–19]
- The limitations of urinary GAGs as a biomarker have also been acknowledged. Alternate biomarkers for treatment efficacy and disease progression have been suggested, including composite markers to capture the multisystemic nature of the disease.[3,20–22]
- There is a paucity of data describing the effect of different treatment doses on somatic manifestations. Pivotal trials of ERT have shown that increased doses improve clinical outcomes, although they are also associated with higher rates of infusion-related reactions.[1,23–25]
- Questions remain about whether increased dosing would result in faster and more consistent urinary GAG normalization than current dosing regimens, without serious immunological responses.[26] The impact of increased dosing on treatment penetration into bradytrophic or hard-to-reach tissues also remains poorly described.

Unmet need 2 – causes of treatment inefficacy

- Despite efficacy of current treatments in certain clinical outcomes, some somatic manifestations worsen with age as the disease progresses, resulting in early-age death, substantial morbidity and impacts on HRQoL.[27–30]
- While ERT has been consistently shown to reduce urinary and serum GAGs, levels often remain above the upper limit of normal even after lengthy periods of treatment and do not normalize in a substantial number of patients.[1,23,24,31–33]
- Excessively high GAG levels for prolonged periods of time (despite significant reductions caused by treatment) indicate an ongoing increase to lifetime GAG burden and the subsequent associated progression of somatic manifestations.[2,3,34] As such, there remains an unmet need for therapeutic strategies that rapidly reduce, normalize and maintain GAG levels to prevent disease progression.
- Current treatment strategies have a limited effect on bradytrophic tissues (such as cardiac valve, aortic root, bone, cartilage and cornea) owing to insufficient enzyme penetration. Penetration into ophthalmological tissue is further limited by the blood–retina barrier. Certain tissues (such as musculoskeletal tissue) express fewer mannose-6-phosphate receptors than others, thereby limiting enzyme endocytosis into target cells.[3,35]
- GAG accumulation activates secondary inflammatory cascades and results in DNA, protein and lipid oxidation. The effect of current treatment strategies on secondary inflammatory cascades is not well described and manifestations with immunological causation may not be adequately addressed by current management. Current treatment strategies have been shown to reduce oxidation, but not to normal levels, indicating ongoing pathogenic oxidative processes.[32,33,36,37]

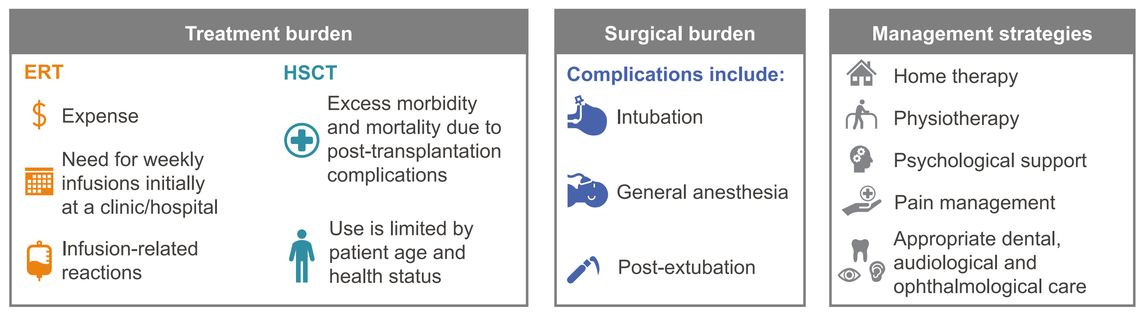
Figure 2. Literature search process



Unmet need 3 – pediatric to adult transition

- Although life expectancy for patients with MPS II remains reduced, improved management strategies have led to more patients surviving into adulthood. Older patients are now presenting more commonly to adult (rather than pediatric) surgeons and anesthesiologists, many of whom are unlikely to have MPS II experience or an awareness of the intubation and anesthetic complications in these patients.[38–40]
- Numerous challenges exist during the transition from pediatric to adult care. Strategies should be introduced to ensure effective coordination, integration and education of healthcare professionals, caregivers and patients during transition.[38,39]

Figure 3. Treatment and surgical burdens of MPS II, with potential auxiliary management strategies to improve HRQoL



Unmet need 4 – patient and caregiver burden

- Somatic manifestations have substantial impacts on the HRQoL of patients and caregivers, affecting their physical, mental and social health.[8] ERT and hematopoietic stem cell transplantations (HSCT) are also both associated with specific burdens (**Figure 3**).[2,41]
- Patients with MPS II also experience substantial surgery-related morbidity and mortality (**Figure 3**). Consequently, surgical procedures are recommended to be performed only by those with previous experience of treating patients with MPS II and patients with difficult airways.[13,19]
- Specific management strategies are recommended to improve HRQoL and certain somatic manifestations, while also reducing disease and treatment burdens (**Figure 3**).[2,7,19,42]

Conclusions

- This TLR uncovered four major unmet needs for the treatment and care of somatic manifestations in people with MPS II, despite the availability of approved treatments.
- These findings can help to guide the development of novel therapies and disease management strategies to improve care for patients with MPS II.

REFERENCES

1. Muenzer J *et al. Genet Med* 2006;8:465–73.
2. D'Avanzo F *et al. Int J Mol Sci* 2020;21:1258.
3. Parini R, Deodato F. *Int J Mol Sci* 2020;21:2975.
4. Lau H *et al. Mol Genet Metab Rep* 2023;37:101005.
5. Zanetti A, Tomanin R. *BioDrugs* 2024;38:639–55.
6. Jones SA *et al. J Inherit Metab Dis* 2009;32:534–43.
7. Guffon N *et al. Orphanet J Rare Dis* 2015;10:43.
8. Needham M *et al. J Genet Couns* 2015;24:635–44.
9. Page MJ *et al. BMJ* 2021;372:n71.
10. Rethlefsen ML *et al. Syst Rev* 2021;10:39.
11. Tajima G *et al. Mol Genet Metab* 2013;108:172–7.
12. Giugliani R *et al. Genet Metab* 2014;16:435–41.
13. Burton BK *et al. Int J Neonatal Screen* 2020;6:73.
14. Burton BK *et al. Mol Genet Metab* 2023;140;107557.
15. Ayodele O *et al. Int J Neonatal Screen* 2024;10:71.
16. Mendelsohn NJ *et al. Genet Med* 2010;12:816–22.
17. Jones SA *et al. Mol Genet Metab* 2020;130:255–61.
18. McBride KL *et al. Genet Med* 2020;22:1735–42.
19. Scarpa M *et al. Orphanet J Rare Dis* 2011;6:72.
20. Clarke LA *et al. J Inherit Metab Dis* 2012;35:355–62.
21. Stapleton M *et al. Expert Opin Orphan Drugs* 2017;5:295–307.
22. Metryka A *et al. J Inborn Errors Metab Screen* 2019;7:1–12.
23. Giugliani R *et al. Mol Ther* 2021;29:2378–86.
24. Sohn YB *et al. Orphanet J Rare Dis* 2013;8:42.
25. Muenzer J *et al. Mol Genet Metab* 2007;90:329–37.
26. Scarpa M. *Expert Opin Orphan Drugs* 2013;1:89–98.
27. Al-Hertani W *et al. Int J Mol Sci* 2024;25:8573.
28. Chan MY *et al. Mol Genet Metab Rep* 2023;36:100991.
29. Okuyama T *et al. Mol Ther* 2021;29:671–9.
30. Ahmed A *et al. Mol Genet Metab Rep* 2016;7:27–31.
31. Muenzer J *et al. Genet Med* 2011;13:95–101.
32. Fujitsuka H *et al. Mol Genet Metab Rep* 2019;19:100455.
33. Khan SA *et al. Mol Genet Metab* 2018;125:44–52.
34. Kampmann C *et al. J Inherit Metab Dis* 2025;48:e12808.
35. Kowalski T *et al. Ophthalmic Genet* 2021;42:631–6.
36. Jacques CED *et al. Biochim Biophys Acta* 2016;1862:1608–16.
37. Jacques CED *et al. Mutat Res Genet Toxicol Environ Mutagen* 2018;835:21–24.
38. Lampe C *et al. Mol Genet Metab Rep* 2019;21:100508.
39. Žuber Z *et al. Biomedicines* 2023;11:1668.
40. Hack HA *et al. Anaesth Intensive Care* 2016;44:660–8.
41. Nan H *et al. Biomed Res Int* 2020;2020:2408402.
42. Elkhatib AA. *Spec Care Dentist* 2023;43:250–7.

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