Disease Burden and Efficacy of Current Treatment for Non-Neuronopathic MPS II Patients: A Systematic Literature Review

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BACKGROUND AND OBJECTIVES

- Mucopolysaccharidosis type II (MPS II, Hunter syndrome) is an ultra-rare genetic disease (incidence rate: 0.38 to 1.09/100,000 live male births)[1] with manifestations caused by mutations in the iduronate-2-sulfatase gene, leading to impaired enzymatic function and subsequent pernicious accumulation of glycosaminoglycans in multiple organs.
- The clinical severity and phenotypical involvement in MPS II exist in a spectrum, but two main forms are recognized[2]:
  - Neuronopathic MPS II (nMPS II), also defined as the early progressive, very severe form[3], is characterized by debilitating central nervous system (CNS) involvement and manifests with cognitive deterioration[4], physical disabilities and death before 15 years of age.[2,5]
  - The non-neuronopathic phenotype (nnMPS II) is characterized by delayed diagnosis, severe physical disabilities, mild to moderate CNS impacts and death typically occurring in the twenties[2], with some living beyond their 50s[6].
- Physical manifestations are a core component of both forms. The trajectory of MPS II is not predictable for most patients as there is not a perfect genotype-phenotype correlation, therefore classification is often made according to clinical course.
- Although an enzyme replacement therapy (ERT) for MPS II was approved in 2006 and is standard of care (SOC) today, this ERT cannot cross the blood-brain barrier (BBB) and thus unable to access the CNS to treat neurologic symptoms.
- Due to the severe neurodegenerative course of the illness, the characterization of unmet need has predominantly focused on the nMPS II population.
- A systematic literature review was conducted to assess clinical, humanistic, and economic burden, mortality, and efficacy/safety of nnMPS II patients on current SOC treatment.

METHODS

- Medline, Embase, Cochrane Central/Reviews were searched from 2003 to February 2023, for peer-reviewed articles and conference abstracts (in English), supplemented by a search on conference websites (last 3 years), and study registries **(Table 1)**.
- While a broad search was conducted for any phenotype, only data for nnMPS II was included during the selection. In total, 57 publications referring to 52 studies were included. The flow chart in **Figure 1** presents the results of the selection process.

Table 1: PICO(+) framework for scope of systematic review

Category	Details
Population	• Non-neuronopathic MPS II or Hunter syndrome
Intervention	• Idursulfase (Elaprase) • Any other pharmaceutical treatment, investigational drugs (Phase 2 or later), off-label use, gene therapy
Comparator	• No restriction
Outcomes	• Clinical burden (prevalence, frequency, severity, and duration of clinical symptoms and comorbidities) • Economic burden (including total costs, direct/indirect costs [work productivity, missed workdays for caregivers], resource utilization) • Humanistic burden (impact on QoL and any PRO, health state utilities), including caregiver burden • Mortality • Efficacy (any endpoints) • Safety (any adverse events, endpoints)

Study types	• Any type of studies, e.g.,
	  • RCTs, clinical trials (at least Phase 2)
	  • Single arm interventional studies, open-label extensions
	  • Observational studies, real-world data studies, registries, non-interventional studies
	  • Case series, case reports (included during search and abstract screening, excluded during full text screening)
	  • Systematic reviews and meta-analyses (for results and reference checking)

Language	• Publications in English language
Search timeframe	• 2003-2023 (20 years); 2020-2023 for conferences (last 3 years)

PRO, Patient-reported outcomes; QoL, quality of life.

RESULTS

- Of 2,590 records screened, following full-text review, 57 publications were included **(Table 2).**
- **Clinical burden** was derived from 40 studies (10 investigating joint-related comorbidities, 10 cardiac, 10 hearing, 9 respiratory, 4 motor function, 9 cognitive outcomes, 4 attention and hyperactivity, 13 daily function) with heterogenous symptoms and varying study quality.
  - **Joint-related outcomes:** Limitations in movement or range of motion (n=7), joint contractures (n=4), and skeletal abnormalities (e.g., spine deformities, spinal cord compression, kyphosis or scoliosis, hip dysplasia, and osteoarthritis; n=3) were common and burdensome in patients with nnMPS II.
  - **Heart-related outcomes:** Seven studies reported on cardiac anomalies, symptoms, or involvement, wherein disorders related to the mitral and the aortic valves were found to be common in patients with nnMPS II. Heart failure was reported to affect a small proportion of the population (n=2) and resulted in death in a few cases.
  - **Hearing-related outcomes:** Hearing loss was reported in seven studies, where the majority of the study population were reported to have experienced hearing loss including deafness. One study identified hearing difficulty as a common clinical feature in non-neuronopathic patients as hearing difficulty was observed in 77% of its study cohort.
  - **Respiratory-related outcomes:** Patients with nnMPS II experience a variety of respiratory manifestations, such as frequent airway infections, nasal obstructions, rhinorrhea, increased upper airway sounds, respiratory-related outcomes requiring hospitalization (e.g., breathing difficulties, aspiration), restrictive ventilatory disorders, obstructive sleep apnea, and obstructive pulmonary dysfunction and chest deformation.
  - **Motor Function:** Patients with nnMPS II were reported to generally have better, but still notable deficits in, motor skills and movement compared to patients with nMPS II (n=4). A decrease in gross motor skills were observed with increasing age (n=2).
  - **Cognitive Outcomes:** Patients with nnMPS II generally had average intelligence and did not exhibit cognitive problems (n=6). Three studies reported none to a minimal portion of the study population having behavioral problems.
  - **Attention deficits:** Despite having normal memory, and executive function on both Stockings of Cambridge and Spatial Working Memory, patients with nnMPS II may have decreased attention span relative to the population norms and controls.
  - **Daily Function:**
    - *Adaptive Behavior*: Patients with nnMPS II had lower adaptive function compared to the normative population as measured by the Vineland Adaptive Behavior Scales-Second Edition (VABS-II). However, their scores on the communication and socialization scales were comparable to the normative population and improved over time.
    - *Activities of Daily Living*: Level of care and movement with cognition (i.e., daily activities requiring cognition, e.g., toileting, dressing, bathing, and eating) generally improved from childhood to adolescence, but slightly declined upon young adulthood (n=2). Two studies assessed function using the Hunter Syndrome-Functional Outcomes for Clinical Understanding Scale (HS-FOCUS). The overall function scores were significantly and highly correlated with objective measures of functional capacity (e.g., 6-minute walk test [6MWT] and joint range of motion [JROM].
- **Humanistic burden** was assessed in a variety of domains using different instruments (patient-reported in 3, caregiver-reported in 4).
  - Moderate to low quality of life (QoL), poor self-esteem, and low family cohesion, as measured through the Health Utilities Index, Pediatric Quality of Life, and the Child Health Questionnaire (CHQ), have been reported among patients with nnMPS II.
  - Caregivers of patients with nnMPS II were reported to have low QoL across a variety of caregiver QoL and family impact scales. A study among a Japanese sample demonstrated high risk of neurosis and high levels of anxiety based on the State-Trait Anxiety Inventory.
- No economic analysis and only limited resource utilization data (5 studies) could be identified.
- Four studies reported mortality and survival among patients with nnMPS II, with death typically occurring in their twenties. In one study, the median survival range was 18.2 years.
- Twenty-five studies investigated efficacy/safety of Elaprase, with urinary glycosaminoglycan, 6MWT, and pulmonary function being most frequently assessed endpoints.

CONCLUSIONS

- Patients with nnMPS II are profoundly affected by deficits in respiratory function, hearing, attention/processing speed, adaptive behavior and continually declining physical abilities, often resulting in early death in their twenties.
- Despite availability of ERT, patients with nnMPS II demonstrate a substantial clinical burden in somatic symptoms as well as symptoms and implications with hearing, attention and activities of daily living, and have a much-shortened lifespan.
- Blood-brain barrier-penetrant therapies may be able to alleviate both CNS-related and somatic symptoms and thereby improve the lives of affected children and caregivers.[7,8]
- Further research into this phenotype is warranted as many studies have not stratified results by nnMPS II and nMPS II.

Figure 1: Study selection flow chart (PRISMA diagram)

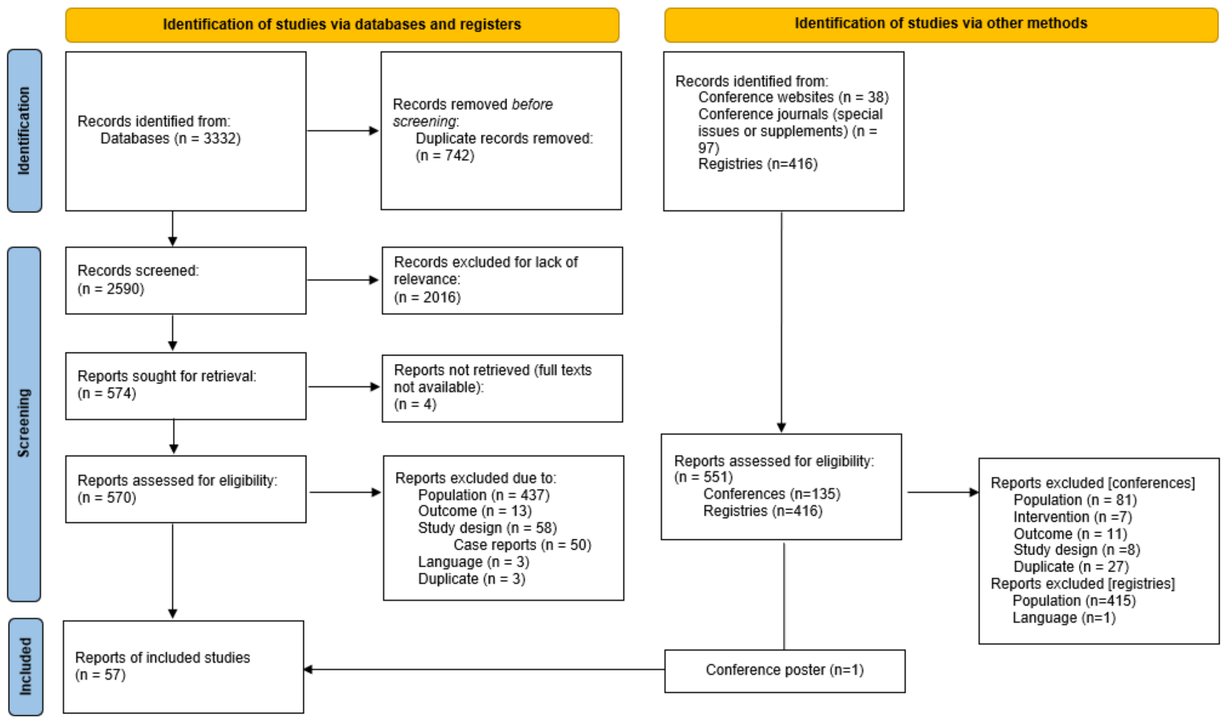

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Table 2: Overview of studies included

Study			Outcomes					
Author, year	Countries	Study type	Clinical burden (n=1,332)[a,b]	Humanistic burden (n=220)[b]	Economic burden (n=42)	Mortality (n=89)[c]	Efficacy (n=510)	Safety (n=259)
Ahmed 2010	NR	Cross-sectional study	✓					
Ahmed 2016a	NR	NR	✓					
Ahmed 2016b	NR	Longitudinal cohort study	✓					
Barbier 2013	USA	Observational prospective trial (ad hoc analysis)					✓	✓
Cho 2008	NR	Prospective study	✓		✓			
Cho 2014	South Korea	Cohort study					✓	
Escolar 2015	NR	Observational prospective study	✓					
Fesslova 2009	NR	Retrospective study	✓		✓			
Giugliani 2014	NR	Open-label clinical trial					✓	✓
Giugliani 2020	Japan	Randomized control trial					✓	
Giugliani 2023	Japan, Brazil	Longitudinal, integrated post hoc analysis	✓				✓	
Guarany 2012	Brazil	Observational prospective study	✓					
Guarany 2015	Brazil	Cross-sectional study		✓	✓			
Guffon 2015	France	Cross-sectional study	✓		✓		✓	
King 2017	USA	NR	✓					
Kubaski 2016	USA	Cross-sectional study					✓	
Kuratsubo 2009	Japan	Cross-sectional study	✓	✓				
Lin 2014	Taiwan	Prospective cohort study	✓				✓	
Lin 2016a	Taiwan	Retrospective study				✓		
Lin 2016b	Taiwan	Retrospective study	✓					
Lin 2020	Taiwan	Retrospective study				✓		
Link 2021	NR	Observational study	✓					
Lourenco 2012	Brazil	Retrospective cohort study	✓				✓	
Manara 2011	NR	Retrospective study	✓					
Marucha 2012	NR	Retrospective study					✓	
Marucha 2022	Poland	Observational prospective study	✓				✓	
Matheus 2004	NR	Retrospective study	✓					
Mattera 2018	USA, UK	Prospective cohort study	✓					
Muenzer 2006	Multinational (exact countries not reported)	Randomized clinical trial					✓	✓
Muenzer 2007	NR	Randomized double-blind trial	✓				✓	✓
Muenzer 2011	NR	Open-labeled clinical trial	✓				✓	✓
Needham 2014	USA, UK, Canada, Ireland, Australia	Cross-sectional study	✓	✓				
Needham 2015	USA, UK, Canada, Ireland, Australia	Cross-sectional study		✓				
Okuyama 2010	Japan	Multi-center open-label study	✓				✓	✓
Orii 2019	Japan	-					✓	✓
Polgreen 2020	NR	Observational prospective study	✓					
Raluy-Callado 2013	USA, UK, Brazil, Germany	Questionnaire study	✓	✓				
Różdżyńska-Świątkowska 2015	Poland	Longitudinal study	✓					
Scarpa 2014	NR	Cross-sectional study	✓					
Scarpa 2015	NR	Survey, observational registry	✓					
Schulze-Frenkin 2011	Germany, UK	Cross-sectional study					✓	
Schwartz 2007	Brazil	Observational study	✓					
Sestito 2022	Italy	Retrospective study	✓				✓	
Shapiro 2016	NR	Longitudinal study	✓	✓	✓			✓
Sohn 2013	South Korea	Randomized controlled trial					✓	
Sohn 2015	South Korea	Single center, single arm, open-label trial					✓	✓
Soni-Jaiswal 2016	NR	Exploratory qualitative study	✓	✓				
Suzuki 2020	Japan	Retrospective study	✓					
Tanjuakio 2015	Japan	Cross-sectional study	✓					
Tomanin 2014	Italy	Prospective cohort study	✓				✓	
Tomita 2021	Japan	Retrospective study				✓	✓	
Tulebayeva 2020	Kazakhstan	Prospective cohort study	✓				✓	
Vedolin 2007	Brazil	Prospective cohort study	✓					
Ueda 2020	Japan	Post-marketing study				✓	✓	
Yund 2013	USA	Observational study	✓					
Yund 2014	NR	Longitudinal study	✓					
Yund 2015	USA	Cross-sectional study	✓					

[a]The sample size for Link 2021 included both n MPS II and nnMPSII patients (not reported separately). In addition, the sample size was not reported in Scarpa 2014.
[b]The sample size in Soni-Jaiswal 2016 was not included in the calculation as the sample consisted of 6 families. The number of participants was not reported.
[c]The sample in Lin 2020 included patients with mixed mild or intermediate MPS II.
NR, not reported. References for Table 2 are available upon request (engmann@dnli.com).

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DNL310 is an investigational agent and has not been approved by any health authority.
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