Poster No: 052

Persistent Clinical Burden and Unmet Needs in Hunter Syndrome (MPS II) in the United States: A Retrospective Cohort Study

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Introduction[1–3]

- MPS II (Mucopolysaccharidosis type II) or Hunter syndrome is a rare, X-linked lysosomal storage disorder caused by iduronate-2-sulfatase deficiency
- Idursulfase IV is the current standard of care and only approved enzyme replacement therapy for MPS II since 2006. While it offers some benefits for somatic disease manifestations, it does not address them fully. Furthermore, Idursulfase does not cross the blood brain barrier and therefore has no impact on the progressive neurologic disease. As a result, patients continue to experience impairments due to progressive cognitive and somatic complications of MPS II.
- Despite extensive clinical use of Idursulfase IV, limited evidence exists on the clinical and economic burden (HCRU) of MPS II and current unmet needs

Objective

- To evaluate the clinical and economic burden on patients with MPS II treated with idursulfase IV in the United States (US)
- To describe the drivers of clinical and economic burden (HCRU) by age subgroup

Methods

This retrospective cohort study utilized the Komodo Health closed claims database (Jan 2015 to Feb 2025), which contains complete medical and prescription claims information from >500 payers across all geographic regions of the US

Key patient selection criteria

- ≥ 1 claim of idursulfase IV between Jan 2017 and Dec 2023 (index date)
- ≥ 2 claims for MPS II (ICD-10: E76.1) 90 days apart and within 365 days of the index date
- Patients who are male
- Continuous enrollment from 1 year before index to up to 3 years after index

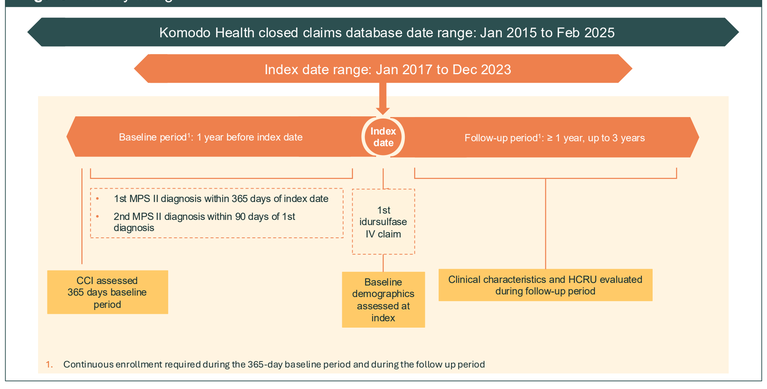
Outcomes (stratified by age)

- Baseline characteristics evaluated at index; CCI assessed during the 1-year pre-index period
- Clinical complications and HCRU evaluated during available follow-up period

Analysis methodology

Descriptive analyses (frequencies, proportions, and annualized rates per patient per year (PPPY))

Figure 1. Study design

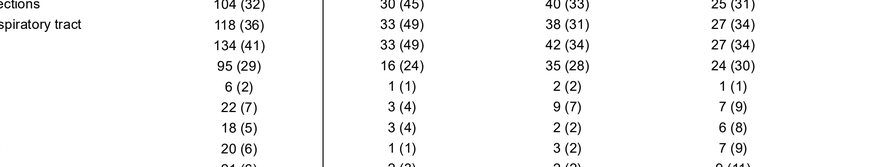


Results

Patient selection

In total, 592 unique patients with MPS II receiving idursulfase IV were identified during the selection period. Among these patients, 329 met further inclusion criteria for the study (Figure 2)

Figure 2. Patient selection



[a]Index date: date of patient's first idursulfase IV claim within the selection period of Jan 2017 to Dec 2023

Baseline characteristics

- On average, patients were adolescents with a mean (SD) age of 12.35 (9.25) years (Table 1; Figure 3)
- Most patients had commercial insurance or Medicaid
- Patients in all age groups had a mean follow-up duration of approximately 3 years

Figure 3. Number of patients by age subgroup (n, %)

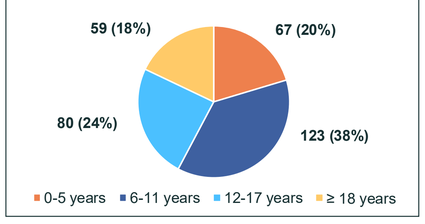


Table 1. Baseline characteristics

Characteristics	Overall (N = 329)
Age	
Mean (SD) years	12.35 (9.25)
Region, n (%)	
Northeast	62 (19)
Midwest	101 (31)
South	101 (31)
West	65 (20)
Insurance status, n (%)	
Commercial	116 (35)
Medicare	10 (3)
Medicaid	165 (50)
Medicaid + commercial	32 (10)
Other	3 (1)
CCI	
Mean (SD)	0.44 (0.65)
Follow-up duration, mean (SD) years	2.94 (0.25)

Clinical complications

- Despite treatment with idursulfase, clinical complications were multisystemic, began early in life, persisted and progressed among older aged patients (Table 2)
- Adults had the highest proportion of serious somatic complications due to disease progression, including known mortality drivers like respiratory and cardiac complications
- Younger patients (age 0-5 years) had the highest evidence of ear and hearing loss-related complications, developmental delay, and lack of physiological development compared with patients in other age groups (Figure 4)

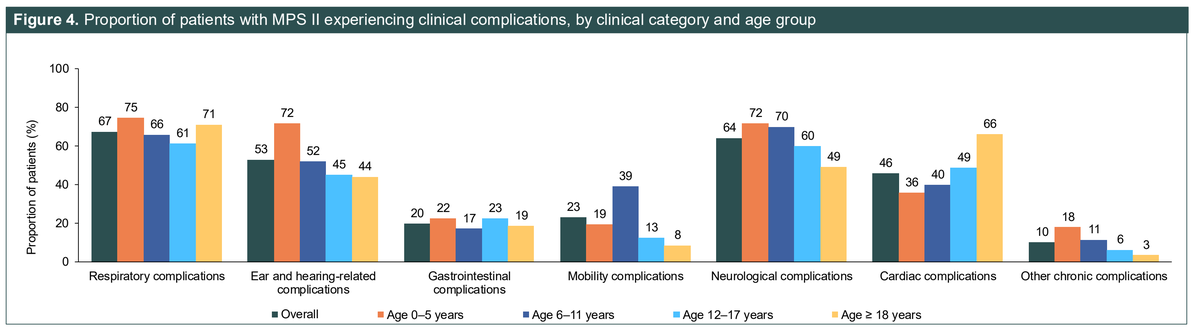
Table 2. Proportion of patients with MPS II experiencing clinical complications, by age group

Clinical complications, n (%)	All MPS II Patients	Age Subgroups			
	Overall (n = 329)	0–5 years (n = 67)	6–11 years (n = 123)	12–17 years (n = 80)	≥ 18 years (n = 59)
Respiratory complications	**222 (67)**	**50 (75)**	**81 (66)**	**49 (61)**	**42 (71)**
Acute upper respiratory infections	104 (32)	30 (45)	40 (33)	25 (31)	9 (15)
Other diseases of upper respiratory tract	118 (36)	33 (49)	38 (31)	27 (34)	20 (34)
Sleep apnea	134 (41)	33 (49)	42 (34)	27 (34)	32 (54)
Asthma	95 (29)	16 (24)	35 (28)	24 (30)	20 (34)
Narrow airways	6 (2)	1 (1)	2 (2)	1 (1)	2 (3)
Sleep-related disorders	22 (7)	3 (4)	9 (7)	7 (9)	3 (5)
Bronchitis	18 (5)	3 (4)	2 (2)	6 (8)	7 (12)
Obstructive airway disease	20 (6)	1 (1)	3 (2)	7 (9)	9 (15)
Tracheobronchomalacia	21 (6)	2 (3)	2 (2)	9 (11)	8 (14)
Ear and hearing-related complications	**174 (53)**	**48 (72)**	**64 (52)**	**36 (45)**	**26 (44)**
Ear infections	77 (23)	29 (43)	21 (17)	18 (23)	9 (15)
Hearing loss	155 (47)	42 (63)	61 (50)	27 (34)	25 (42)
Hearing aids	50 (15)	18 (27)	22 (18)	6 (8)	4 (7)
Gastrointestinal complications	**65 (20)**	**15 (22)**	**21 (17)**	**18 (23)**	**11 (19)**
Abdominal/inguinal hernia	14 (4)	6 (9)	3 (2)	1 (1)	4 (7)
Diarrhea	14 (4)	4 (6)	7 (6)	2 (3)	1 (2)
Constipation	47 (14)	9 (13)	15 (12)	17 (21)	6 (10)
Mobility complications	**76 (23)**	**13 (19)**	**48 (39)**	**10 (13)**	**5 (8)**
Joint stiffness	22 (7)	4 (6)	14 (11)	3 (4)	1 (2)
Carpal tunnel syndrome	50 (15)	7 (10)	35 (28)	6 (8)	2 (3)
Hip dysplasia	15 (5)	2 (3)	8 (7)	3 (4)	2 (3)
Neurological complications	**211 (64)**	**48 (72)**	**86 (70)**	**48 (60)**	**29 (49)**
Developmental delay	136 (41)	38 (57)	64 (52)	27 (34)	7 (12)
Lack of physiological development	125 (38)	38 (57)	52 (42)	27 (34)	8 (14)
Mood disorders	27 (8)	2 (3)	9 (7)	7 (9)	9 (15)
Anxiety disorders	25 (8)	4 (6)	4 (3)	7 (9)	10 (17)
Seizures	41 (12)	5 (7)	14 (11)	13 (16)	9 (15)
Behavioral issues	22 (7)	9 (13)	7 (6)	4 (5)	2 (3)
Attention-deficit hyperactivity disorder	35 (11)	4 (6)	19 (15)	8 (10)	4 (7)
Hydrocephalus	27 (8)	1 (1)	14 (11)	10 (13)	2 (3)
Cardiac complications	**151 (46)**	**24 (36)**	**49 (40)**	**39 (49)**	**39 (66)**
Valvular heart disease	139 (42)	22 (33)	45 (37)	36 (45)	36 (61)
Cardiac arrhythmia	30 (9)	5 (7)	4 (3)	7 (9)	14 (24)
Hypertension	22 (7)	2 (3)	4 (3)	4 (5)	12 (20)
Aortic ectasia	10 (3)	3 (4)	3 (2)	2 (3)	2 (3)
Heart failure	8 (2)	1 (1)	2 (2)	2 (3)	3 (5)
Cardiomyopathy	7 (2)	1 (1)	3 (2)	1 (1)	2 (3)

Conclusions

- **All MPS II patients treated with Idursulfase IV experienced progressive clinical morbidity due to multisystemic disease complications that develop at an early age, persist, and progressed as patient aged into adulthood. As evidenced by the clinical burden in older aged subgroups**
- **Across age groups, this morbidity translated into substantial all-cause HCRU and economic burden. The most economically burdensome impacts of MPS II were driven primarily by advanced cardiac and respiratory complications leading to lengthy and frequent IP hospitalizations and IP surgical procedures. Neurologic and hearing related complications were prevalent and noteworthy drivers of clinical burden, driving substantial outpatient HCRU but are relatively less burdensome than complications associated with inpatient HCRU.**
- **Age-related patterns were observed: older patients had greater cardiopulmonary complications and intensive surgical burden, contributing to more frequent hospitalizations and longer IP LOS, whereas younger patients more commonly experienced neurologic and hearing complications, with spinal and outpatient surgeries representing a prominent driver of burden in these patients.**
- **Collectively, these data underscore that the clinical burden and economic burden in MPS II are interrelated and driven by unmet needs due to disease progression that exist despite treatment with current SOC**

Figure 4. Proportion of patients with MPS II experiencing clinical complications, by clinical category and age group



All-cause HCRU

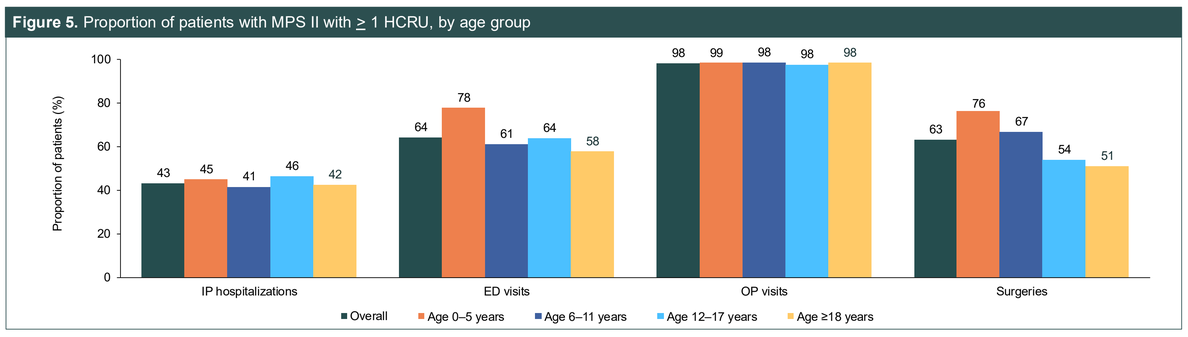
- The prevalence of all-cause HCRU was substantial overall (IP visits: 43%, ED visits: 64%, OP visits: 98%, Surgeries: 63%) and similar across all age subgroups.
- Average annual rates of HCRU were frequent across different settings of care regardless of age: outpatient (OP visits: 26.6), inpatient (IP hospitalizations: 3.2).
- Inpatient LOS was substantial overall (LOS: 13.8 days). Generally, older patients had higher annual rates of inpatient hospitalizations and mean LOS increased: LOS by age subgroup: 0-5 years: 4.9 days; 6-11 years: 6.0 days; 12-17 years: 36.5 days; ≥18 years: 6.8 days (Table 3).
- The youngest subgroup (age 0–5 years) had the highest proportions of patients that required ED visits and surgeries.While the proportion of patients utilizing OP services was similar across age groups, younger patients had the highest annual frequency of OP visits (Table 3, Figure 5).

Table 3. All-cause HCRU among patients with MPS II, by age group

All-cause HCRU	All MPS II Patients	Age Subgroups			
	Overall (n = 329)	0–5 years (n = 67)	6–11 years (n = 123)	12–17 years (n = 80)	≥ 18 years (n = 59)
IP hospitalizations, n (%)[a]	143 (43)	30 (45)	51 (41)	37 (46)	25 (42)
Admissions, mean annual rate (SD)[b]	3.2 (5.0)	2.0 (1.5)	4.4 (7.5)	3.2 (3.1)	2.5 (2.9)
LOS, mean number of days (SD)[c]	13.8 (38.1)	4.9 (9.1)	6.0 (11.7)	36.5 (68.7)	6.8 (7.9)
ED visits, n (%)[a]	212 (64)	52 (78)	75 (61)	51 (64)	34 (58)
Visits, mean annual rate (SD)[b]	1.1 (1.1)	1.2 (1.1)	1.0 (1.0)	1.1 (1.0)	1.2 (1.4)
OP visits, n (%)[a]	323 (98)	66 (99)	121 (98)	78 (98)	58 (98)
Visits, mean annual rate (SD)[b]	26.6 (29.9)	40.3 (35.6)	30.4 (32.9)	14.5 (17.7)	19.0 (19.8)
Surgeries, n (%)[a]	206 (63)	51 (76)	82 (67)	43 (54)	30 (51)
Surgeries, mean annual rate (SD)[b]	1.1 (1.0)	1.2 (1.2)	0.9 (0.7)	1.2 (1.1)	1.0 (0.9)

[a]n is the number of patients with any relevant visit in CE follow up period capped at 3 years from index/match date, and the denominator for the (%) is all patients in the cohort.
[b]Annualized average rate of event or visit per patient per year (PPPY) among patients with ≥ 1 event in the 3 year follow up period
[c]Mean number of days (LOS) per inpatient hospitalization among patients with ≥ 1 inpatient hospitalization

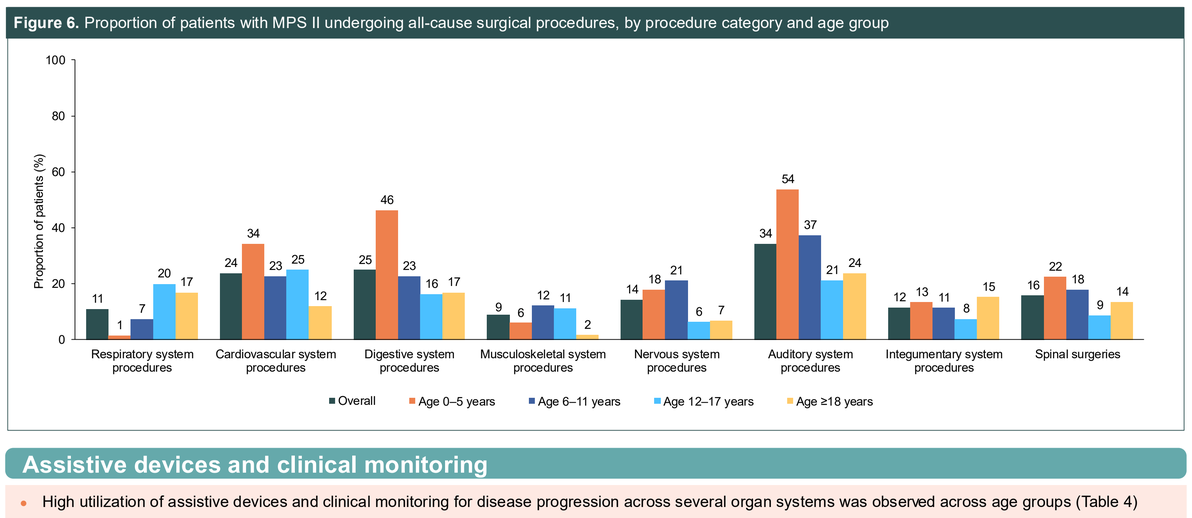
Figure 5. Proportion of patients with MPS II with ≥ 1 HCRU, by age group



HCRU drivers – surgeries

- Generally, patients in the younger subgroups (age 0-5 and 6-11 years) had higher prevalence of surgeries. Respiratory system procedures were more prevalent in the older age groups, reflecting clinical complications more commonly observed among older patients (Figure 6)
- Patients with MPS II in the 0-5 age group had the most frequent procedures associated with the cardiovascular system, digestive system, auditory system, and spine
- Common procedures observed in the youngest age group included vascular access procedures, port placement, adenoidectomy, tonsillectomy, and ear tube procedures (Supplemental file)

Figure 6. Proportion of patients with MPS II undergoing all-cause surgical procedures, by procedure category and age group



Assistive devices and clinical monitoring

- High utilization of assistive devices and clinical monitoring for disease progression across several organ systems was observed across age groups (Table 4)
- Compared with adult patients, a greater proportion of younger patients had evidence of utilizing a new hearing aid during the study period
- Clinical monitoring utilization was consistently higher among patients age 0-5 relative to other age groups

Table 4. Utilization of assistive devices and clinical monitoring among patients with MPS II, by age group

Other HCRU, n (%)	All MPS II Patients	Age Subgroups			
	Overall (N = 329)	0–5 years (n = 67)	6–11 years (n = 123)	12–17 years (n = 80)	≥ 18 years (n = 59)
Assistive devices					
Wheelchair	76 (23)	15 (22)	36 (29)	18 (23)	7 (12)
Walker	10 (3)	1 (1)	4 (3)	3 (4)	2 (3)
Hearing aids	50 (15)	18 (27)	22 (18)	6 (8)	4 (7)
Monitoring					
ECHO	227 (69)	50 (75)	85 (69)	51 (64)	41 (69)
EKG	210 (64)	45 (67)	77 (63)	48 (60)	40 (68)
MRI	127 (39)	27 (40)	52 (42)	25 (31)	23 (39)
Sleep study	94 (29)	34 (51)	30 (24)	19 (24)	11 (19)
Nerve testing	47 (14)	17 (25)	21 (17)	4 (5)	5 (8)
Hearing assessments	168 (51)	53 (79)	71 (58)	22 (28)	22 (37)
Eye exams	137 (42)	37 (55)	55 (45)	22 (28)	23 (39)
X-rays	238 (72)	52 (78)	88 (72)	59 (74)	39 (66)

Limitations

- The study population included patients with MPS II in the US, limiting the generalizability of findings to other geographies or healthcare systems
- Requiring ≥ 1 year of pre- and post-index continuous enrollment may have skewed the population towards an older age than observed in the real world
- As with any claims study, miscoding or delayed coding can lead to under-identification or misclassification of complications and procedures
- Mortality data and MPS II phenotype do not exist in claims and therefore the complications seen in the older age patients may not include a similar mix of patient phenotypes that are likely included within the younger age cohorts

ABBREVIATIONS

CCI, Charlson Comorbidity Index; ED, Emergency Department; HCRU, healthcare resource utilization; ICD-10, International Classification of Diseases, Tenth Revision; IP, inpatient; IV, intravenous; LOS, length of stay; MPS II, mucopolysaccharidosis type II; OP, outpatient; OT, occupational therapy; PT, physical therapy; RWE, real-world evidence; SD, standard deviation; ECHO, echocardiography; EKG, electrocardiography; MRI, magnetic resonance imaging; CE, continuous enrollment; IQR, interquartile range; Rx, prescription

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DISCLOSURES

BB is a Professor of Pediatrics at Northwestern University Feinberg School of Medicine and an attending geneticist at Ann & Robert H. Lurie Children's Hospital of Chicago. She also serves as a paid consultant for Denali.]. **JB** and **NE** are employees of Denali. **WY** is an employee of Aesara and serves as a paid consultant for Denali. **RK** and **SS** are employees of ZS and serve as paid consultants for Denali

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Table S1. HCRU drivers: All-cause surgical procedures related to MPS II complications

Surgical procedures n (%)	**All MPS II patients**	**Age subgroups**			
	Overall (n = 329)	**0–5 years (n = 67)**	**6–11 years (n = 123)**	**12–17 years (n = 80)**	**≥ 18 years (n = 59)**
All-cause surgical procedures	**206 (63)**	**51 (76)**	**82 (67)**	**43 (54)**	**30 (51)**
Respiratory system procedures	**36 (11)**	**1 (1)**	**9 (7)**	**16 (20)**	**10 (17)**
Tracheostomy	19 (6)	0 (0)	3 (2)	8 (10)	8 (14)
Respiratory procedures	15 (5)	0 (0)	3 (2)	9 (11)	3 (5)
ENT surgery: respiratory system[a]	14 (4)	1 (1)	4 (3)	7 (9)	2 (3)
Cardiovascular system procedures	**78 (24)**	**23 (34)**	**28 (23)**	**20 (25)**	**7 (12)**
Vascular access procedures	67 (20)	14 (21)	28 (23)	19 (24)	6 (10)
Port placement	45 (14)	18 (27)	17 (14)	7 (9)	3 (5)
Digestive system procedures	**82 (25)**	**31 (46)**	**28 (23)**	**13 (16)**	**10 (17)**
Dental procedures	30 (9)	5 (7)	18 (15)	6 (8)	1 (2)
Adenoidectomy	26 (8)	21 (31)	4 (3)	1 (1)	0 (0)
Gastrointestinal procedures	23 (7)	2 (3)	7 (6)	8 (10)	6 (10)
Tonsillectomy	22 (7)	18 (27)	2 (2)	1 (1)	1 (2)
Other	10 (3)	5 (7)	2 (2)	2 (3)	1 (2)

Nervous system procedures	**47 (14)**	**12 (18)**	**26 (21)**	**5 (6)**	**4 (7)**
Carpal tunnel	29 (9)	7 (10)	19 (15)	2 (3)	1 (2)
Non-spinal CNS or PNS procedures[b]	11 (3)	2 (3)	6 (5)	2 (3)	1 (2)
Spinal procedures	**52 (16)**	**15 (22)**	**22 (18)**	**7 (9)**	**8 (14)**
Spinal cord decompression	2 (1)	0 (0)	0 (0)	1 (1)	1 (2)
Other spinal surgeries[c]	52 (16)	15 (22)	22 (18)	7 (9)	8 (14)
Auditory system procedures	**113 (34)**	**36 (54)**	**46 (37)**	**17 (21)**	**14 (24)**
ENT surgery[d]	73 (22)	12 (18)	32 (26)	16 (20)	13 (22)
Ear tubes	60 (18)	31 (46)	23 (19)	4 (5)	2 (3)
Musculoskeletal system procedures	**29 (9)**	**4 (6)**	**15 (12)**	**9 (11)**	**1 (2)**
Integumentary system procedures	**38 (12)**	**9 (13)**	**14 (11)**	**6 (8)**	**9 (15)**
Hematopoietic stem cell transplantation	**1 (0.3)**	**1(1)**	**0 (0)**	**0 (0)**	**0 (0)**

[a]ENT (ear, nose, and throat) surgery related to respiratory system: surgeries of nasal passage, voice box, vocal cords

[b]Non-spinal CNS (central nervous system) or PNS (peripheral nervous system) procedures: surgeries and procedures of brain and peripheral nerve or branch

[c]Other spinal surgeries: procedures related to diagnostics (e.g., fluid removal, injections into spinal canal, etc.), interventions (e.g., bone removal, fusion for deformity correction, stabilizing devices, grafting, etc.), and computer-assisted techniques for spinal repair and fluid management

[d]ENT surgery related to auditory system: surgeries of eardrum, ear canal, mastoid cavity, etc.

Table S2. Top 20 Hospitalizations[a]

Category	ICD code	Code description	MPS II patients (n = 329)	%
MPS II	E761	Mucopolysaccharidosis, type II	127	89%
	E763	Mucopolysaccharidosis, unspecified	21	15%
Respiratory complications	G4733	Obstructive sleep apnea (adult) (pediatric)	46	32%
	J45909	Unspecified asthma, uncomplicated	31	22%
	J189	Pneumonia, unspecified organism	30	21%
	J9811	Atelectasis	26	18%
	R0603	Acute respiratory distress	25	17%
	J984	Other disorders of lung	24	17%
	J398	Other specified diseases of upper respiratory tract	24	17%
	R918	Other nonspecific abnormal finding of lung field	22	15%
Cardiovascular complications	I340	Nonrheumatic mitral (valve) insufficiency	27	19%
	Z452	Encounter for adjustment & management of vascular access device	25	17%
	R0902	Hypoxemia	20	14%
Physiological/ developmental delay	R6250	Unspecified lack of expected normal physiological development in childhood	36	25%
Other	R509	Fever, unspecified	37	26%
	G40909	Epilepsy, not intractable, without status epilepticus	21	15%
	Z931	Gastrostomy status	21	15%
	K5900	Constipation, unspecified	20	14%
	F88	Other disorders of psychological development	20	14%
	Z79899	Other long term (current) drug therapy	19	13%

[a]Based on top diagnosis claims as listed in KOMODO