Original Article

Journal of Inborn Errors of Metabolism & Screening
2018, Volume 6: 1–12
© The Author(s) 2018
DOI: 10.1177/2326409818800346
journals.sagepub.com/home/iem
SAGE

Understanding the Early Presentation of Mucopolysaccharidoses Disorders: Results of a Systematic Literature Review and Physician Survey

Lorne Clarke, MD[1], Carolyn Ellaway, MBBS, PhD[2], Helen E. Foster, MD, MBBS[3], Roberto Giugliani, MD, PhD[4], Cyril Goizet, MD, PhD[5], Sarah Goring, MSc[6], Sara Hawley, MSc[7], Elaina Jurecki, MS, RD[7], Zaeem Khan, MPH, BSc[6], Christina Lampe, MD[8], Ken Martin, MD[9], Suzanne McMullen, MHA, BSc[6], John J. Mitchell, MD[10], Fathima Mubarack, MSc, MHA[7], H. Serap Sivri, MD[11], Martha Solano Villarreal, MD, PhD[12], Fiona J. Stewart, MB, BS[13], Anna Tylki-Szymanska, MD, PhD[14], Klane White, MD, MSc[15], and Frits Wijburg, MD, PhD[16]

Abstract

As therapies are developed for rare disorders, challenges of early diagnosis become particularly relevant. This article focuses on clinical recognition of mucopolysaccharidoses (MPS), a group of rare genetic diseases related to abnormalities in lysosomal function. As quality of outcomes with current therapies is impacted by timing of intervention, minimizing time to diagnosis is critical. The objective of this study was to characterize how, when, and to whom patients with MPS first present and develop tools to stimulate earlier recognition of MPS. A tripartite approach was used, including a systematic literature review yielding 194 studies, an online physician survey completed by 209 physicians who described

[1] British Columbia Children's Hospital Research Institute, University of British Columbia, Vancouver, British Columbia, Canada
[2] Sydney Children's Hospital Network, Sydney University, Sydney, Australia
[3] Great North Children's Hospital and Newcastle University, Newcastle upon Tyne, United Kingdom
[4] Medical Genetics Service HCPA, Dep Genet UFRGS & INAGEMP, Porto Alegre, Brazil
[5] Service de Génétique, CHU Bordeaux, Laboratoire MRGM, INSERM U 1211, University of Bordeaux, Bordeaux, France
[6] ICON plc, Vancouver, British Columbia, Canada
[7] BioMarin Pharmaceutical Inc., Novato, CA, USA
[8] Centre for Rare Diseases, Clinic for Children and Adolescents, Helios Dr. Horst Schmidt Kliniken, Wiesbaden, Germany
[9] UCSF Benioff Children's Hospital Oakland, Oakland, CA, USA
[10] Montreal Children's Hospital, Montreal, Quebec, Canada
[11] Hacettepe University Children's Hospital, Ankara, Turkey
[12] Fundacion Cardioinfantil, Bogota, Colombia
[13] Belfast City Hospital, Belfast, United Kingdom
[14] Children's Memorial Health Institute, Warsaw, Poland
[15] Seattle Children's Hospital, Seattle, WA, USA
[16] Academic Medical Center, University Hospital of Amsterdam, Amsterdam, the Netherlands

Received June 7, 2018, and in revised form August 8, 2018. Accepted for publication August 8, 2018.

Corresponding Author:
Lorne Clarke, MD, British Columbia Children's Hospital Research Institute, University of British Columbia, Vancouver, British Columbia, Canada.
Email: lclarke@bcchr.ca

859 MPS cases, and a global panel of MPS experts who distilled the findings. Red flag signs/symptoms were identified for cardiology, pediatric neurology, otorhinolaryngology, rheumatology, orthopedics, pediatrics, and general medicine and converted into simple, specialty-specific tools intended to facilitate early diagnosis of MPS, enabling improved patient outcomes.

Keywords
mucopolysaccharidoses, mucopolysaccharidosis I, mucopolysaccharidosis II, mucopolysaccharidosis III, mucopolysaccharidosis IV, mucopolysaccharidosis VI, mucopolysaccharidosis VII, diagnosis

Introduction

The mucopolysaccharidoses (MPS) are rare genetic conditions caused by a deficiency of 1 of 11 lysosomal enzymes involved in glycosaminoglycan (GAG) catabolism. MPS is characterized by the accumulation of partially degraded GAGs (heparan sulfate, dermatan sulfate, keratan sulfate, chondroitin sulfate, or hyaluronan) within lysosomes and by the subsequent increase in GAGs in urine, blood, and cerebral spinal fluid.[1,2] Progressive damage occurs as GAGs accumulate within the cells. As lysosomes are found throughout the body, MPS can manifest through a myriad of signs and symptoms. Over time, MPS may result in multiple organ failure, cognitive impairment, and premature death.[1] Typically, symptom onset occurs between infancy and childhood.[3] The overall birth prevalence for MPS is approximately 1 in 25000 and varies by region and ethnic background.[4–7]

Seven MPS types have been identified (I, II, III, IV, VI, VII, and IX); MPS III has 4 subtypes (A, B, C, and D) and MPS IV has 2 (A and B). Although the subtypes are clinically similar, each one is linked to a specific enzyme deficiency. MPS II is inherited as an X-linked disorder, whereas all others are autosomal recessive conditions.[1]

MPS is usually diagnosed through biochemical testing for deficient enzymes and can be confirmed through molecular genetic testing. However, early clinical recognition of potential cases with MPS, which is needed to trigger this diagnostic testing, continues to pose a substantial challenge.[8] This is largely due to the disease rarity, phenotypic heterogeneity, and the wide range of nonspecific early signs and symptoms.

Diagnostic delays often involve referrals from one physician to another and place a substantial burden on the patient and caregivers. Patients are also at risk of misdiagnosis and undergoing inappropriate interventions or receiving ineffective treatments. Timely referral for diagnostic testing allows for prompt initiation of definitive therapy such as enzyme replacement therapy or hematopoietic stem cell transplantation for some types of MPS as well as enabling the appropriate management of secondary complications.[9] Earlier recognition also allows patients to partner with a physician with expertise in their rare disease and facilitates support through a patient organization sooner. Furthermore, early recognition alerts at-risk carriers and enables them to seek accurate genetic counseling and pursue prenatal testing and preimplantation genetic diagnosis.

A better understanding of the initial presentation of MPS is needed to improve early recognition of potential cases with MPS and facilitate a timely diagnosis, enabling optimal patient management and treatment when available. Unfortunately, previous efforts made in this area have not met with success.[8] Thus, a new approach is needed. The objectives of this review were to use a novel, evidence-based, multimethod approach to characterize how, when, and to whom individuals with MPS first present, identify specialty-specific red flag signs and symptoms, and develop clinical awareness diagnostic tools that have the potential to shorten the current diagnostic delay. The effectiveness of the tools will depend on how well the information they contain is disseminated and retained by the target audiences. By making different tools for each subspecialist, we aim to present only the most relevant information to each. However, effective dissemination of the tools subsequent to publication will be the most challenging and critical factor for ultimate success.

Materials and Methods

To achieve the objectives of this study, a systematic literature review was conducted first, followed by a physician survey to supplement the published evidence with real-world clinical experience and compensate for the possibility of publication bias in the results of the literature review (ie, overrepresentation of rare signs and symptoms and under representation of common ones). The results from the systematic literature review and physician survey were then reviewed by a panel of 16 international clinical MPS experts in order to identify specialty-specific red flag signs and symptoms evident in the early stages of the disease and generate specialty-specific tools to increase clinical awareness of potential cases with MPS.

Systematic Literature Review

Search strategy and study selection. The following electronic databases were searched: Embase (1970 to 27 June 2016) and MEDLINE via PubMed (1970 to 27 June 2016). Handsearches for registry studies, clinical surveillance, natural history, and genotype–phenotype correlation studies were also conducted in PubMed using a key word search. A transparent and reproducible search strategy (Supplemental Files 1 and 2) was developed in accordance with best practice guidelines.[10,11] Searches

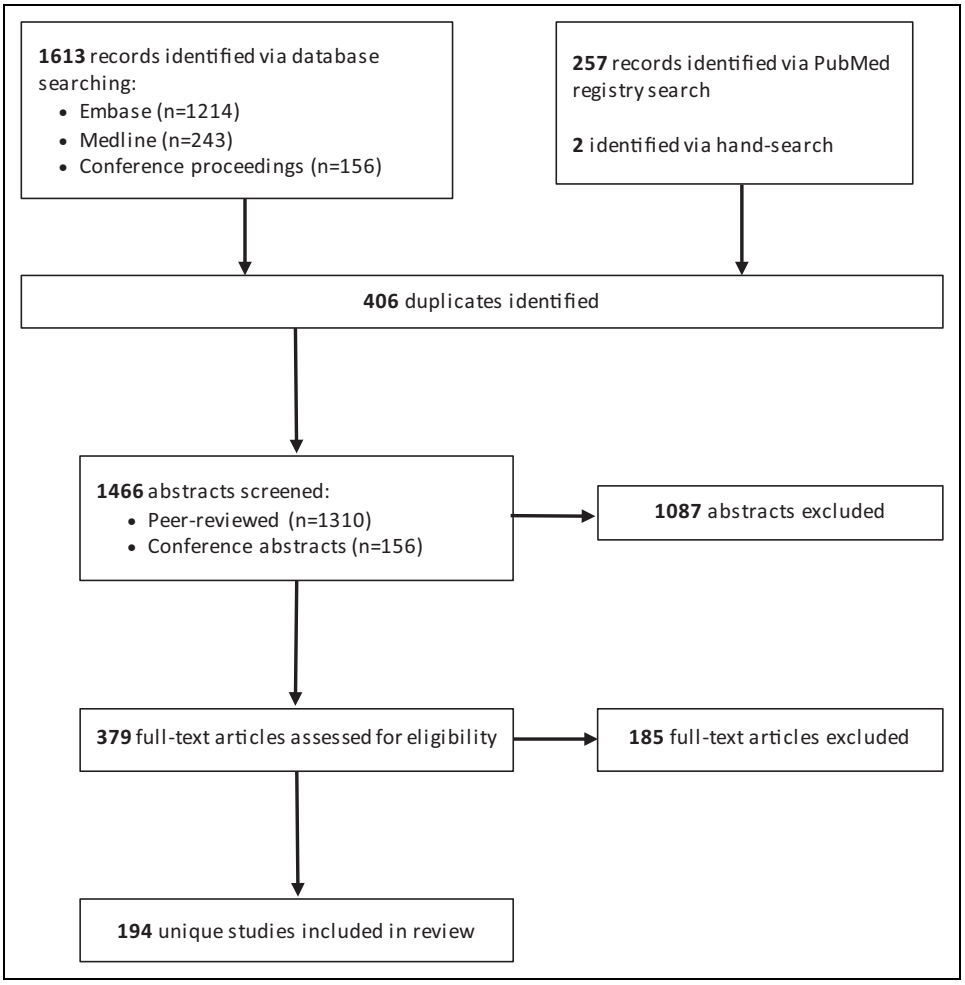

Figure 1. Literature review: PRISMA diagram.
N indicates number; PRISMA indicates Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

were limited to English language and human studies only and were run on June 27, 2016.

Titles and abstracts of all articles obtained by the search were reviewed by a single reviewer (F.M.) against prespecified eligibility criteria. Titles and abstracts indicated as "unsure" were reviewed by a second reviewer (E.J.) for a final decision. Inclusion criteria were specified in terms of population, intervention and comparators, outcomes and study design (PICOS) framework. The population of interest was MPS (all types). No restrictions were placed on interventions, comparators, or study design. "Outcomes" included the clinical course leading to diagnosis, clinical presentation, presentation of signs and symptoms, clinical features, clinical assessment, phenotype, phenotype–genotype correlation, severity, or descriptions of slow or rapid progression of disease. All studies meeting the eligibility criteria were included in this review. Studies were excluded if they lacked information on presenting signs and symptoms or if they focused on therapeutics, diagnostics, newborn screening, or biochemical or molecular assays. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Figure 1) was developed indicating the numbers of studies included and excluded at each stage of the review.

Data extraction and analysis. For each study, MPS type-specific data were extracted, meaning that a single study describing signs and symptoms of 2 different types of MPS was extracted as 2 separate records. Data were captured in Microsoft Excel extraction tables, and extraction fields were spot checked for potential errors.

Extracted data included median age of symptom onset, median age of diagnosis, median diagnostic delay, signs and symptoms (including presence/absence at case presentation and role in triggering the diagnosis), reporting physician specialty, and diagnostic errors. As most publications reported findings in aggregate, the units for reporting of the systematic literature review results are records as opposed to patients. Data were synthesized in tabular format; clinical features of MPS were stratified according to MPS type, age-group (<1, 1-4, 5-9, $\geq$10 years), major symptom categories, reporting physician specialty, or date of publication. Median values and ranges were used to present the data in aggregate.

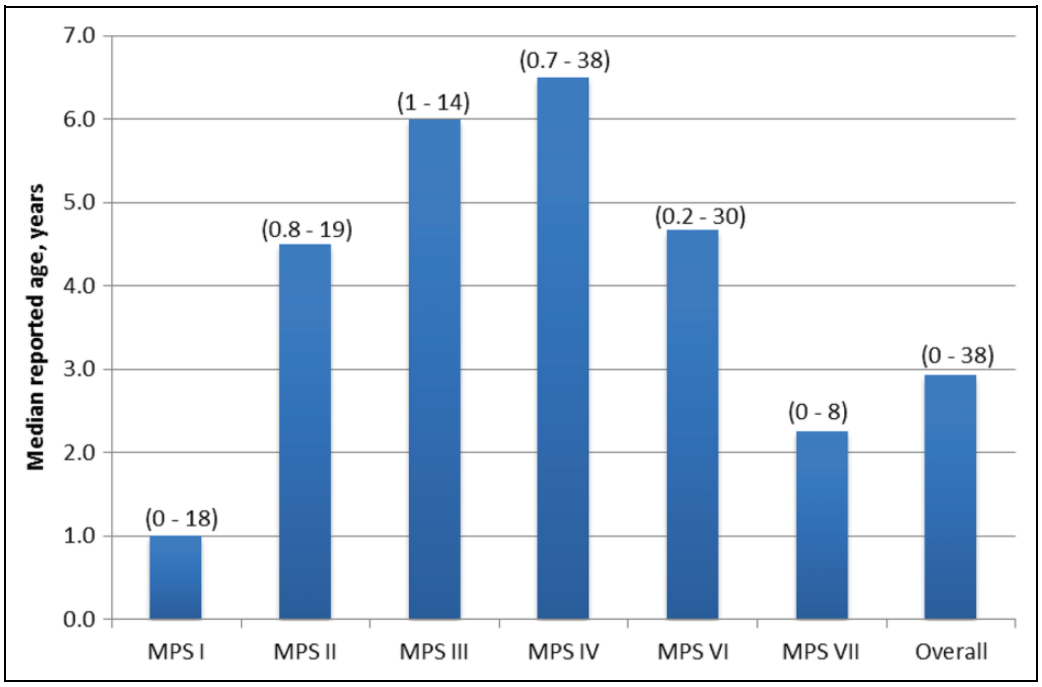

Figure 2. Literature review: duration of delays in diagnosis by mucopolysaccharidosis (MPS) type.
*Some studies excluded due to nonreporting. Age of diagnosis and duration of delay in diagnosis may not be consistent as results have been synthesized from different sources in the literature. Ranges are provided in brackets.

Physician Survey

Distribution and eligibility. The target population for the physician survey was physicians to whom potential patients with MPS first present. Physicians were recruited from an online research panel that had previously consented to participate in surveys. Eligibility criteria included physician specialty, country of practice, and a requirement to have currently or previously identified, diagnosed, or managed a minimum of 1 patient with confirmed or suspected MPS. Specialties were selected based on expert feedback of the most likely physicians to whom patients with MPS would present. Eligible specialties included general medicine, orthopedics, rheumatology, neurology, internal medicine, ophthalmology, cardiology, pediatrics, clinical genetics/metabolic genetics, and otorhinolaryngology. Eligible countries were selected based on where known MPS clinics were located to increase the likelihood of identifying eligible physicians and to provide geographic variability within the study sample. Eligible countries included Argentina, Australia, Brazil, Canada, Colombia, France, Germany, Italy, Japan, Malaysia, Singapore, South Korea, Spain, Turkey, the United Kingdom, and the United States. Eligible physicians completed the survey online.

Survey contents. The survey included questions regarding the physicians' demographics and clinical practice, as well as experience with MPS including specific presenting signs and symptoms, referral patterns and laboratory and radiology investigations; they may order for patients with suspected MPS. Physicians were asked to describe up to 10 potential cases with MPS they could recall, including the clinical features at presentation of the patient, the MPS type, the patient's age when symptoms first presented, and the duration that the patient had these presenting symptoms when they were either referred to them or referred on. The survey was available in 4 languages: English, Japanese, Portuguese, and Spanish. The survey took approximately 20 minutes to complete, and participants were compensated for their time. See Supplemental File 3 for the English version of the survey.

Data analysis. Data were synthesized in tabular format; clinical features of MPS were stratified according to MPS type, age-group (<1, 1-4, 5-9, ≥10 years), reporting physician specialty, and/or major symptom categories.

Clinical Expert Panel

An international panel of 16 physicians highly experienced in managing cases with MPS was convened. Members of this panel provided input into the systematic literature review and physician survey methods and reviewed the results. Using these findings, along with group discussion based on personal expertise and clinical experience, the panel members recommended key red flag early signs and symptoms with relatively good sensitivity and specificity for detecting MPS based on the physician survey and the panel's clinical experience. The panel members provided recommendations for key red flag signs and symptoms that would be suitable for specialist and nonspecialist physicians. The tools developed based on these

Table 1. Physician Survey: Number of Surveyed Physicians by Specialty.

	Physician Respondents (n = 209)	
	n	(%)
Specialty		
General practice/family medicine	42	(20.1)
Orthopedics	12	(5.7)
Rheumatology	18	(8.6)
Neurology	13	(6.2)
Internist	23	(11)
Ophthalmology	23	(11)
Medical genetics[a]	0	(0)
Cardiology	25	(12)
Pediatrics	25	(12)
Metabolic disease/metabolic genetics	18	(8.6)
Otorhinolaryngologist	10	(4.8)

[a]Physicians were recruited from specialist panels; however, a panel of prespecified medical geneticists was not available

red flag signs and symptoms underwent iterative review cycles with the panel as well as cross-referencing with the physician survey and literature review results to ensure that each sign or symptom was common enough among patients with MPS to warrant inclusion and seen sufficiently infrequently by the physician type in question to be a realistic trigger for screening. The exact balance of specificity versus sensitivity determining inclusion/exclusion of an individual sign or symptom was based on the collective clinical judgment of the expert panel.

Results

Systematic Literature Review

A total of 1466 unique abstracts were identified. From these, 379 full-text publications were reviewed and 194 met the inclusion criteria (Figure 1). The majority (76%) of these studies reported on a single MPS type. A total of 330 MPS type-specific records, representing 194 unique studies, were identified.

Of the 194 studies included, 38% were reviews, 22% were case reports, and the remainder included case series, observational studies, surveys, and guidelines. MPS type-specific sample sizes ranged from 1 patient to 1041 patients; 42% of records contained fewer than 10 patients and only 3% of records contained 75 or greater patients. Overall, 44% of studies were European in origin, followed by Asian (15% of studies), and North American (14% of studies). Each MPS type was described in at least 1 study; descriptions of MPS I (39% of studies) and MPS IV (32% of studies) were most frequent.

In studies where the specialty of the diagnosing physician was described, it was most frequently geneticists, pediatricians, or metabolic specialists. Delays in diagnosis are reported in Figure 2 (additional data in Supplemental File 4). The typical delay in diagnosis, from time of symptom onset, was reported to be 2.9 years (ranging from 0 to 38 years). In approximately 20% of records, the median delay in diagnosis was reported to be at least 10 years. Some variability was observed across MPS types; the longest delays in diagnosis tended to be reported for MPS IV.

Coarse facial features, short stature, corneal clouding, hepatomegaly, and/or splenomegaly were the predominant signs and symptoms at presentation. Other frequently published presenting signs and symptoms included heart valve abnormality, neurological abnormality, joint abnormality, and varying levels of facial dysmorphism (additional data in Supplemental File 5).

Physician Survey

A total of 521 physicians were screened; 209 were eligible, and they participated in the survey. Between 5 and 20 participants were included per country, with general medicine being the most frequently represented specialty (20% of participants) and otorhinolaryngology the least frequent (5% of participants; Table 1). The majority of participants practiced in an academic setting (65%), and the study sample had a median of 16 years' experience postresidency (range: 2-56 years). Participants had experience with a median of 1 current MPS case (range: 0 to 200), and 3 previous MPS cases (range: 0 to 300). The majority (78%) of physicians had experience with MPS I. Participants reported having the least experience with MPS VII (14% reported any experience).

Physician participants described a total of 859 cases with MPS, with just over half of the cases being MPS I (n = 435) and only 17 cases being MPS VII. For all MPS types, 67% of cases described first presented under the age of 12 years, with 25% presenting under the age of 4 years.

Skeletal malformations and joint problems were the presenting signs and symptoms most frequently noted by the physicians, reported in more than 20% of cases across all MPS types (Figure 3). Gait disturbances, growth retardation, dysmorphic facial features, psychomotor retardation, and liver enlargement were also frequently reported, observed in more than 20% of reported cases for most MPS types. Corneal clouding was the most frequently observed ophthalmological sign for most MPS types (26% of all cases with MPS). Heart abnormalities and liver enlargement were observed at presentation in more than 20% of all cases with MPS reported, with heart abnormalities in over 30% of cases with MPS I, IV, and VI. MPS III was the type for which neurological signs and symptoms were most frequently reported at presentation.

Among cases presenting under the age of 4, just over half of patients presented with skeletal abnormalities or dysmorphic facial features (52% and 51%, respectively). Other frequently reported signs and symptoms in this age-group included developmental delay (45% of patients), growth retardation (38%), psychomotor retardation (36%), hypotonia (31%), and cognitive impairment (30%).

Forty-one percent of physicians reported that their patient had signs and symptoms that they did not know were associated

		MPS I (n=435) %	MPS II (n=42) %	MPS III (n=148) %	MPS IV (n=106) %	MPS VI (n=21) %	MPS VII (n=17) %	MPS IX (n=21) %	Unknown (n=69) %	Overall (n=859) %
Skeletal/muscular	Skeletal malformations	49.4	50	30.4	68.9	61.9	29.4	52.4	34.8	47.4
	Joint problems (stiffness or hypermobility)	33.8	28.6	37.2	34.9	42.9	35.3	52.4	30.4	34.7
	Gait disturbance	26.9	19	18.9	39.6	28.6	29.4	33.3	24.6	26.8
	Growth delays/short stature	30.6	26.2	27.7	42.5	57.1	11.8	23.8	27.5	31.2
	Knee deformities	18.4	26.2	12.8	28.3	28.6	23.5	23.8	13	19.1
	Hip deformities	17	4.8	16.9	27.4	19	5.9	14.3	11.6	17
	Gibbus deformity	10.1	14.3	2.7	15.1	14.3	5.9	14.3	7.2	9.5
	Other	1.1	0	0	0	0	5.9	4.8	1.4	0.9
Develop-mental	Dysmorphic/coarse facial features	40.2	35.7	37.8	36.8	38.1	29.4	19	27.5	37.4
	Psychomotor retardation	32	33.3	38.5	35.8	42.9	11.8	28.6	24.6	32.8
	Hypotonia	22.3	21.4	30.4	17	19	35.3	23.8	14.5	22.6
	Other	0.5	0	0	0	0	0	0	0	0.2
Organ system involvement	Heart abnormalities	30.6	16.7	12.8	36.8	42.9	5.9	14.3	17.4	26
	Breathing abnormalities	16.8	9.5	16.2	21.7	19	11.8	23.8	24.6	17.7
	Sleep apnea/sleep disordered breathing	13.1	9.5	18.9	13.2	28.6	11.8	23.8	17.4	14.9
	Liver enlargement	26.2	23.8	29.1	23.6	23.8	23.5	19	8.7	24.6
	Spleen enlargement	21.6	21.4	18.2	21.7	23.8	11.8	9.5	13	19.9
	Hearing deficits	11.3	16.7	16.9	10.4	14.3	5.9	4.8	15.9	12.6
	Multiple or recurrent hernia	5.3	14.3	4.1	10.4	14.3	17.6	4.8	4.3	6.5
	Other	0.2	0	0	0	0	0	0	0	0.1
Ophthalmo-logical	Clouding of the cornea	34	19	16.2	24.5	33.3	35.3	9.5	7.2	26.3
	Retinal degeneration	14.3	9.5	14.2	12.3	9.5	5.9	38.1	8.7	13.6
	Glaucoma/increased intraocular pressure	9.7	11.9	16.9	13.2	14.3	29.4	4.8	8.7	11.8
	Other	0.9	0	2	0	0	0	9.5	1.4	1.2
Neurological	Developmental delays	33.8	19	32.4	23.6	23.8	11.8	28.6	20.3	29.7
	Cognitive delays	22.1	9.5	34.5	13.2	28.6	11.8	28.6	18.8	22.4
	Hyperactivity	12	11.9	41.9	17.9	19	11.8	23.8	14.5	18.5
	Autism spectrum disorder	8.7	0	26.4	9.4	14.3	11.8	4.8	8.7	11.5
	Attention deficits	13.3	19	31.8	10.4	19	17.6	23.8	7.2	16.4
	Carpal tunnel syndrome	6.2	4.8	5.4	5.7	9.5	0	0	5.8	5.7
	Other	0.5	0	1.4	0	0	0	0	0	0.5
Otorhinolaryngo-logical	Frequent ear infections	20.2	21.4	10.8	19.8	9.5	11.8	28.6	15.9	18
	Frequent sinus infections	13.8	9.5	20.3	19.8	14.3	23.5	9.5	15.9	15.7
	Frequent tonsil infections	9.4	11.9	18.9	6.6	23.8	5.9	19	10.1	11.4
	Frequent placement of ear tubes	6	7.1	11.5	9.4	9.5	5.9	19	5.8	7.8
	Hearing impairment	9.4	9.5	15.5	12.3	23.8	0	14.3	4.3	10.7
	Other	0.2	0	0	0	0	0	0	0	0.1
Other	Skin abnormalities	12.4	26.2	11.5	14.2	14.3	11.8	14.3	10.1	13
	Hair abnormalities	12.6	11.9	16.9	7.5	19	17.6	9.5	1.4	12
	Hydrops fetalis	4.1	0	11.5	9.4	4.8	11.8	14.3	2.9	6.2
	Poor dentition/dental abnormalities	13.1	14.3	15.5	16	19	0	9.5	7.2	13.3
	Frequent colds/upper respiratory tract infections	9	2.4	10.8	9.4	9.5	23.5	33.3	10.1	10
	Macroglossia	12.2	7.1	15.5	13.2	19	0	9.5	11.6	12.5
	Family history of MPS	5.7	0	6.1	4.7	14.3	17.6	4.8	5.8	5.8
	Other	0.7	2.4	0.7	0	0	0	4.8	4.3	1

Figure 3. Physician survey: signs/symptoms present when mucopolysaccharidosis (MPS) first suspected or patient referred with suspected MPS*.

*Proportion among reported cases. Physicians were permitted to enter data for up to 10 patients; however, they were not asked to pull these data from patient charts—these are likely from memory. Cells are shaded if greater than 20%, with darkest shading for maximum values; "Other" fields within each subsection are populated by free-text fields. Ns in the column headers represent the number of patients entered where at least one symptom was also provided.

with MPS, including various behavioral abnormalities (5%), abdominal conditions such as hernias or hepatosplenomegaly (4%), skeletal manifestations (3%), and visual conditions (2%).

Large variation was observed in the duration that patients had MPS features prior to being referred or tested for MPS, ranging from 1 month to 5 years. The signs and symptoms that were present for the longest mean duration prior to referral included carpal tunnel syndrome, skin abnormalities, recurrent ear, nose, and/or sinus infection, gibbus, heart abnormalities, and a family history of MPS, all present for a mean of over 13 months prior to referral (Table 2).

Referral patterns demonstrated that a large number of specialties were involved in the pathway to an MPS diagnosis (Figure 4). General practice and pediatrics were the 2 specialties from which the surveyed physicians most frequently received referrals. Metabolic specialists and pediatricians were the specialties to which the surveyed physicians most frequently referred patients. Among the surveyed physicians, 27% indicated that they would order an initial screening test for MPS prior to referring a patient with suspected MPS. This highlights the need for better education of the medical community on MPS screening and testing.

Table 2. Physician Survey: Duration of Specific Signs/Symptoms at the Time of Decision to Test/Referral.[a]

		Duration of Symptom Prior to Testing or Referral (months)	
	Patients with symptom (n)	Mean (SD)	Median (Range)
Skeletal/muscular			
Skeletal malformations	407	12.2 (11.3)	10 (1-60)
Joint problems (stiffness or hypermobility)	298	12.8 (11.5)	9 (1-60)
Gait disturbance	230	10.4 (9.6)	6 (1-60)
Growth delays/short stature	268	11.6 (10.9)	7 (1-53)
Knee deformities	164	12.2 (10.6)	9 (1-48)
Hip deformities	146	12.9 (11.9)	10 (1-53)
Gibbus deformity	82	14.5 (12.8)	10 (1-60)
Developmental			
Dysmorphic/coarse facial features	321	11.0 (10.7)	7 (1-60)
Psychomotor retardation	282	10.2 (9.9)	6 (1-60)
Hypotonia	194	7.3 (6.4)	6 (1-30)
Organ system involvement			
Heart abnormalities	223	14.8 (11.8)	12 (1-53)
Breathing abnormalities	152	11.2 (9.8)	6.5 (1-53)
Sleep apnea/sleep disordered breathing	128	10.6 (9.0)	7 (1-60)
Liver enlargement	211	12.4 (12.1)	9 (1-60)
Spleen enlargement	171	12.5 (12.3)	10 (1-60)
Hearing deficits	108	11.3 (9.4)	7 (1-48)
Multiple or recurrent hernia	56	12.6 (11.9)	10 (1-60)
Ophthalmological			
Clouding of the cornea	226	11.9 (11.2)	10 (1-60)
Retinal degeneration	117	8.7 (5.8)	6 (1-24)
Glaucoma/increased intraocular pressure	101	10.5 (10.2)	6.5 (1-48)
Neurological			
Developmental delays	255	10.8 (10.8)	6 (1-60)
Cognitive delays	192	12.2 (11.4)	7 (1-60)
Hyperactivity	159	9.7 (10.8)	6 (1-60)
Autism spectrum disorder	99	10.6 (12.2)	6 (1-60)
Attention deficits	141	9.9 (8.7)	6 (1-40)
Carpal tunnel syndrome	49	15.1 (13.3)	13 (1-60)
Otorhinolaryngological			
Frequent ear infections	155	13.2 (10.9)	12 (1-60)
Frequent sinus infections	135	13.2 (11.3)	11 (1-60)
Frequent tonsil infections	98	9.6 (9.3)	6 (1-48)
Frequent placement of ear tubes	67	9.2 (7.0)	7 (1-30)
Hearing impairment	92	12.6 (10.5)	10 (1-48)
Other			
Skin abnormalities	112	14.9 (12.5)	12 (1-60)
Hair abnormalities	103	12.4 (11.0)	10 (1-60)
Hydrops fetalis	53	6.2 (4.0)	6 (2-20)
Poor dentition/ dental abnormalities	114	11.6 (10.1)	8 (1-48)
Frequent colds/ upper respiratory tract infections	86	12.3 (9.7)	12 (1-40)
Macroglossia	107	11.1 (9.7)	7 (1-48)
Family history of MPS	50	16.1 (14.1)	12 (1-60)

Abbreviations: MPS: Mucopolysaccharidosis; SD: Standard deviation.
[a]At time the surveyed physician decided to test for MPS or refer on or before the case was referred to the surveyed physician.

Clinical Expert Panel

The expert panel identified red flag signs and symptoms for consideration based on the systematic literature review, physician survey, and their own clinical experience. The red flag signs and symptoms were selected to be specific to physicians in pediatrics or general medicine as well as those in 5 subspecialty types to whom patients with early signs of MPS are likely to be referred: cardiology, pediatric neurology, otorhinolaryngology, rheumatology, and orthopedics. These specialties were selected based on the referral patterns reported in the physician survey, the early signs and symptoms identified in the systematic literature review and physician survey, and expert experience. One to 6 key red flag signs and symptoms were identified for each specialty type and were further augmented with lists of corroborating signs/symptoms to aid in the establishment of

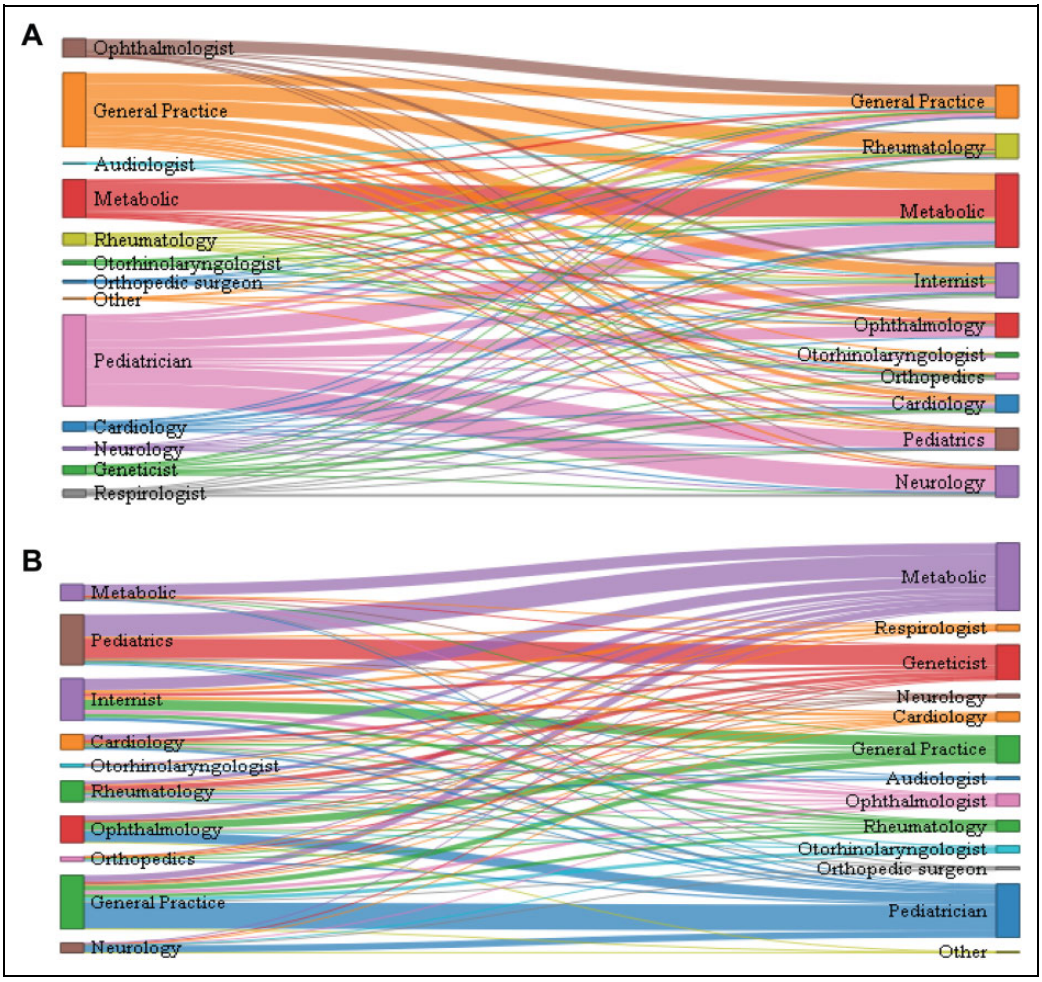

Figure 4. Physician survey: alluvial plots showing which specialties the surveyed physicians received the mucopolysaccharidosis (MPS) referrals from (A) and which specialties the surveyed physicians referred suspected MPS patients to (B).
Notes: The alluvial plot is weighted by the number of patients such that if a specialist said they had received 10 referrals from a general practitioner and 20 from a pediatrician, these weights are captured in the diagram.

clinical suspicion of MPS (Table 3). These red flag signs and symptoms were then converted into specialty-specific clinical awareness diagnostic tools (Supplemental Files 6, 7, 8, 9, 10, 11, and 12). The tools were developed to be simple and visual. They also highlight the incidence of MPS and urgency of early diagnosis, provide information on additional signs and symptoms to help establish stronger clinical suspicion of MPS and motivate testing, and list next steps.

While discussing next steps, the panel noted the differing availability of screening and diagnostic test options globally and the continuous improvement in testing technologies over time. These factors, combined with those previously noted highlight the need to better educate the medical community on MPS screening and testing, led to the identification of the need for a global MPS testing website with up-to-date, region-specific information. As a result, www.test4mps.com website was developed to provide information on how to test for MPS and to house a searchable database of laboratories that conduct MPS testing around the world.

Discussion

The largely unappreciated need for early diagnosis of MPS was evident in the physician survey and systematic review. Patient cases described in the physician survey were observed to have signs and symptoms for over a year prior to referral, ranging up to 5 years. Additionally, the observed referral patterns indicate that patients are presenting to a variety of specialists and are being referred on to a variety of other specialists. The systematic literature review reflected similar trends, with nearly 40% of records reporting a delay in diagnosis of 1 to 4 years and 20% reporting a delay of greater than 10 years. This clearly demonstrates a need to improve the early recognition of signs and symptoms to facilitate earlier MPS screening and referral to metabolic specialists or clinical geneticists.

Results of the survey and literature review also highlighted challenges of early MPS diagnosis: rarity and the varied and sometimes subtle nature of signs and symptoms at presentation. Forty one percent of physicians in the survey reported that their patient(s) had signs or symptoms that they were not initially

Table 3. List of Specialty-Specific Red Flag Symptoms for MPS Developed by International Panel of MPS Experts.

Specialty	Red Flag Symptoms						Corroborating Symptoms
Orthopedics	Bilateral hip dysplasia/ osteonecrosis (perthes-like)		Vertebral body abnormality (hypoplasia, beaking, platyspondyly, kyphosis/gibbus)				Abnormal skeletal features (such as gibbus, pectus, broad ribs, hypoplastic odontoid, enlarged sella turcica, genu valgus)
Cardiology	Cardiac valve thickening						Atypical Mongolian spots
Otolaryngology	Recurrent ear, nose, or throat infection		Upper airway obstruction	Progressive hearing loss			Carpal tunnel syndrome (bilateral)
Pediatric Neurology	Developmental delay/regression		Language delay	Hyperactivity			Chronic rhinorrhea
Rheumatology	Unexplained arthropathy (with or without pain)		No evidence of inflammation				Clawed hands
Pediatricians	Short stature/ Decreasing growth velocity	Gibbus	Developmental delay	Recurrent ENT-related symptoms or infections	Enlarged liver and/or spleen	Inguinal or umbilical hernia, especially recurrent/history of hernia repair	Coarse facial features Corneal clouding
General Practitioners	Unexplained arthropathy with or without pain	Early onset spinal disease	Joint restrictions/stiffness or laxity/ hypermobility		Cardiac valvular disease	Early corneal clouding	Dental abnormalities Developmental delay Difficulty opening mouth Dilated Virchow-Robin spaces
							Enlarged tonsils/adenoids Glaucoma (bilateral) Hearing loss Heart valve disease Hernias, including previous hernia repair Hirsutism History of hernia repair Hydrocephalus Joint abnormalities (restriction/stiffness or hyper-mobility/laxity) Kyphosis Left ventricular hypertrophy Liver and/or spleen enlargement Macroglossia Multi-systemic involvement Nerve compression syndrome Psychomotor delay/regression Recurrent ear nose and throat infections Seizures Short stature Sleep apnea Spinal deformity Unexplained arthropathy, with/without pain

Abbreviations: ENT, ear, nose, throat; MPS, mucopolysaccharidoses.

aware were associated with MPS. Even with increased awareness among those with little or no experience in managing an MPS patient, a further challenge lies in providing a description of a common presentation of MPS. While skeletal deformities and joint problems are the hallmarks of most of the MPS disorders, we compiled an extensive list of other clinical features with early onset that should make one consider MPS. For example, some of the early presenting signs and symptoms that were frequently reported in the literature and physician survey included growth retardation; recurrent ear, nose, and/or throat infections; coarse facial features; developmental delay; heart valve thickening; corneal clouding; progressive hearing loss; and hernias.

Although others have attempted to generate tools and/or algorithms based on presenting signs and symptoms to aid in the diagnosis of MPS, these efforts have resulted in no noticeable change in the average length of the diagnostic delay over time.[8] The difficulty in distributing this information and its very limited half-life with the target audiences are substantial contributing factors in the failure of these previous attempts. Unfortunately, we will be facing the same challenges with these tools. However, previous efforts have also had several notable limitations. They often targeted only a subset of the specialists likely to encounter undiagnosed individuals with MPS,[12–15] were limited to a particular MPS type[14,15] or a sub-group of the MPS population,[12,13] resulted in complex, multitiered algorithms with a high degree of specificity and inadequate sensitivity,[12,13] and relied solely on expert opinion.[12–15] Several steps were taken to overcome these previous limitations in the current project.

The majority of specialists to whom individuals with MPS present were included. All MPS disorders were targeted collectively, thereby increasing the incidence to within a range that may be more relevant for the target audience[8] and enabling physicians to proceed with the suspicion of MPS in general, without needing specific knowledge of the types of MPS. The proposed screening is based on simple red flags that are easier to recall than a complex algorithm. And importantly, the quality and quantity of data gathered through systematic review and physician survey provided a solid evidence-based foundation.

The literature review was conducted using systematic and reproducible methods and captured a broad range of study designs, including reviews, case reports, case series, and larger observational studies. The physician survey was internationally-based, multilingual, and included data collected from a wide range of specialties, thus reflecting the variation in symptom presentation and patterns of referrals across geographies and specialties. This multimethod approach is important for rare diseases where there is a paucity of large studies that capture the data needed to inform the research question.

Despite the extensive set of data collected, there were some notable limitations. For example, in the literature review, there is an inherent risk of publication bias (ie, there may have been a risk that particularly unusual presentations of MPS were included, as these were considered worthy of publication). However, given the large number of studies returned, and inclusion of several large observational studies, it is expected that these extremely unusual presentations would also be relatively infrequent in the synthesized data set. This limitation of the systematic literature review was also addressed by supplementing the review with a physician survey and by seeking clinical expert feedback on the generalizability of the results. A main limitation of the physician survey was that the data were, by the design of the study, based on physician recall rather than from a chart review. A sign or symptom not reported at presentation may have been due to it not being present, or alternatively, the physician may not have recalled the sign or symptom, or it may not have been identified at that time. Nonspecific signs and symptoms that could be identified by specialists outside of those included in this analysis may also have been missed. Furthermore, the MPS type was reported by the responding physician who may not have been the diagnosing physician, and thus, there may have been inaccuracies. Additionally, not all MPS types were equally represented; however, this limitation was mitigated by analyzing the data by MPS type and by including clinical experts to provide insight into all MPS types. To increase the likelihood of finding eligible physicians to participate in the survey, physicians were selected only from countries where there were known MPS clinics. Although this includes the majority of countries with a well-known population of patients with MPS, it is a limitation that not all countries with potential MPS patients were represented in the analysis.

The compilation of evidence from the systematic literature review and survey is extensive; however, through review and discussion with the international panel of clinical experts, the findings were distilled into targeted lists of specialty-specific red flag signs and symptoms, together with an additional list of corroborating signs and symptoms. These were synthesized into simple, specialty-specific tools that can help raise awareness while reducing the potentially overwhelming amount of information for practitioners who may only ever see 1 or 2 MPS patients in their entire career. The specialty-specific nature of these tools further maximizes their relevance. Importantly, these tools have also been coupled with real-world, up-to-date laboratory information to facilitate rapid action following initial suspicion of MPS.

The ability of these tools to have an impact for MPS patients and their families is completely dependent on what happens next. Due to the rarity of the disease, specialists may only see 1 patient with MPS during their career, perhaps years after this paper is published. The key knowledge we have assembled here will need to be available to physicians whenever they happen to encounter that patient. Using repetitive dissemination of our simple, evidence-based, specialty-specific tools and striving to ensure their continual presence (ie, tools posted on hospital walls, incorporation into guidelines, inclusion in an online application), we hope to have the critical information available at the right time for as many cases as possible. The effectiveness of our approach will need to be evaluated in a future study.

Ultimately, though these clinical awareness diagnostic tools will not completely close the diagnostic gap, we hope that they

will help to narrow it until a more comprehensive solution, such as newborn screening, automated electronic medical record flagging, or mandatory subpopulation screening, is feasible.

Authors' Note

Sarah Goring, Suzanne McMullen, Sara Hawley, and Elaina Jurecki contributed to study design, and physician survey conduct. Fathima Mubarack and Elaina Jurecki designed the systematic literature review and Fathima Mubarack performed data extraction and Sarah Goring and Zaeem Khan contributed to the analysis of the systematic literature review. Lorne Clarke, Carolyn Ellaway, Helen E. Foster, Roberto Giugliani, Cyril Goizet, Christina Lampe, Ken Martin, John J. Mitchell, Martha Solano Villarreal, H. Serap Sivri, Fiona J. Stewart, Anna Tylki-Szymanska, Klane White, and Frits Wijburg were members of the clinical expert panel, and provided interpretation of the study results and selection of the relevant symptoms based on the study results. All authors read and approved the final manuscript.

Acknowledgments

We would like to acknowledge Dr Mira de Kruijf (Royal Manchester Children's Hospital), Dr Kuo Sheng Lee (Mackay Memorial Hospital), Dr Elizabeth Braunlin (University of Minnesota), Neil James, Tiffany Wong, Grace Chen, and Emanuela Izzo (BioMarin Pharmaceutical Inc.) for their contributions to this study.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Lorne Clarke receives honoraria and travel support from Sanofi, BioMarin, and Shire related to participation in disease registry boards and speakers bureaus. Carolyn Ellaway has received travel support and honoraria from BioMarin, Sanofi Genzyme, and Shire. Helen E. Foster on behalf of Newcastle University, United Kingdom has received speaker/chair honoraria and unrestricted educational bursaries from BioMarin and Sanofi Genzyme. Roberto Giugliani has received investigator fees, and/or travel grants, and/or speaker honoraria from Actelion, Amicus, Armagen, BioMarin, GC Pharma, JCR Pharmaceuticals, Lysogene, Sanofi Genzyme, Shire, and Ultragenyx. Cyril Goizet has received consulting fees from Sanofi Genzyme and BioMarin; honorarium for participation in advisory boards from BioMarin and Sanofi Genzyme; financial support for research activities from Sanofi Genzyme, Shire, and BioMarin; and funding for inscriptions and travels for congresses from Sanofi Genzyme, Shire, and BioMarin. Sara Hawley, Elaina Jurecki, and Fathima Mubarack are employees and stockholders of BioMarin. Christina Lampe has received honoraria/consultation fees from Shire, Alexion, Actelion, BioMarin and Genzyme, and has participated in company sponsored speaker's bureau for Shire, Alexion, Actelion, BioMarin and Genzyme. Ken Martin has accepted consulting fees or honoraria from the following companies engaged in developing MPS-related therapies: BioMarin, Sangamo, REGENXBIO, Ultragenyx, and Shire. John J. Mitchell has received speaker fees, consulting fees and research support from BioMarin and Shire, and receives funding support from the Harpur Foundation. H. Serap Sivri has received travel support and honoraria from BioMarin. Martha Solano Villarreal has received speaker fees and consulting fees from BioMarin. Fiona J. Stewart has received speaker fees and consultancy fees from BioMarin. Anna Tylki-Szymanska has received honoraria/consultation fees from Shire, BioMarin, Chiesi and Genzyme, and has participated in company sponsored speaker's bureau for Shire, BioMarin and Genzyme. Klane White has received honoraria/travel support from BioMarin, Genzyme, and Medicrea, and receives royalties from UpToDate.com and grant support from BioMarin. Frits Wijburg has received honoraria for presentations and board meetings, travel expenses to meetings and honoraria for consultancy work from Sanofi Genzyme, BioMarin, Actelion and Shire, and has received unrestricted educational grants and research grants from Sanofi Genzyme, BioMarin and Actelion. Sarah Goring, Zaeem Khan, and Suzanne McMullen declare that they have no competing interests.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded by BioMarin Pharmaceutical Inc.

ORCID iD

Christina Lampe http://orcid.org/0000-0003-4953-7119

Supplemental Material

Supplemental material for this article is available online

References

1. Muenzer J. Overview of the mucopolysaccharidoses. *Rheumatology*. 2011;50:v4-v12.
2. Bittar T. Mucopolysaccharidosis. In: Grogan DP, ed. Medscape. New York, NY: Medscape; 2013.
3. Neufeld EU, Muenzer J. The mucopolysaccharidoses. In: Scriver CR, Beaudet AL, Sly WS, Valle D, Childs B, Kinzler KW, Vogelstein B, eds. *The metabolic and molecular bases of inherited disease*. New York: McGraw-Hill; 2001: pp. 3421-3452.
4. Baehner F, Schmiedeskamp C, Krummenauer F, et al. Cumulative incidence rates of the mucopolysaccharidoses in Germany. *J Inherit Metab Dis*. 2005;28(6):1011-1017.
5. Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. *JAMA*. 1999;281(3):249-254.
6. Poorthuis BJ, Wevers RA, Kleijer WJ, et al. The frequency of lysosomal storage diseases in the Netherlands. *Human Genet*. 1999;105(1-2):151-156.
7. Lin HY, Lin SP, Chuang CK, et al. Incidence of the mucopolysaccharidoses in Taiwan, 1984-2004. *Am J Med Genet A*. 2009; 149A(5):960-964.
8. Kuiper GA, Meijer OL, Langereis EJ, Wijburg FA. Failure to shorten the diagnostic delay in two ultra-orphan diseases (mucopolysaccharidosis types I and III): potential causes and implications. *Orphanet J Rare Dis*. 2018;13(1):2.
9. Wilson GN. Hunter syndrome (mucopolysaccharidosis II): diagnosis, genetic testing, treatment, and referral. *Consultant for Pediatricians*. 2015;14(5):206-212.
10. Centre for Reviews and Dissemination. *Systematic Reviews: CRD's Guidance for Undertaking Reviews in Health Care*. Layerthorpe, York: University of York. 2009. https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf
11. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.

12. Cimaz R, Coppa GV, Koné-Paut I, et al. Joint contractures in the absence of inflammation may indicate mucopolysaccharidosis. *Pediatr Rheumatol*. 2009;7:18.
13. Lehman TJA, Miller N, Norquist B, Underhill L, Keutzer J. Diagnosis of the mucopolysaccharidoses. *Rheumatology*. 2011;50(5): v41-v48.
14. Wood T, Bainbridge K, Beck M, et al. Diagnosing mucopolysaccharidosis IVA. *J Inherit Metab Dis*. 2013;36(2): 293-307.
15. Wood T, Bodamer OA, Burin MG, et al. Expert recommendations for the laboratory diagnosis of MPS VI. *Mol Genet Metab*. 2012; 106(1):73-82.