Contemporary approach to joint hypermobility and related disorders

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Purpose of review
Joint hypermobility is a common, although largely ignored physical sign. Joint hypermobility is often asymptomatic but may be a feature of an underlying genetic disorder with systemic manifestations. The present article presents a comprehensive approach to considering joint hypermobility and clinically related issues in children and adults.

Recent findings
Ehlers–Danlos syndrome (EDS) is an umbrella term for various Mendelian connective tissue disorders sharing joint hypermobility, skin hyperextensibility, and tissue fragility. Hypermobile EDS is the default diagnosis in many individuals and still lacks of any confirmatory test. There is also a continuous spectrum of phenotypes between asymptomatic, nonsyndromic joint hypermobility, and hypermobile EDS. In 2017, a new international classification of EDSs, joint hypermobility, and related disorders was published. EDSs are now classified in 13 different variants because of mutations in 19 genes. The gap between joint hypermobility and hypermobile EDS is filled by the descriptive diagnosis of 'hypermobility spectrum disorders'. Alongside the new criteria recommendations for the assessment and management of selected issues related to joint hypermobility such as fatigue and physical therapy have also been published by expert panels.

Summary
Asymptomatic, nonsyndromic joint hypermobility, hypermobility spectrum disorders and EDS (particularly, the hypermobile type) are the most common phenotypes in children and adults with joint hypermobility. Their prompt recognition is crucial to the appropriate application of evidence-based management and the reduction in burden of ill health.

Keywords
Ehlers–Danlos syndrome, international classification, joint hypermobility, management, nosology

INTRODUCTION

Joint hypermobility is a clinical sign commonly encountered in various populations, particularly children and females [1]. It defines the ability that a joint (or a group of joints) has to move beyond its (their) normal range of motion (ROM). Because its first description in the international literature as a clinically relevant feature, joint hypermobility is usually associated with musculoskeletal complaints [2]. Although this holds true in many cases, joint hypermobility may also be a feature of multisystem and occasionally severe hereditary disorders. The Ehlers–Danlos syndromes (EDSs) are prototypes of these conditions, and defined by the triad of joint hypermobility, skin hyperextensibility, and fragility of vessels and organs [3]. In the past century, scientific interest in joint hypermobility was very limited. Publication of the 1997 Villefranche nosology of EDSs [4] and, 2 years afterwards, of the revised criteria for joint hypermobility syndrome (JHS) [5] fostered increasing attention on the clinical significance of joint hypermobility. This culminated in the 2017 international classification of EDSs [6▪▪], and in more accurate definitions for joint hypermobility and related disorders [7▪▪]. The need for an updated nosology of EDS and well outlined procedural diagnostics for the various phenotypes of joint hypermobility was prompted by the discovery of an

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KEY POINTS

- Joint hypermobility is a common physical sign, especially in children and women.
- Joint hypermobility should be always assessed with specific tools and procedures; joint hypermobility is classified in localized, peripheral, and generalized, according to body distribution.
- Ehlers–Danlos syndrome (EDS) is the most common genetic diagnosis in patients with joint hypermobility; the 2017 international classification identifies 13 subtypes due to mutations in 19 different genes.
- Hypermobile EDS still lacks a molecular confirmatory test and its diagnosis remains based on a set of revised diagnostic criteria.
- Joint hypermobility syndrome has been removed from the contemporary nosology, and the gap between isolated, nonsyndromic joint hypermobility, and the hypermobile EDS is filled by the more flexible 'hypermobility spectrum disorders'.

increasing number of disease-genes, and by the lack of a consensus on the use of the terms 'joint hypermobility', 'JHS', and 'EDS', and specifically the hypermobile variant (hEDS) [8].

DEFINITIONS OF JOINT HYPERMOBILITY

Joint hypermobility is a sign, not a diagnosis. Hence, recognizing joint hypermobility does not allow the clinician to make a diagnosis, but rather may prompt additional assessment. Joint hypermobility is observed in 2–34% of males and 6–57% of females [1]. That said most of the literature has focused on the prevalence of 'generalized' or widespread hypermobility. This is just the 'tip of the iceberg' when considering the possible distribution. Bodily localization is a good perspective for classifying joint hypermobility as follows:

(1) Localized joint hypermobility (LJH): an excessive ROM is appreciated at a single site with possible bilateral presentation in the case of limb and temporomandibular joints.
(2) Generalized joint hypermobility (GJH): joint hypermobility is visible at multiple sites involving the four limbs and axial skeleton.
(3) Peripheral joint hypermobility (PJH): joint hypermobility is observed at multiple and bilateral sites but limited to hands and feet [7▪▪].

ROM naturally decreases with age; this also happens in hypermobile joints [1,9,10]. Cross-sectional observation in cohorts of patients with JHS and hEDS according to the Villefranche nosology suggested progressive reduction in the extent of joint hypermobility in these conditions also [11–13]. This prompted speculation as to the prior existence of joint hypermobility in older adults who on examination have lost their hypermobility but whose history suggests it was likely present ['historical' joint hypermobility (HJH)].

Joint hypermobility often is asymptomatic for the entire life of the 'double-jointed' individual. The mechanisms underlying symptom onset and progression in joint hypermobility are poorly understood. The coexistence of (or the evolution in) joint instability, that is the excessive or improper movement of a joint along nonphysiological axis/axes, is likely a major factor influencing generation of symptoms. Both joint hypermobility and joint instability could facilitate microtrauma and macrotrauma to tissues and predispose to a variety of biomechanical and neuromuscular dysfunctions [7▪▪]. Although ligamentous laxity contributes to joint instability in the hypermobile individual, joint instability may also occur in other disorders with different pathogeneses, including muscle disorders (e.g. some hereditary myopathies), neurological disorders (e.g. spinal muscular atrophy), and skeletal disorders (e.g. some bone dysplasias).

HOW TO ASSESS JOINT HYPERMOBILITY IN A CLINICAL SETTING

Assessing joint hypermobility correctly is not an easy task. The clinical approach to joint hypermobility should always take into account a number of variables influencing quality of data and limits of available tools. The presence of extreme joint hypermobility at a single or multiple sites is clear-cut. Problems rise for borderline joint hypermobility, when the practitioner needs to distinguish between LJH, GJH, and PJH, and in cases of congenital or acquired limitations of major joints.

Borderline joint hypermobility should be always assessed by appropriate tools, that is orthopedic goniometer, adequate procedure [14] and comparison of the obtained values with available standards [15]. That said such parameters do not exist for many when considering their race, age, and sex. Nevertheless, scrutiny of all major joints with objective methods and comparison with published normal ranges is the best way to limit interobserver variability, and avoids over-emphasis on patient self-reporting.

Distinguishing LJH, GJH, and PJH is essentially based on the observed pattern of joint hypermobility. Although LJH and PJH are descriptive terms, GJH is usually assessed with the Beighton score (Table 1). This score was originally proposed as an

Table 1. Clinical use of the Beighton score and 5-point questionnaire.

Beighton score(for more details see ref. no. 17)
Items (presence = 1 point each; absence = 0 points each)
1. Passive flexion of the thumb allows the touch of the volar aspect of the forearm (repeat on both sides)
2. Passive hyperextension (>90°) of the fifth finger with the palm and wrist touching a solid surface (repeat on both sides)
3. Active hyperextension (>190°) of the elbows with the upper limb extended and the palm turned up (repeat on both sides)
4. Active hyperextension (>190°) of the knees while the subject stands up (repeat on both sides)
5. Active hyperextension of the lumbar spine by inviting the subject to touch the floor with both palms but without flexing the knees
Interpretation – Children
Score ≥6 → Test positive
Score 5 or less → Test negative
Interpretation – Adults
Score ≥5 → Test positive
Score 4 or less → Test negative
5-Point Questionnaire
Items (yes = 1 point each; no = 0 points each)
1. Can you now (or could you ever) place your hands flat on the floor without bending your knees?
2. Can you now (or could you ever) bend your thumb to touch your forearm?
3. As a child, did you amuse your friends by contorting your body into strange shapes or could you do the splits?
4. As a child or teenager, did your shoulder or kneecap dislocate on more than one occasion?
5. Do you consider yourself 'double jointed'?
Interpretation
Score ≥2 → Test positive
Score 0 or 1 → Test negative

epidemiological tool for evaluating joint hypermobility in South African children and young adults [16]. In the following decades its use was translated into clinical practice with minor modifications. To date, a score of five and six or more (out of nine) is considered the cut-off for GJH in adults and children, respectively [17▪]. Ideally, LJH is established in presence of joint hypermobility at a single joint (or group of joints collaborating to the same segmental/simple movement). In the case of limb joints, the term LJH is still valid also despite presence of bilateral hypermobility. All individuals with LJH have a negative (i.e. <5) Beighton score, by virtue of the joints included in the score.

PJH regularly affects hands and this may imply a score up to 4 (i.e. bilateral positive volar flexion of the thumb and dorsal extension of the V finger). However, PJH commonly associates with negative score. In practice, individuals with joint hypermobility may have hypermobility in two, three or a few different joints but with negative Beighton score and without a clear PJH pattern. These individuals should be classified as LJH. At the same time, individuals with a predominant peripheral pattern of joint hypermobility may also present hypermobility in a few other more proximal joints. These subjects should be labeled with PJH only in the case of negative Beighton score. A positive Beighton score is a marker of GJH, independent of the predominant peripheral, proximal or axial observed pattern of joint hypermobility.

Acquired and congenital limitations of joints included in the Beighton score hamper adequate differential diagnosis in LJH, PJH, and GJH. The use of standardized questionnaires might help in collecting data in support of a past history of GJH. The five-point questionnaire (5PQ) is the most commonly used (Table 1) [18]. A positive reply to ≥2 of the 5 items *suggests* that the patient was born 'double-jointed'. Positivity of the 5PQ is clinically relevant only in patients without appreciable joint hypermobility (HJH). In fact, phenotypic classification of joint hypermobility is primarily based on physical examination which stands before any historically collected data [7▪▪]. The 5PQ is used in a slightly different way during the assessment and differential diagnosis of hEDS accordingly the 2017 international classification; in particular, positive 5PQ may count as one point of the Beighton score when the patient has a score 1 point below the cut-off (see below) [6▪▪].

Diagnosing joint hypermobility does not necessarily mean that this finding is the 'cause' of the reported symptoms! Careful systemic, personal and family data collection is always needed before asserting a role for this common sign in the overall clinical picture.

PHENOTYPIC BOUNDARIES OF JOINT HYPERMOBILITY

Joint hypermobility is often a familial trait [19], but it may also rise from trauma, surgery, and inflammatory diseases such as rheumatoid arthritis [20], and can be amplified by exercise. Differentiating between 'acquired' and 'hereditary' joint hypermobility is not always straightforward. However, hereditary joint hypermobility is usually congenital and affects multiple sites, whereas acquired joint hypermobility is commonly limited to a single or few joints. Family and personal history, and physical examination of close relatives support differentiation.

Table 2. Definition of hypermobility spectrum disorders

Feature	Notes
Joint hypermobility	Localized JH (negative BS) → localized HSD
	Peripheral JH (negative BS) → peripheral HSD
	Generalized JH (positive BS)→ generalized HSD
	Historical (BS 0, no objective JH; positive 5PQ) → historical HSD.
Plus one or more of the following	
Musculoskeletal pain	Musculoskeletal pain can be linked to JH usually if is (i) not associated with inflammatory/autoimmune diseases, (ii) recurrent or chronic (also comprising myofascial pain and fibromyalgia), (iii) localized in joints with evidence or history of JH.
Dislocations	Dislocations can be related to JH usually if (i) occur repeatedly (two or more episodes), (ii) are not related to external forces sufficiently explaining the trauma, (iii) affect joints with evidence or history of hypermobility.
Musculoskeletal physical traits	All the following may be interpreted as developmental consequences of JH affecting the involved body segment(s), in the absence of other known predisposing factors (e.g. vertebral malformations):
	Flexible flatfoot
	Scoliosis
	Genua valga
	Cubita valga
Degenerative joint and bone disease	The following are demonstrated or are considered associated with JH if other predisposing factors have been excluded:
	Premature osteoarthritis
	Reduced bone mass.
Neurodevelopmental attributes	All the following are apparently more common in children with JH, but request accurate differential diagnosis:
	Benign, congenital hypotonia
	Simple motor delay
	Developmental coordination disorder
	Attention deficit/hyperactivity disorder
Plus	
Exclusion of hEDS and all other recognizable syndromes with JH	Check the new criteria for hEDS also comprising the exclusion criteria (Table 5).
	Consider selected or extensive molecular testing in doubtful cases.

5PQ, 5-point questionnaire; BS, Beighton score; hEDS, hypermobile Ehlers–Danlos syndrome; HSD, hypermobility spectrum disorder; JH, joint hypermobility.

Joint hypermobility may associate with a multitude of secondary musculoskeletal manifestations (Table 2) [7▪▪]. In these circumstances, joint hypermobility has triggered, accelerated or amplified the pathogenic process leading to the eventual onset/evolution of the related musculoskeletal symptom(s). Types and distribution of such symptoms is likely different between hereditary and acquired joint hypermobility, as the former should be more commonly associated with widespread, early-onset symptoms as well as neurodevelopmental attributes, while acquired joint hypermobility reasonably contributes to loco-regional manifestations.

Joint hypermobility may also be a marker of an underlying genetic disorder. A wide range of genetic conditions regularly or commonly present Joint hypermobility (Table 3). These disorders are singularly considered rare and, in all of them, the association of joint hypermobility and extra-articular manifestations is attributed to the perturbation of a pleiotropic gene. Symptomatic joint hypermobility (joint hypermobility with secondary musculoskeletal manifestations) and syndromic joint hypermobility (joint hypermobility with other pleiotropic manifestations) are not synonyms. In fact, many patients with symptomatic joint hypermobility are not affected by a genetic syndrome, and individuals with syndromic joint hypermobility may not report significant musculoskeletal complications.

Recent evidence indicates that children and adults with joint hypermobility may be ascertained by apparently not related, common clinical problems, such as chronic fatigue, anxiety, and a range of gastrointestinal functional disorders [20,21,22▪,23].

Table 3. Genetic/Mendelian conditions presenting with joint hypermobility

Condition
Hereditary (soft/nonossified) connective tissue disorders
Ehlers–Danlos syndromes and related disorders
Fibrillinopathies (Marfan and Beals syndromes) and other disorders of the transforming growth factor β pathway (e.g. Loeys–Dietz syndromes, Shprinzen–Goldberg syndrome)
Hereditary cutis laxae
Skeletal dysplasias
Achondroplasia and hypochondroplasia
Dysplasias with multiple dislocations (e.g. Larsen and Desboquis syndromes, *CST3*-related and gPAPP-related disorders)
Some spondyloepimetaphyseal dysplasias
Some *COL2A1*-related and *COL11*-related disorders
Diastrophic dysplasia
Trichorinophalangeal dysplasia
Hereditary myopathies
COL6-related disorders
SEPN1-related and *RYR1*-related disorders
MYH7-related and *TTN*-related disorders
Limb girdle muscular dystrophy 2E with joint hypermobility and contractures
Chromosomal and genomic disorders
Trisomy 21
47,XXY and *47,XXX*
Some microdeletion and microduplication syndromes
Multiple congenital anomalies/intellectual disability disorders (selected)
RASopathies
Kabuki syndrome
FG syndrome
Fragile X syndrome

The significant association of joint hypermobility with common disorders is not sufficient for declaring the existence of a genetic syndrome, but rather is an indicator of a strong pathogenic link. Joint hypermobility-associated comorbidities is the contemporary term used to define such associations. Their concurrence in individuals with various joint hypermobility-related disorders indicates the existence of a broad clinical problem (rather than nosologic singularity), whose elucidation needs more research.

EHLERS–DANLOS SYNDROMES AND HYPERMOBILITY SPECTRUM DISORDERS

Hereditary connective tissue disorders are the leading disease category among patients with syndromic joint hypermobility. EDSs, Marfan syndrome, disorders of the transforming growth factor β, and some skeletal dysplasias are the most common diagnoses to consider during the assessment of individuals with joint hypermobility. The 2017 international classification of EDSs identifies 13 variants with mutations in 19 different genes (Table 4) [6▪▪,24]. Although most EDS variants can now be confirmed by molecular testing, this is not the case for hEDS, which remains the default diagnosis of many patients with EDS without features of other variants and/or mutations in known genes. The diagnosis of hEDS still stands on clinical criteria. These and their procedural diagnostics are now clearer (Table 5) [6▪▪,25]. A printable checklist of the hEDS diagnostic criteria is available for professionals at the Ehlers–Danlos Society website (https://ehlers-danlos.com: hEDS Diagnostic checklist).

A phenotypic spectrum exists bridging asymptomatic joint hypermobility and hEDS. This gap is filled by still poorly defined phenotypes of joint hypermobility in combination with a range of secondary musculoskeletal manifestations. In the recent past, the term JHS was introduced to describe and support patients who present with chronic/recurrent, potentially disabling symptoms but cannot be classified under other rheumatologic or neurologic labels [5]. By the end of the last decade, the lack of a clear distinction between the Brighton criteria for JHS and the Villefranche criteria for hEDS led to the suggestion of extending the term hEDS to all individuals respecting either one of the two (or both)diagnoses, that is JHS, hEDS, or JHS+hEDS [26]. This approach was also supported by a segregation study [27]. The 2017 criteria of hEDS confines this diagnosis to patients with overt articular and systemic manifestations or to those with a clear Mendelian transmission of the disease [6▪▪]. All other individuals with joint hypermobility and secondary musculoskeletal manifestations, who do not meet the new hEDS criteria and cannot be recognized by other disorders featuring joint hypermobility, are now diagnosed as hypermobility spectrum disorders (HSDs). HSDs are intended as the *default diagnoses* for all individuals who present with complaints and/or life quality limitations because of joint hypermobility, when the overall clinical picture does not allow a more specific/genetic diagnosis [7▪▪]. HSDs are exclusion diagnoses without definite criteria, and are regularly attributed when the application of appropriate diagnostic tests and/or criteria do not confirm alternative diagnoses, also comprising hEDS (Table 2).

To date, HSD classification is roughly based on the type of observed joint hypermobility (i.e. generalized HSD, peripheral HSD, localized HSD, and historical HSD). Further research is needed in order to improve the rationale of this classification. However, separating these patients from individuals with

Table 4. New classification of the Ehlers–Danlos syndromes

New classification	Previous classification	Inheritance	Genes	Prevalence[a]	Major distinguishing features
Classical	Classic	AD	*COL5A1, COL5A2, COL1A1* (rare)	1/20 000	Papyraceous and hemosiderotic scars Velvety, hyperextensible skin
Classical-like	Tenascin XB-deficient	AR	*TNXB*	24 pts	Velvety, hyperextensible skin
Cardiac-valvular	Cardiac-valvular	AR	*COL1A2*	6 pts	Severe cardiac valvular involvement Velvety, hyperextensible skin
Vascular	Vascular	AD	*COL3A1, COL1A1* (rare)	No less than 1/200 000	Extensive easy bruising Vascular accidents/ruptures
Hypermobile	Hypermobility	AD	None	No less than 1/5000	Musculoskeletal pain Dislocations
Arthrochalasia	Arthrocalasia	AD	*COL1A1, COL1A2*	49 pts	Marked joint hypermobility Bilateral hip dysplasia
Dermatosparaxis	Dermatosparaxis	AR	*ADAMTS2*	15 pts	Extreme skin fragility Velvety, hyperextensible skin
Kyphoscoliotic	Kyphoscoliotic type 1	AR	*PLOD1*	84 pts (*PLOD1*) and 10 pts (*FKBP14*)	Congenital, progressive scoliosis Congenital hypotonia
	Kyphoscoliotic type 2	AR	*FKBP14*		
Brittle cornea syndrome	Brittle cornea syndrome type 1	AR	*ZNF469*	51 pts	Thin cornea Early-onset ketatoconus/globus
	Brittle corna syndrome type 2	AR	*PRDM5*		
Spondylodysplastic	Progeroid type 1	AR	*B4GALT7*	7 pts (*B4GALT7*), 47 pts (*B3GALT6*) and 8 pts (*SLC39A13*)	Short stature Congenital hypotonia Limb bowing
	Progeroid type 2	AR	*B3GALT6*		
	Spondylocheiro-dysplastic	AR	*SLC39A13*		
Musculocontractural	Musculocontractural type 1 or Kosho type	AR	*CHST14*	39 pts (*CHST14*) and 3 pts (*DSE*)	Velvety, hyperextensible skin Congenital contractures Facial features
	Musculocontractural type 2	AR	*DSE*		
Myopathic	Myopathy overlap	AD or AR	*COL12A1*	9 pts	Congenital hypotonia Proximal contractures
Periodontal	Periodontal	AD	*C1R, C1S*	>100 pts	Severe, early-onset periodontitis Tibial plaques

[a]Number of published patients are from ref. no. 31. Pts, patients.

asymptomatic, nonsyndromic joint hypermobility and those with a recognized genetic syndrome is prudent. In fact, the term HSD combines the need of assuring appropriate care to these individuals with the opportunity of avoiding the simplistic diagnosis of a genetic disorder which is chronic, systemic and still without a definitive cure. Also, HSD is not always a permanent diagnosis and may change into asymptomatic joint hypermobility in case of complete resolution of symptoms or into hEDS (or, perhaps, other genetic disorders) at follow-up when additional features may appear (Fig. 1).

PRINCIPLES OF MEDICAL MANAGEMENT OF JOINT HYPERMOBILITY AND RELATED DISORDERS

Medical approaches to patients with joint hypermobility is a subspecialty issue and consists of three phases: assessment of joint hypermobility and differential diagnosis, secondary prevention and monitoring of emerging complications by phenotype, and treatment of secondary musculoskeletal manifestations. Phase I is summarized in Fig. 1, which assumes a prevalence of asymptomatic, isolated joint hypermobility, HSDs, and hEDS among individuals referred to joint hypermobility-specialized clinics. Although these phenotypes are the most common, differential diagnosis by accurate medical recording, selected investigations/consultations and, if needed, molecular testing is always warranted (Table 3) [6▪▪,7▪▪,28▪]. Differences in pathogenesis, natural history, rate/type of vascular complications and inheritance pattern among the various joint hypermobility-related disorders are the pillars of this rationale that is now supported by next-generation sequencing facilities. Correct diagnosis may guide an evidence-based monitoring schedule for treatable, and potentially disabling or catastrophic complications. Separating individuals with unspecific phenotypes (isolated joint hypermobility and HSDs) from those with syndromes predicting systemic involvement (hEDS and Table 3) helps in prioritizing prevention strategies.

Table 5. New diagnostic criteria for the hypermobile Ehlers–Danlos syndrome

Criterion 1: Generalized joint hypermobility
Prepubertal children and adolescents: BS ≥6 or BS ≥5 + positive 5PQ
Women to age 50 and pubertal men: BS ≥5 or BS ≥4 + positive 5PQ
Women over the age of 50 and men: BS ≥4 or BS ≥3 + positive 5PQ
Criterion 2: Two or more of the following features (i.e. A+B, A+C, B+C or A+B+C)
Feature A (five or more of the following)
Unusually soft and velvety skin
Skin hyperextensibility (approx. 2 cm at the volar aspect of hands)
Unexplained striae distensae/rubrae in adolescents, men or prepubertal women without a history of significant gain or loss of body fat/weight
Bilateral piezogenic papules of the heels
Recurrent or multiple abdominal hernias
Atrophic, nonpapyraceous or nonhemosiderotic scars at two or more sites
Pelvic floor, rectal, or uterine prolapse in children, men or nulliparous women without a history of other predisposing factors
Dental crowding and high/narrow palate
Arachnodactyly (as defined by positive wrist on both sides and/or positive thumb sign on both sides)
Arm span-to-height ratio ≥1.05
Mitral valve prolapse of mild or greater degree
Aortic root dilatation with *Z*-score > +2 SD
Feature B
An independent diagnosis of hypermobile Ehlers–Danlos syndrome in one or more first-degree relatives
Feature C (one or more of the following)
Musculoskeletal pain in two or more limbs recurring daily for at least 2 months
Chronic, widespread pain for ≥3 months (also comprising fibromyalgia)
Recurrent joint dislocations: three or more dislocations in the same joint, or two or more dislocations in two or more sites; medical confirmation of joint instability in two or more joints in the absence of trauma
Criterion 3: exclusion diagnosis (all the following must be excluded)
Skin/soft tissue fragility suggestive or other Ehlers–Danlos syndromes
Other hereditable or acquired soft connective tissue disorders
All other known genetic conditions featuring joint hypermobility (Table 3)

The diagnosis of hypermobile Ehlers–Danlos syndrome is fixed is ALL the three (1, 2, and 3) above reported criteria are met. 5PQ, 5-point questionnaire; BS, Beighton score.

Available data on natural history and common complications of the three most common (classical, vascular and hypermobile), as well as of the rare variants of EDS are now available [26,29,30▪▪,31], and inform the nature of follow-up and monitoring.

PRINCIPLES OF TREATMENT OF MUSCULOSKELETAL MANIFESTATIONS OF JOINT HYPERMOBILITY

Exploring the various therapeutic resources for joint hypermobility and related disorders is beyond the scope of this review. Contemporary recommendations for treating pain [32] fatigue [33], cardiovascular dysautonomia [34], temporomandibular joint and oral issues [35], and gastrointestinal nonsurgical manifestations [36] have been recently published for EDS. Concerning musculoskeletal manifestations, many 'double-jointed' people never experience the detrimental effects of joint hypermobility. Symptoms may occur occasionally because of joint macrotrauma or recurrently and caused by minimal but repetitive joint microtrauma (possibly exacerbated by impaired biomechanics). Occasionally, symptoms are chronic and potentially disabling. Mechanisms remain incompletely understood but may include premature osteoarthritis, small fiber neuropathy, central sensitization, and maladaptive cognitions [37]. Education and active participation of the patient and family, graduated exercise programs, and active physical therapy intervention are all recommended to treat/prevent musculoskeletal manifestations of joint hypermobility [38,39,40▪]. Only fragmented data are available on long-term efficacy and appropriate methodology of physical therapy interventions, and on the correct application of orthotics, orthopedic surgery, and nontraditional resources [37,41–44].

CONTROVERSIES

The nosology of EDS and the clinical dimensions of joint hypermobility are yet to be completely elucidated. The 2017 international classification offers a nearly complete update of the clinical manifestations, molecular characteristics, and distinguishing features of the heterogeneous connective tissues disorders grouped under the umbrella term of EDS. However, atypical phenotypes are expected for all known genes especially for those with only a few mutated patients reported to date. In addition, many EDS patients (mostly hEDS) still remain without molecular confirmation of their diagnosis. This generates uncertainties as to what constitutes the 'minimal' set of clinical features for EDS that should be used for diagnosing patients and defining emerging disorders. The formal inclusion of disorders with marked involvement of the skeleton (i.e. spondylodysplastic EDS), muscles (i.e. myopathic EDS), and

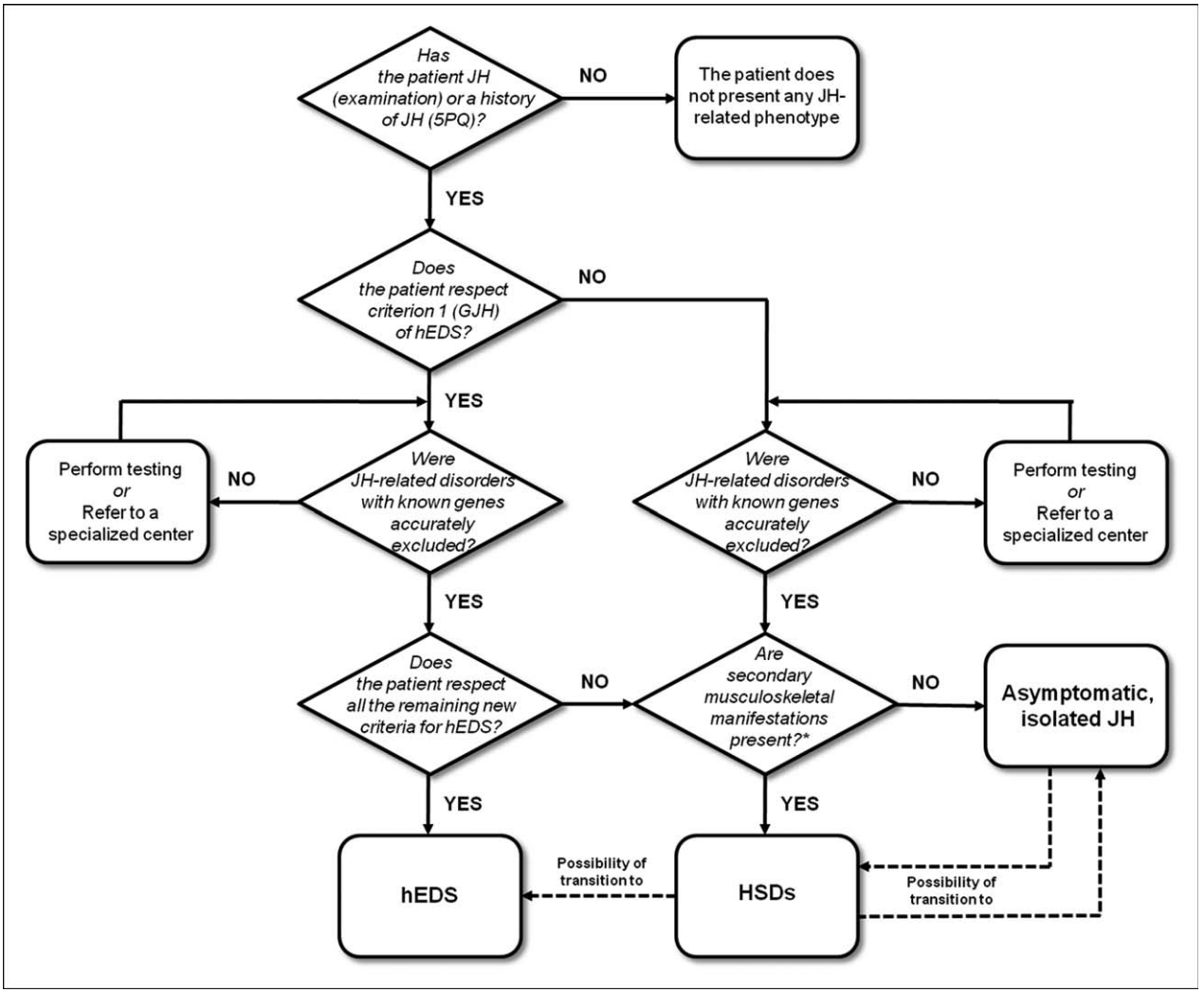

FIGURE 1. Diagnostic flow-chart of joint hypermobility. A flow-chart helping in attributing the correct diagnosis in patients with joint hypermobility and in understanding the relationships among isolated, nonsyndromic joint hypermobility, hypermobility spectrum disorders and hypermobile Ehlers–Danlos syndrome. 5PQ, 5-point questionnaire; hEDS, hypermobile Ehlers–Danlos syndrome; JH, joint hypermobility. ∗, secondary musculoskeletal manifestations include musculoskeletal pain, dislocations, musculoskeletal physical traits, degenerative joint and bone disease, and neurodevelopmental attributes (Table 2).

eyes (i.e. brittle cornea syndrome) dramatically expands the systemic boundaries of EDS. However, in the past decade the term 'EDS' was used as a broader term to diagnose an increasing number of patients with symptomatic joint hypermobility but lacking other features of the syndrome or other clearly definable heritable disorders of connective tissue. The stricter criteria for hEDS and the introduction of HSDs are intended to increase coherence within the nosology and assure a diagnostic class for all symptomatic subjects falling outside the new classification. Although this approach is shared by most researchers involved in the international initiative supported by the Ehlers–Danlos Society, others disagree and think of EDS as a broad term including all clinically relevant forms of joint hypermobility.

CONCLUSION

Joint hypermobility is a common physical sign that is attracting increasing attention in both adult and pediatric medicine. Appropriate recognition and assessment of joint hypermobility, and its use as a clue for further investigation, is still a cultural niche mastered by a very few experts worldwide. Recent publications help pediatricians and other specialists in approaching the issue with reliability in order to highlight the appropriate setting in which issues related to joint hypermobility should be raised.

Approaching this field is an orientation exercise between overemphasizing normal physical variation and neglecting a potentially severe disorder. Existing areas of uncertainty have been outlined which need the efforts of a new generation of researchers in order to be elucidated.

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Conflicts of interest

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Papers of particular interest, published within the annual period of review, have been highlighted as:
- ■ of special interest
- ■■ of outstanding interest

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