Expert Review of Clinical Pharmacology

ISSN: 1751-2433 (Print) 1751-2441 (Online) Journal homepage: https://www.tandfonline.com/loi/ierj20

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To cite this article: Anwar Baban & Marco Castori (2018) Pharmacological resources, diagnostic approach and coordination of care in joint hypermobility-related disorders, Expert Review of Clinical Pharmacology, 11:7, 689-703, DOI: 10.1080/17512433.2018.1497973

To link to this article: https://doi.org/10.1080/17512433.2018.1497973

Accepted author version posted online: 06 Jul 2018.
Published online: 19 Jul 2018.

EXPERT REVIEW OF CLINICAL PHARMACOLOGY
2018, VOL. 11, NO. 7, 689–703
https://doi.org/10.1080/17512433.2018.1497973

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REVIEW

Pharmacological resources, diagnostic approach and coordination of care in joint hypermobility-related disorders

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ABSTRACT

Introduction: Joint hypermobility (JH) is the hallmark of many hereditary soft connective tissue disorders, including Ehlers-Danlos syndromes and related disorders, disorders of the TGFβ-pathway, lateral meningocele syndrome, arterial tortuosity syndrome, and *cutis laxa* syndromes. Contemporary practice separates individuals with isolated, non-syndromic JH from patients with Mendelian syndromes and those with hypermobility spectrum disorders. The latter is a new nosologic entity grouping together individuals with JH and related musculoskeletal manifestations, but lacking inclusion criteria for well-defined and/or single-gene disorders.

Area covered: Nomenclature of JH and JH-related disorders are summarized on a practically oriented perspective. Critical areas of clinical management comprise pain; cardiovascular and respiratory issues; fatigue and dysautonomia; bone fragility; and capillary, skin and soft tissue fragility. Medical management stands on low-evidence data. Ongoing preclinical and clinical studies are aimed to reach a more personalized pharmacological approach to the management of the cardiovascular risk, musculoskeletal pain, and reduced bone mass.

Expert commentary: Correct classification of patients with JH-related disorders needs a systematic approach, in which a wide array of molecular tests should be intermingled with strong clinical competences in highly specialized settings. A multispecialty, hierarchical approach should be encouraged for optimal coordination of care in systemic phenotypes.

ARTICLE HISTORY
Received 15 March 2018
Accepted 4 July 2018

KEYWORDS
Cutis laxa; Ehlers-Danlos syndrome; joint hypermobility; Marfan syndrome; osteogenesis imperfecta; pain

1. Joint hypermobility

1.1. Terminology

Joint hypermobility (JH) is a clinical sign indicating the ability that a joint (or a group of joint) has to move beyond normal limits. Synonyms of JH include joint laxity and joint hyperlaxity [1]. JH is largely ignored, but is common in specific clinical settings, such as physical therapy sessions [2].

Presence of JH does not necessarily imply a disease, as JH is harmless or, perhaps, an asset in many circumstances. However, as any other clinical signs, JH should elicit practitioner's attention on specific pre-morbid or pathologic underlying conditions. According to its definition, JH manifests with excessive motion of a joint along physiological axes. Laxity of ligaments, tendons, and joint capsules is probably the most common cause of JH. Such a laxity may affect a single or a few joints (localized JH; LJH) or occur widespread (generalized JH; GJH) [1]. Acquired factors, such as traumas, past surgery, and training, are common explanations for ligamentous laxity affecting a limited number of joints. On the other side, GJH is often a constitutional trait. However, etiology of JH does not always mirror dichotomously its distribution, and, hence, should be interpreted holistically.

Additional phenotypes of JH comprise peripheral JH (PJH), a form of bilateral JH limited to the joints of hands and/or feet, and historical JH (HJH), which is a term referring to a positive history of double-jointedness in the absence of objective JH at the time of examination [1]. Little is known on the clinical correlates of these different forms of JH. However, their recognition helps the physician in further patients' classification among the different JH-related disorders (JHRDs; see below).

1.2. Epidemiology

Literature review indicates that JH is common in many ethnic groups. JH also occurs more frequently in females than males, with a rate of 6–57% and 2–35%, respectively [3]. Nevertheless, these data present major limitations. In the recent past, the operational definition of JH varied among publications and research groups. In addition, sometimes the terms JH and GJH were used synonymously, with the erroneous perception that JH indicates per se excessive motion in multiple joints. Conversely, JH should be considered a phenomenological descriptor, while LJH, GJH, PJH, and HJH are the phenotypes by which JH manifests. The rate of (the various phenotypes of) JH is indirectly associated with age with an excess in children who are naturally more 'lax' than adults [3,4]. While JH, as a whole, is a common trait, no data are available at present on its different clinical presentations.

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1.3. Assessment

Assessing JH needs experience with the use of an orthopedic goniometer and access to available standards to compare with the measured values. Phenotypes of JH are established after the evaluation of a critical number of joints. No real consensus exists on the definition of GJH. At the moment, the Beighton score (BS) is considered the best way to distinguish between GJH and other forms of JH. It was conceived as an epidemiological tool for assessing JH in African children and consists in nine maneuvers involving nine groups of joints [5]. Positivity of a maneuver means that group of joints is hypermobile and counts 1. A score of 5 or more and of 6 or more allows a 'diagnosis' of GJH in adults and children, respectively [6]. LJH, PJH, and HJH associate with negative BS. Localization on hands and/or feet and bilaterality distinguish PJH from LJH, which is usually appreciable in large joints and may be unilateral [1]. A BS of 0 is typical of HJH which is usually restricted to those who tell a past history of double-jointedness in the absence of JH at any joint at the time of examination. HJH may be explored by the 5-point questionnaire (5PQ) by Hakim and Grahame [7]. No further questionnaire has been validated for assessing HJH. In a clinical setting, the BS and 5PQ are the most commonly used tools for patients' classification according the current nosology (see below). Anyway, the assessment of all or most joints, also including those outside the BS, is needed for appropriate management and treatment planning. Medical literature describes other, less universal tools and methods to assess JH and associated manifestations, some of them dating back to the second half of the last century [8].

1.4. Clinical correlates

Many individuals with (the various phenotypes of) JH do not develop any detrimental effect related to JH. In the remaining, JH associates with variable secondary and/or syndromic manifestations. Secondary manifestations of JH are a wide range of musculoskeletal signs and symptoms triggered or facilitated by the presence of JH in the affected joints. Among them, there are joint pain, dislocations, proneness to soft-tissue traumatisms, and, perhaps, early osteoarthritis. Individuals with constitutional and non-localized forms of JH more frequently present developmental coordination disorder in childhood and/or reduced bone mass in adulthood [9,10].

Joint instability (JI) is probably the intermediate phenotype linking JH to localized musculoskeletal secondary manifestations. JI is a pre-pathological condition of excessive joint motion along non-physiological axes which predisposes joints to repetitive micro- and/or macro-traumas. JI may complicate but is not a synonym of JH. Accordingly, JI can also occur in disorders which do not regularly feature JH [1].

In a more restricted group of 'symptomatic' individuals, JH also (or alternatively) associates with structural/congenital anomalies in other organs or tissues. These patients are likely affected by JHRDs, such as the Ehlers-Danlos syndromes (EDS) and *osteogenesis imperfecta* (OI). Syndrome recognition typically needs molecular confirmation of the diagnosis and/or the presence of specific clinical diagnostic criteria or signs.

Emerging evidence indicates the existence of a range of common co-morbidities of JH. The term JH-related co-morbidities groups together an increasing number of functional diseases, such as pelvic disease, functional gastrointestinal disorder, postural orthostatic tachycardia syndrome, chronic fatigue (syndrome), and psychological distress, which occur more frequently in subjects with JH. While pathogenesis and pleiotropy seems appropriate to explain the link between JH with secondary musculoskeletal manifestations and other structural anomalies, respectively, less is known on the association of JH with its co-morbidities.

2. Joint hypermobility-related disorders

For decades after its first appearance as a specific clinical phenomenon in the medical literature [11], JH was considered a benign trait and a cultural *niche* for those interested in non-inflammatory causes of joint pain. At the same time, JH was recognized as a common, though unspecific feature of many genetic disorders, especially those caused by mutations in genes involved in the biogenesis of collagen and extracellular matrix (i.e. the so-called hereditary soft connective tissue disorders). EDS are considered a prototype of JHRDs. Nevertheless, now it is clear enough that EDS is not the unique genetic disorder characterized by JH and that, in Clinical Genetics, JH is not limited to hereditary connective tissue disorders. Accordingly, a recent international classification of EDS and related disorders pointed out the need of separating 'syndromic' patients and those who present musculoskeletal manifestations of JH but do not clearly satisfy the criteria of known syndromes. Hence, the term 'hypermobility spectrum disorders' (HSD) is introduced. A summary of the hereditary soft connective tissue disorders associated with JH is reported in Table 1.

2.1. The 2017 nosology of the Ehlers-Danlos syndromes

Before the 2017, the EDS nosology was based on the Villefranche criteria, which identified six major types, including classical, hypermobile, vascular, kyphoscoliotic, arthrochalasis and dermatosparaxis [12]. At that time, all types except hypermobile EDS (hEDS) had known molecular basis and molecular testing was recommended for diagnosis confirmation in the other five variants. hEDS was known as an exclusion diagnosis for those individuals who share a background phenotype of multi-site JH and softness of skin, but lack the pathognomonic findings of the other variants. Two years after the publication of the Villefranche nosology, the British rheumatologists proposed the Brighton criteria for the joint hypermobility syndrome (JHS); a condition originally separated from hEDS [13]. In 2009, a core of experts published an Editorial pointing out the striking overlap between hEDS and JHS, and the need to consider them undistinguishable on clinical grounds [14]. A single work demonstrated that the phenotypes defined by the Villefranche criteria for hEDS and Brighton criteria can segregate as a single entity in familial cases [15]. Nevertheless, both sets of criteria had major weak points, such as lack of specificity and a low reproducibility rate. In addition, since the publication of the Villefranche criteria, many novel phenotypes and disease-genes have linked to the EDS

Table 1. Hereditary disorders of the soft connective tissues featuring joint hypermobility.

Condition	Inheritance	Genes	Major distinguishing features
Ehlers-Danlos syndromes and related disorders, common variants			
Classical	AD	*COL5A1, COL5A2, COL1A1* (rare)	Papyraceous and hemosiderotic scars Velvety, hyperextensible skin
Vascular	AD	*COL3A1*	Extensive easy bruising Vascular accidents/ruptures Sudden death
Hypermobile	AD, complex ?	None	Secondary musculoskeletal manifestations Unspecific systemic involvement Other EDS variants excluded
Ehlers-Danlos syndromes and related disorders, rare variants			
Classical-like	AR	*TNXB*	Velvety, hyperextensible skin Absence of papyraceous scars
Cardiac-valvular	AR	*COL1A2*	Severe cardiac valvular involement Velvety, hyperextensible skin
Arthrochalasia	AD	*COL1A1, COL1A2*	Marked joint hypermobility Bilateral hip dysplasia
Dermatosparaxis	AR	*ADAMTS2*	Extreme skin fragility Velvety, hyperextensible skin Acquired *cutis laxa*
Kyphoscoliotic	AR	*PLOD1, FKBP14*	Congenital, progressive scoliosis Congenital hypotonia
Brittle cornea syndrome	AR	*ZNF469, PRDM5*	Thin cornea Early-onset ketatoconus/globus
Spondylodysplastic	AR	*B4GALT7, B3GALT6, SLC39A13*	Short stature Congenital hypotonia Limb bowing
Musculocontractural	AR	*CHST14, DSE*	Velvety, hyperextensible skin Contractures Facial features
Myopathic	AD, AR	*COL12A1*	Congenital hypotonia Proximal contractures
Periodontal	AD	*C1R, C1S*	Severe, early-onset periodontitis Tibial plaques
Hypermobility spectrum disorders	Unknown	*None*	Secondary musculoskeletal manifestations hEDS criteria excluded
Disorders of the TGFβ-pathway			
Marfan syndrome	AD	*FBN1*	Dilatation/dissections of the thoracic aorta Lens dislocation Marfanoid habitus
Loeys-Dietz syndromes	AD	*TGFBR1, TGFBR2, TGFB2, TGFB3, SMAD2, SMAD3*	Dilatation/dissections of the thoracic aorta Middle arteries fragility/anomalies Facial dysmorphism
Shprinzen-Goldberg syndrome	AD	*SKI*	Dilatation/dissections of the thoracic aorta Cranosynostosis Facial dysmorphism Marfanoid habitus
Meester-Loeys syndrome	XLR	*BGN*	Dilatation/dissections of the thoracic aorta Facial dysmorphism Mild skeletal dysplasia
Lateral meningocele syndrome	AD	*NOTCH3*	Multiple Tarlov's cysts and spinal lateral meningoceles Facial dysmorphism
Arterial tortuosity syndrome	AR	*SLC2A10*	Aortic tortuosity Dilatation/dissections of the thoracic aorta Middle arteries fragility/anomalies Acquired *cutis laxa* Eye anomalies
Cutis laxae			
ALDH18A1-related *cutis laxa*	AR	*ALDH18A1*	*Cutis laxa* Cataract Intellectual disability/GDD Retarded growth
De Barsy syndrome	AR	*PYCR1*	*Cutis laxa* Intellectual disability/GDD Pseudo-athetoid movements Eye anomalies Retarded growth
EFEMP2-related *cutis laxa*		*EFEMP2*	*Cutis laxa* Pulmonary emphysema Middle arteries fragility/anomalies Diaphragmatic hernia
ELN-related *cutis laxa*	AD	*ELN*	*Cutis laxa* Dilatation/dissections of the thoracic aorta

(*Continued*)

Table 1. (Continued).

Condition	Inheritance	Genes	Major distinguishing features
FBLN5-related *cutis laxa*	AR, AD	*FBLN5*	*Cutis laxa* Pulmonary emphysema Peripheral pulmonary stenosis
Geroderma osteodysplasticum	AR	*GORAB*	*Cutis laxa* Reduced BMD and fractures Retarded growth
LTBP4-related *cutis laxa*	AR	*LTBP4*	*Cutis laxa* Peripheral pulmonary stenosis Diaphragmatic hernia Congenital heart defect
PYCR1-related *cutis laxa*	AR	*PYCR1*	*Cutis laxa* Intellectual disability/GDD Hypoplasia of the corpus callosum

AD, autosomal dominant. AR, autosomal recessive. BMD, bone mineral density. EDS, Ehlers-Danlos syndrome. GDD, global developmental delay. hEDS, hypermobile Ehlers-Danlos syndrome. XLR, X-linked recessive.

community. For all these reasons, an International initiative lead by the Ehlers-Danlos Society generated an updated nosology with 13 different types of EDS associated with variants in 19 distinct genes. All EDS variants are described with major and minor criteria that should be met for a clinical suspect. In most variants, molecular testing is now considered mandatory for diagnosis confirmation [16]. Twelve of these types are linked to mutations in specific genes. hEDS remains without known molecular bases, but new stricter and, hopefully, reproducible criteria are proposed for this type, which is now recognized as likely the most common variant. GJH, with minor adaptations by age and sex (i.e. BS ≥ 6 in prepubertal children and adolescents; BS ≥ 5 in women to age 50 and pubertal men; BS ≥ 4 in women over the age of 50 and men; a positive 5PQ counts 1 point), is now considered mandatory for the diagnosis hEDS, which also needs the formal exclusion of all partially overlapping disorders and the presence of at least two features among (i) systemic involvement, (ii) positive family history, and (iii) specific musculoskeletal manifestations (16). The operational definition of these features is reported below.

Systemic involvement (or 'Feature A')—at least five 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 pre-pubertal 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, non-papyraceous or -hemosiderotic 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;
- aortic root dilatation with Z-score > + 2 SD;
- mitral valve prolapse of mild or greater degree.

Positive family history (or 'Feature B'):

- An independent diagnosis of hypermobile Ehlers-Danlos syndrome in one or more first-degree relatives.

Musculoskeletal manifestations (or 'Feature C')—at least one 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.

2.2. Other joint hypermobility-related disorders

JH is the hallmark of EDS but is not specific of these conditions. In other words, clinical evidence of JH should prompt the exclusion of EDS but differential diagnosis must be carried out on a wider perspective. Genetic disorders of the transforming growth factor β (TGFβ) is the second most relevant category of hereditary soft connective tissue disorders with JH. Marfan syndrome (MFS) is characterized by a typical body built (the so-called Mafanoid habitus with long and disproportionate limbs/dolichostenomelia, and long and thin digits), dilatation of the thoracic aorta with proneness to spontaneous dissections and ruptures, and lens dislocations. JH and related orthopedic traits are quite common. MFS is now recognized according to the revised Ghent criteria [17] and the diagnosis is usually confirmed by the identification of heterozygous pathogenetic variants in *FBN1*.

Loeys-Dietz syndromes are a group of phenotypes which share dilatation of the thoracic aorta, slender habitus and JH with MFS. Loeys-Dietz syndromes are autosomal dominant conditions due to mutations in five different components of the TGFβ pathway, including *TGFBR1, TGFBR2, SMAD2, SMAD3, TGFB2,* and *TGFB3*. Besides the different molecular bases,

Loeys-Dietz syndromes (LDS) can be separated from MFS by additional features, comprising facial dysmorphism, cleft uvula, skin fragility, easy bruising, and kinking/coiling of middle arteries, that are quite rare or absent in the latter [18]. There are additional rarer hereditary soft connective tissue disorders usually presenting JH. Major examples include hereditary *cutis laxae*, such as De Barsy syndrome, arterial tortuosity syndrome and lateral meningocele syndrome.

Other genetic disorders, which commonly feature multi-site JH or GJH, are conditions recognized by primary involvement of other tissues and organs. A restricted number of hereditary myopathies and muscular dystrophies [19], as well as spinal muscular atrophy [20] show JH as a possible additional presenting feature. Various skeletal dysplasias manifest with JH and affected individuals may later develop musculoskeletal secondary manifestations of JH, such as joint pain and orthopedic traits [21]. Among them, typical examples include Stickler syndrome, achondroplasia [22], and tricho-rino-phalangeal syndrome [23]. Finally, JH is not rare in some chromosomal disorders, such as Down syndrome [24,25], and in a variety of multiple congenital anomalies/intellectual disability disorders, such as Kabuki syndrome [26] and Noonan syndrome.

2.3. The 'spectrum' and hypermobility spectrum disorders

Previous sections easily illustrate the need of considering seriously JH in the clinical contest, and of requesting consultation by an expert center in all cases of suspected systemic disorder. In such a scenario, clinical genetics assessment and, in selected cases, molecular testing are paramount for appropriate diagnosis and long-term management planning. However, all practitioners working in areas with a high chance of patients' referral for JH or related manifestations and including pediatricians, rheumatologists, physiatrists, orthopedic surgeons, physical therapists and clinical geneticists, need to recognize a continuous phenotypic spectrum ranging from isolated JH to hEDS [1,21].

The existence of such a spectrum emerges from practice, which tells us that in pedigrees with JH, but without a typical Mendelian/monogenic disorder, the 'segregating' phenotype is highly variable. For example, in families ascertained by an index case meeting the 2017 criteria for hEDS, close relatives might present a mixture of asymptomatic, non-syndromic JH, symptomatic JH, and hEDS. Furthermore, in patients with different ages and ascertained by the Villefranche criteria for hEDS and the Brighton criteria, the BS decreases and turns negative by age, while symptoms usually increase in rate and severity [4,27]. Hence, the 2017 criteria for hEDS likely identify only one end of this spectrum and, in particular, those individuals with a high rate of systemic structural anomalies and/or those families with a clearer Mendelian transmission.

HSD has been introduced to recognize all symptomatic individuals with JH (all forms) and secondary musculoskeletal manifestations, who do not meet the 2017 hEDS criteria and are not mutated in any of the know genes associated with JH. Four types of HSD are identified, one for each type of JH (i.e. generalized HSD, localized HSD, peripheral HSD and historical HSD). It is noteworthy that not all musculoskeletal and neurodevelopmental complaints coupled with JH should be considered a priori the companion feature leading to the diagnosis of HSD. A set of musculoskeletal and neurodevelopmental manifestations internationally accepted as bona fide secondary manifestations of JH is lacking. However, they may include (1):

- Recurrent or chronic pain without features of an inflammatory/autoimmune origin, and localized in joint/body regions with a known history of JH.
- Non-episodic (i.e. recurrent or multisite) joint dislocations which occur in the absence of an external force sufficiently explaining the trauma, and localized in joints with a known history of JH.
- Selected minor orthopedic traits (i.e. genua valga, cubita valga, flatfoot, scoliosis) in subjects with GJH or a history of GJH, in the absence of other reasonable causes.
- Selected musculoskeletal degenerative diseases (i.e. osteoarthritis and reduced bone mass) in subjects with GJH or a history of GJH, in the absence of other reasonable causes.
- Selected neurodevelopmental attributes (i.e. simple motor delay, developmental coordination disorder, attention deficit/hyperactivity disorders) in children with GJH, in the absence of other reasonable causes.

HSDs fill the gap between asymptomatic, non-syndromic JH and hEDS [1,21,28]. Clinical phenotypes included in this spectrum comprise: GJH (asymptomatic, non-syndromic), LJH (asymptomatic, non-syndromic), PJH (asymptomatic, non-syndromic), HJH (asymptomatic, non-syndromic), generalized HSD, localized HSD, peripheral HSD, historical HSD, and hEDS [1].

Once compared with the previous Brighton criteria and Villefranche nosology, the 2017 classification recognizes two separate symptomatic phenotypes within the same spectrum which are clearly distinguished by meeting (hEDS) and not meeting (HSD) the new hEDS criteria. It is expected that only a few (perhaps, ~ 10%) patients, who were classified as JHS/hEDS by the Brighton/Villefranche criteria, are recognized as hEDS according to the 2017 classification. Hence, HSD will presumably become the most representative diagnosis for symptomatic individuals belonging to the spectrum (Figure 1).

3. State of the art on the pharmacological treatment of joint hypermobility-related disorders

Disorders featuring JH are diverse and clinically heterogeneous. All of them, perhaps except for the recently defined HSD, are rare disorders often with protean and multisystemic manifestations. Main areas of potential application of a tailored pharmacological therapy include musculoskeletal pain, reduced bone mass, cardiovascular manifestations, and clotting disorders and soft tissue fragility. Most of these manifestations seem 'primary' and reported in different JHRDs. Available scientific data are nearly absent or very scanty for many of these areas of treatment. Evidence is often of Level IV and supported by very small patients' cohorts, single case reports, or expert opinion. The unique areas of increasing evidence comprise pharmacological prevention of cardiovascular manifestations in Marfan and Loeys-Dietz syndromes, and pharmacological treatment of bone mass reduction in OI. For these areas, data are extracted from the most recent

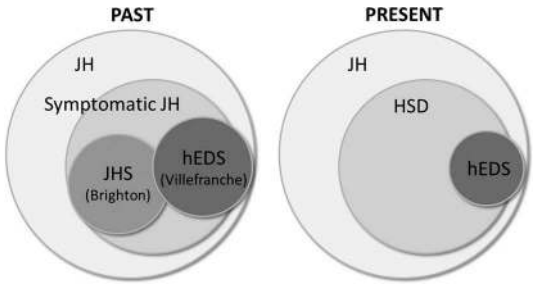

Figure 1. Comparison of patients' grouping in accordance to the Brighton/Villefranche criteria (past) and 2017 classification (present). For individuals with joint hypermobility not belonging to syndromes with alterations in known genes, the 'old' nomenclature identified two partially overlapping 'syndromes' (i.e. joint hypermobility syndrome and hypermobile Ehlers-Danlos syndrome). These two 'syndromes' were comprised within a presumably broader group of patients with 'symptomatic' joint hypermobility, which also comprised phenotypes remaining without a label because not respecting both the Brighton and Villefranche criteria. The 2017 classification is simpler and more inclusive. In fact, hEDS is now a stricter but more definite diagnosis separated from other phenotypes of 'symptomatic' joint hypermobility, all encapsulated within the label of hypermobility spectrum disorders. hEDS, hypermobile Ehlers-Danlos syndrome. HSD, hypermobility spectrum disorder. JH, joint hypermobility. JHS, joint hypermobility syndrome.

published trials, and available narrative and highly selective systematic reviews.

A wider range of multisystemic manifestations are recognized, at least, in some JHRDs. The 2017 classification of EDS and related disorders uses the term 'JH-related co-morbidities' to define common chronic disorders that are overrepresented among individuals with JH, compared to the general population. Among them, there are: psychological distress, cardiovascular dysautonomia, bladder and pelvic dysfunction, and gastrointestinal functional disorders [1]. The impact of these manifestations on patients' health status is often relevant, but their ethiopathogenetic link with the (presumed) primary dysfunction of the connective tissue remains poorly explored. At present, their treatment should follow available general assessment and management guidelines. This holds true also for the recently proposed association between EDS and mast cell disorders [29].

4. Drug resources for musculoskeletal pain

Different forms of pain are associated with JH and JHRDs. Preliminary data on the natural history of JHS and hEDS (old nomenclature) suggest the identification of four types of musculoskeletal pain in these conditions [4,27,30,31]:

- **Type 1**. Localized and acute (nociceptive) pain associated with episodic joint macrotraumas (e.g. dislocations and soft-tissue injuries).
- **Type 2**. Recurrent and often multilocus arthralgias (nociceptive pain) likely related to recurrent joint microtraumas.
- **Type 3**. Recurrent or chronic pain with neuropathic features and usually with bilateral/acral distribution.
- **Type 4**. Chronic widespread pain with features of central pain sensitization.

HSDs and hEDS represent a model for studying the relationships between JH and pain due to the high prevalence of this diagnosis in patients referred to specialized clinics and due to the apparent higher rate of pain in HSDs and hEDS compared to other JHRDs. While JI, as a natural complication of JH, can explain type 1/2 pain, more complex mechanisms should be evoked to understand type 3/4 pain. A couple of works suggest that ulnar nerve luxations/subluxations and small fiber neuropathy (SFN) are common in JHS and hEDS (old nomenclature), and both features are likely explanations for type 3 pain [32,33]. Voermans et al. [34] indicate compression and axonal neuropathies as additional mechanisms to be further investigated. In the opinion of the authors, SFN seems the major contributor to type 3 pain in JHRDs on both clinical and experimental grounds. Finally, generalized hyperalgesia, as a sign of central sensitization, has been recently demonstrated in JHS and hEDS (old nomenclature) by Rombaut et al. [35] and Di Stefano et al. [36]. Therefore, the mechanisms underlying the link between JH and type 3/4 pain remain only partially explored, and might include the role of extracellular matrix in peripheral nerves morphology/function and synaptogenesis in central pathways of pain modulation.

No specific clinical trial has been published on the efficacy of drug therapies in pain related to JHRDs. Hence, management strategies are fully based on practitioner's experience and knowledge of pain generation and modulation in JHRDs. Paracetamol and non-steroidal anti-inflammatory drugs, particularly ibuprofen and naproxen, at full dosage are the first-line approach for type 1/2 pain. Supportive procedures, such as immobilization for short periods, and application of cold or heat, usually improve recovery. Dislocations need immediate reduction. However, patients are often self-trained in managing such complications and spontaneous resolution due to laxity of tissues is not rare. In case of intense and acute pain, and/or soft-tissue injuries with persistent entesopathies, such as bursitis and tendonitis, local application/injections of lidocaine or steroids, as well as the use of opioids (and cannabinoids), such as tramadol, and oral steroids may be considered for short periods. Chronic use of opioids and steroids should be avoided due to a presumed increased rate of related complications in patients with JHRDs [37]. Non-episodic use of non-steroidal anti-inflammatory drugs should consider an increased risk of hemorrhages related to mucosal capillary fragility in some JHRDs, such as EDS.

Various medications for neuropathic pain exist, but their use should be always approached cautiously in JHRDs. Ideally, the attribution of a 'neuropathic component' needs some supporting evidence, such as the results of one or more psychometric test and/or laboratory findings for SFN or other forms of peripheral nerve pathology. Tricyclic antidepressants, anti-convulsants and selective norepinephrine reuptake inhibitors are all possible resources, with duloxetine being considered the best option in HSDs and hEDS by some authors [38]. Chronic widespread pain with hyperalgesia (pain sensitization) can be hardly managed by pharmacological resources to date. Similarly to fibromyalgia (which is often confused with or included in JH-related pain), this form of pain needs a multimodal approach including adaptation of lifestyle habits, psychotherapy, physical therapy and 'wise' drug use [39,40]. Cognitive behavioral therapy is considered a promising non-pharmacological treatment approach to pain in JHS/HSD and hEDS [38].

5. Drug resources for reduced bone mass

Reduced bone mass is a relatively common feature in JHRDs. Bone mineral density (BMD) is commonly assessed by dual energy X-ray absorptiometry (DEXA) and lower values are considered a proxy of bone fragility (i.e. an increased incidence of fractures). Such an assumption does not stand true in all JHRDs. For example, published data on JHS/HSDs and hEDS show a general reduction of DEXA values in adults, but the same is not available for children and the reduction of the BMD at DEXA do not clearly correlate with an increased rate of long bone fractures in adults [10,28].

OI is the prototype of JHRDs with true bone fragility leading to low bone mass at DEXA, a variable increase of vertebral and long bone fractures, bone deformities, and growth deficiency [41]. Treatment of bone fragility and its consequences needs a multimodal approach in OI. Physical therapy, lifestyle modifications/adaptation, nutritional interventions, and, if appropriate, drugs and surgery for treating deforming and respiratory impacting scoliosis, fractures and long bone deformities should be orchestrated based on the relatively few available data. Adequate daily intake of vitamin D is recommended in OI patients [42,43]. In OI children, high-dose (2000 IU) and low-dose (400 IU) vitamin D daily intake provides similar results in increasing lumbar spine mass density [44]. Therefore, the schedule on vitamin D intake is not different in OI compared to osteoporosis. The relatively common occurrence of growth restriction in OI indicates the need of appropriate weight adjustment in order to prevent potential side effects of long-term vitamin D supplementation in these patients.

Biphosphonate therapy is the gold standard for the treatment of bone mass reduction in children with moderate to severe OI [45]. Biphosphonates may improve bone mineral density, vertebral shape and height, growth, mobility and, in many but not all studies, fracture incidence in OI children [45]. Long-term cycles of bisphosphonates (intravenous injections is preferred to oral intake thanks to the reduced rate of gastrointestinal side effects) are a key resource for the treatment of children with moderate to severe OI. In these patients, acute phase infusion reactions can be managed by nonsteoroidal anti-inflammatory drugs and paracetamol, while the risk of osteonecrosis of the jaw and worsening of the linear growth are reasonably rare side effects [46,47]. The risk of transient hypocalcemia may be prevented by vitamin D and calcium supplementation. Less convincing data are available on the efficacy of bisphosphonates in patients with mild OI and adults, in which long-term treatment with these drugs is still questioned.

Additional drugs are under evaluation and could represent further or complementary pharmacological resources for bone fragility in OI. Denosumab, a human monoclonal antibody targeting the receptor activator of nuclear factor kappa-B ligand, has been used in four children with OI type VI, who were resistant to bisphosphonates. The treatment was well-tolerated, improved biochemical markers of bone turnover, and improved fracture rare, BMD and vertebral morphology at a 2-year follow-up [48,49]. A clinical trial with denosumab on 10 OI patients confirmed improvement of BMD [50]. Two studies showed that teriparatide, a parathyroid hormone analog, is effective in improving BMD in adults with mild OI, but less effect was observed in more severe forms [51,52]. Cathepsin K, sclerostin and TGFβ inhibitors are further promising drugs for clinical research in OI [45].

Available resources and management plans available for OI are considered the reference standards also for other JHRDs with reduced bone mass. No data is available for rare JHRDs with reduced mineral density and a presumably increased rate of fractures. Accordingly, the therapeutic recommendations available for OI were considered effective also in patients with selected rare EDS variants and propensity to bone fractures [53]. Concerning the more common HSD and hEDS, literature is not clear due to the too recent introduction of the 2017 nosology and the general confusion which dominates previous publications on JH, GJH, JHS, and hEDS [28]. No specific assessment and management schedules exist for HSD and hEDS. Current trend includes exclusion of co-morbidities potentially contributing to reduced bone mass and, if identified, their appropriate treatment. Drugs for the treatment of reduced bone mass in JHRDs mirror the accumulated knowledge in OI. Assessment of vitamin D serum levels and the appropriate correction seems wise at all ages (Castori and Guarnieri, submitted).

6. Drug resources for cardiovascular features

Management of cardiovascular (CV) abnormalities is an essential issue in determining prognosis and quality of life in selected JHRDs. The progressive nature of CV involvement makes early diagnosis, surveillance and treatment cornerstones in the management of disorders of the TGFβ-pathway, vascular EDS, arterial tortuosity syndrome and some *cutis laxa* syndromes. Some guidelines exist and report personalized approach to CV management in JHRDs, such as the statements from the American College of Cardiology and American Heart Association [54], Canadian Cardiovascular Society Position Statement [55], and European Society of Cardiology for the management of valvular heart disease [56]. Key CV features include aortic disease, valvular anomalies, myocardial changes, and arterial fragility and structural anomalies. Their complex etiopathogenesis implies the need of a multispecialty Heart Team (HT), which is a major prerequisite for appropriate decision making.

In selected cases, cardiac involvement is the presenting sign eventually leading to the syndromic diagnosis. Heart ultrasound is the most frequent primary approach for the diagnosis of valvular or aortic changes and should include specific data of aortic root measurements that are interpreted based on normal values for age and body size. Selected findings may require the immediate attention of a cardiologist or cardiothoracic surgeon (e.g., congenital heart defects, severe valvular dysfunction, severe aortic dilatation, heart failure, and history or evidence suggestive of arrhythmias). Secondary level investigations, including angio-CT and magnetic resonance angiography, are frequently performed, after diagnosis confirmation and procedural risk stratification, for a more accurate cardiac and widespread vascular assessment. In selected cases, imaging follow-ups are indicated with focus on thoracic aorta (e.g. MFS), pulmonary arteries (e.g. selected *cutis laxae*), or all large and middle arteries (e.g. LDS and arterial tortuosity syndrome) [56,57].

MFS is a prototype for CV involvement in JHRDs. CV changes can be structural (e.g. bicuspid aortic valve and abnormally prolapsing mitral valve apparatus), progressive (e.g. plurivalvular regurgitation and aortic root dilatation), or dysfunctional such as hypertension and primary myocardial changes (cardiomyopathy). Acute aortic disease is the main cause of death in MFS, followed by congestive heart failure secondary to mitral valvulopathy. Compared to MFS, in LDS life-threatening aortopathy is highly prevalent, can have an earlier onset and presents comparable risk of rupture with less dilated diameters. Management of MFS and LDS includes conservative treatment and surgical approach. Surgery is indicated in MFS patients with a maximal aortic diameter ≥ 50 mm. In MFS patients with additional risk factors (see below) and in those with LDS, surgery should be considered at a maximal aortic diameter >_45mm [58]. Major risk factors include:

- family history of aortic dissection (or personal history of spontaneous vascular dissection);
- severe valvular regurgitation (aortic or mitral);
- desire for pregnancy in fertile women;
- systemic hypertension;
- aortic size increase > 3 mm/year (on repeated measurements using the same ECG-gated imaging technique measured at the same level of the aorta with side-by-side comparison and confirmed by another technique);
- dyslipidemia;
- atrial fibrillation.

Surgical options can be even more stringent for women with low body surface area, *TGFBR2* mutation or patients with severe extra-aortic features. In these categories, surgery may be considered already at a lower threshold of 40 mm [58].

Conservative management includes prevention of primary manifestations. The routinely prescribed medications are those with expected effects on shear stress and heart rate, and a potential anti-stiffness role on the aortic wall, such as beta-blockers (β-blockers) and angiotensin receptor blockers (ARBs). This therapy should be managed by a specialist (usually, cardiologist or clinical geneticist) familiar with its use. Therapy is generally initiated at the time of the formal diagnosis of MFS or LDS (diagnostic criteria met; causative mutation identified) at any age, or upon appreciation of progressive aortic root dilatation even in the absence of a definitive diagnosis [59]. A systematic review of the pharmacological management of aortic root dilatation in MFS has concluded that β-blockers, angiotensin-converting enzyme inhibitors (ACEI), and ARBs all reduce the rate of aortic dilatation. However, studies had small sample sizes and were not sufficiently powered to demonstrate an impact on mortality, aortic dissection, need for elective surgical intervention, or adverse events [60]. A recent Cochrane analysis on β-blockers use for the prevention of aortic dissection in MFS shows that literature review is based on only one, low-quality randomized controlled trial comparing long-term propranolol to no treatment in people with MFS. The authors were unable to draw definitive conclusions for clinical practice. Moreover, they underlined the need for high-quality, randomized trials to evaluate the long-term efficacy of β-blockers in MFS [61]. Canadian Cardiovascular Society Position Statement on the Management of Thoracic Aortic Disease states that β-blockers use are associated with improved survival in chronic aortic dissection, and ACEI are not associated with improved survival [62]. The authors recommend the use of β-blockers or ARBs in MFS to reduce the rate of aortic dilatation. If tolerated, combined therapy is encouraged (strong recommendation, low-quality evidence) [55].

Therapeutic trials of a limited observational study in children with severe MFS showed a reduction in aortic root growth with the combination of β-blockers and ARB (losartan) [63]. This initial study opened the path to multiple prospective trials that confirmed the combination of β-blockers and losartan in offering better protection against aortic root enlargement than β-blockers alone in both children and adults with MS [64–66]. There is an important pharmacokinetic aspect to take in consideration when giving β-blockers especially in infants and young children with MFS and LDS. In fact, studies on β-blockers children with other CV issues show major effects when children were treated with relatively higher doses than adult doses [67]. Accordingly, a large multicenter clinical trial of losartan versus atenolol in MFS children and young adults demonstrates a comparable efficacy of losartan at standard dosing and β-blockers at atypically high dosage. Both medication schedules show a very low rate of aortic root progressive dilatation compared to many previous studies on MFS children, either untreated or treated with standard β-blocker dosing. Moreover, both treatment groups show a significant decline in aortic root Z-score over the course of the trial (number of standard deviations from average when referenced to age and body size) [68].

Studies on EDS reveal a wider array of CV manifestations in hereditary soft connective tissue disorders. Vascular EDS is dominated with a restricted quantity of life due to an increased risk of sudden death for ruptures of the middle arteries [69]. A single multicenter, randomized, open trial on 53 vascular EDS adults suggests that celiprolol (a specific β-blocker) reduces the risk of adverse vascular events in these patients. Celiprolol was administered twice daily and uptritated by 100 mg steps every 6 months up to 400 mg/day [70]. A similar approach seems reasonable also in other EDS variants with increased vascular fragility.

7. Drug resources for fatigue and cardiovascular dysautonomia

In the last two decades, increasing literature supports the existence of fatigue and CV autonomic dysfunction in EDS. Fatigue was first reported as a common feature of different EDS variants in 2010 [71]. Available data on CV dysautonomia are mostly on JHS and hEDS (old nomenclature) adults [72] and show a high prevalence of postural orthostatic tachycardia syndrome and orthostatic intolerance in these patients [73]. Presumably, these data will be replicated in the newly defined categories of hEDS (new nomenclature) and HSD. Although fatigue seems to have a complex pathogenesis in EDS, CV dysautonomia is likely a major determinant. Fatigue is also common in MFS and it seems related to low orthostatic tolerance [74,75].

No clinical trial was published with the aim to explore the effects of medication on fatigue and other symptoms related to CV dysautonomia in JHRDs. Available non-pharmacological and pharmacological resources have been recently summarized in a well-written review in EDS [72]. Among them, there are: optimal sleep hygiene, avoiding/reducing exposure to triggering factors for cardiovascular dysautonomia, avoiding the use of drugs capable to worsen dysautonomic symptoms, maintaining good hydration with adequate liquid and salt daily intake, reducing venous pooling with lower limb and/or abdominal compressions, increasing adapted exercises (particularly, gradual exercise programs in case of fatigue), and considering physical therapy [72,76]. Fludrocortisone (in adults, 100–200 mg/day), midodrine (in adults, from 2.5 to 10 mg/4 h for a maximum of 2–3 doses/day), β-blockers, and ivabradine are all considered effective in postural orthostatic tachycardia syndrome and orthostatic hypotension. Other agents that might be considered in selected cases include stimulants (e.g. methylphenidate), hormonal contraceptives, desmopressin, pyridostigmine, clonidine, selective serotonin reuptake inihibitors and serotonin-norepinephrine reuptake inhibitors, octeotride, different forms of sodium loading (e.g. intravenous administration fo 1–2 L of normal saline infused over 1–2 hr), and *rescus aculeatus* [72].

8. Drug resources for clotting disorders and soft tissue fragility

No specific drug with proved efficacy in reducing the hemorrhagic risk and soft tissue fragility is available for JHRDs. General measures of prevention remain the most effective strategy. In patients with a positive history of significant skin and capillary fragility (this often happens in those affected by classical, vascular and dermatosparaxis EDS), the use of protective pads and bondages on sites with major risk (knees, pretibial areas, elbows, and forehead) can be considered especially in children involved in social and sport activities. Avoiding contact sports and heavy exercise may be considered in patients with extensive easy bruising and extreme skin fragility. In those with molecularly proved vascular EDS, and the other EDS types with increased arterial fragility (e.g. classical EDS with *COL1A1* mutations and kyphoscoliotic EDS), as well as disorders of the TGFβ pathway, arterial tortuosity syndrome and *cutis laxae* with vascular fragility, drugs interfering the hemostatic process should be avoided or prescribed with care due an increased risk of hemorrhagic catastrophic events. Among these drugs there are acetylsalicylic acid, some non-steroidal anti-inflammatory drugs (e.g. ibuprofen), coumarins, heparins, and pentasaccharides. Invasive endovascular diagnostic and therapeutic interventions should be performed cautiously and surgery should always consider the risk of deadly complications due to arterial fragility. Some general recommendations for surgery in EDS and, more specifically, vascular EDS have been published [77].

Cycles of vitamin C supplementation may improve capillary fragility, and minor mucosal (e.g. nasal and gingival) bleeding. 1-desamino-8-D-arginine vasopressin (DDAVP) may be used to reduce bleeding tendency in case of dental intervention and surgery, especially in patients with a previous history of extensive easy bruising and/or post-operative hemorrhages, or in those with a prolonged bleeding time [78]. DDAVP use could be also considered in the management of continued bleeding after surgery in these patients. Among the various JHRDs, these complications are more typical of EDS and are considered secondary to abnormalities of the vessel wall. Efficacy of DDAVP should be always proved before its use as a prophylactic resource in case of surgery.

9. Expert opinion: diagnostic approach

Diagnosis and coordination of care of JH and JHRDs are not an easy task. Major issues concern the need of not over-emphasizing an often harmless trait, but also of promptly recognizing systemic disorders with a disability and/or life-threatening potential.

Assessing patients for a suspect of JHRD needs a systematic approach, which includes:

- Evaluation of a representative number of joints.
- Objective assessment of their range of motion.
- Computation of the BS.
- Administration of the 5PQ.
- Comprehensive assessment of pain and its patterns, by the identification of painful sites, their possible association with macrotraumas, duration, type(s) (i.e. nociceptive vs neuropathic; presence of features suggestive of peripheral or central sensitization). The use of validated questionnaires may be considered, at least, in selected cases or studies.
- Comprehensive assessment of fatigue and its possible worsening or triggering factors (e.g. blood pressure in orthostatism and clinostatism, thyroid and other hormonal baseline function, hematocrit). Also in this case, the use of validated questionnaires may be considered, at least, in selected cases or studies.
- Exclusion of acquired/multifactorial rheumatologic disorders compatible with the associated musculoskeletal complaints.
- Anthropometrics (e.g. height, weight, head circumference, arm span and arm span/height ratio, wrist and thumb signs in both hands).
- Investigation of cardiovascular manifestations by full cardiologic examination, and at rest electrocardiogram and heart ultrasound.
- Investigation for other key extra-musculoskeletal features (i.e. skin texture anomalies and fragility, neurodevelopmental involvement, facial dysmorphism and characteristic eye anomalies, reduced bone density).
- Family history for specific issues (e.g. congenital contortionism, proneness to fractures, sudden death, aortic disease). If available, direct examination of selected first-degree relatives.

Usually, presence of non-generalized patterns of JH (i.e. LJH, PJH and HJH) and absence of key extra-musculoskeletal features prompt against the hypothesis of an underlying systemic connective tissue disorder. Now it is clear enough that the range of extra-musculoskeletal features is wide but their manifestations may be very subtle. Hence, the doubtful cases should always be referred to a clinical geneticist. Molecular testing is indicated in full-blown phenotypes of Mendelian syndromes for diagnosis confirmation and genetic counselling, but also in all doubtful cases with

multisystem involvement and without clear-cut phenotypic discriminators for complete differential diagnosis. At the moment, the repertoire of laboratory investigations include Sanger sequencing for selected genes, multi-gene next generation sequencing panels, whole exome sequencing and array-based comparative genomics analyses, which should be selected with an evidence-based approach and in a highly specialized setting (Figure 2).

10. Expert commentary: coordination of care

Clinical manifestations in patients with JHRDs may be interpreted as follows:

(1) Musculoskeletal features secondary to JH.
(2) Primary multisystem features directly related to the pleiotropic nature of the disorder and/or mutated gene.
(3) JH-related, well-known co-morbidities (i.e. cardiovascular dysautonomia—specific patterns; bladder dysfuction; gastrointestinal functional disorders; psychological distress and its variable manifestations).
(4) Independent co-morbidities not directly associated with JH and JHRDs (according to current knowledge).

Increasing literature is aimed at a better understanding of the mechanisms underlying the clinical manifestations of the first three points and at their tailored management.

Review of systems and stratification of reported complaints/issues by clinical-molecular phenotype is paramount for an evidence -based management of patients with JHRDs. In JHRDs, medical implications directly related to JH (point 1 manifestations) and primary involvement of the other systems/organs (point 2 manifestations) can be grouped in five domains:

- **Musculoskeletal**: recurrent/chronic arthralgias, neuropathic pain, widespread pain, clumsiness, abnormal motor development (children), muscle weakness, reduced transfer autonomy (adults and elders).
- **Bone/orthopedic**: multiple/recurrent/habitual dislocations, reduced bone mass/proneness to fractures, scoliosis, coxa vara/valga, flexible flatfoot, contractures, long bone deformities.
- **Cardiovascular and respiratory**: aortic root dilatation, cardiomyopathy, heart valve disease (both congenital and progressive), proneness to arterial ruptures/dissections, pulmonary emphysema, nocturnal upper airways obstruction.

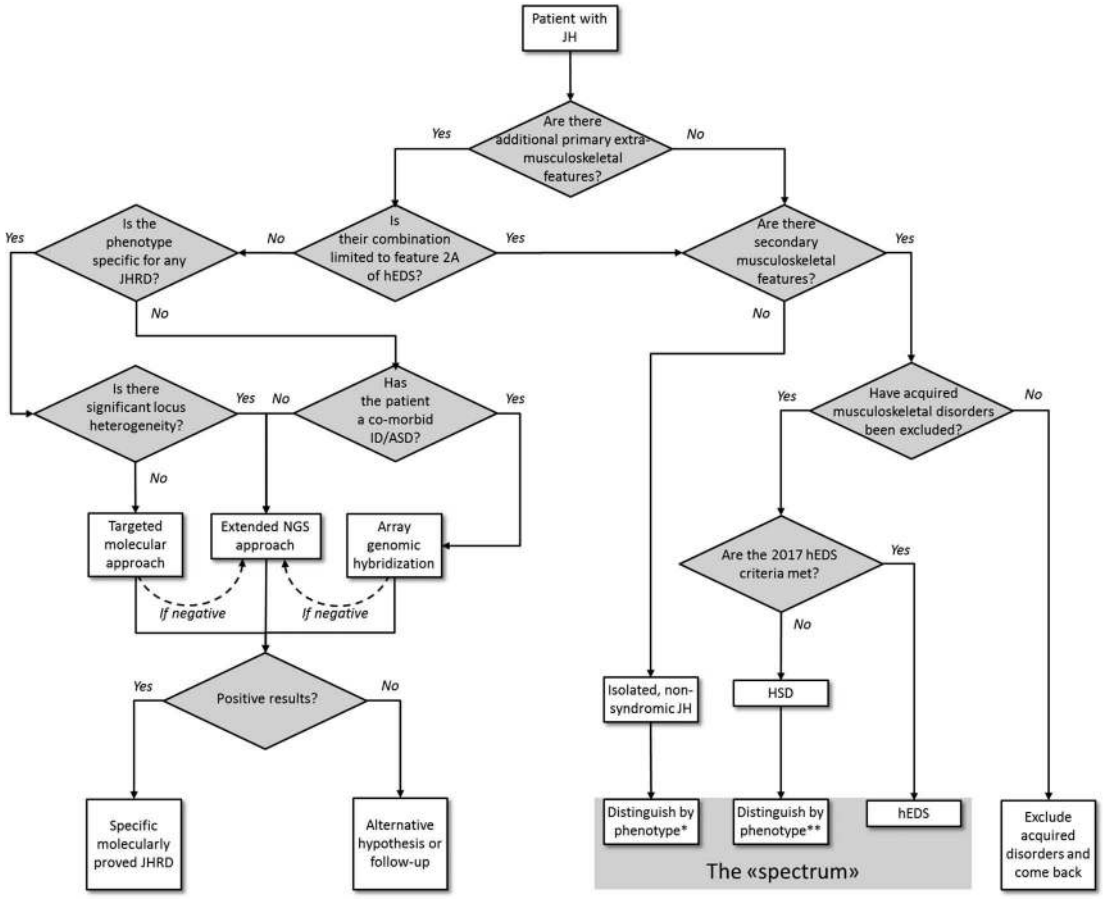

Figure 2. Nosologic approach to patients with joint hypermobility. hEDS, hypermobile Ehlers-Danlos syndrome. HSD, hypermobility spectrum disorder. ID/ASD, intellectual disability/autism spectrum disorder. JH, joint hypermobility. JHRD, joint hypermobility related disorder. NGS, next generation sequencing. *Isolated, non-syndromic JH includes generalized JH, peripheral JH, localized JH and historical JH according to the Beighton score, 5-point questionnaire and distribution of JH. **HSD includes generalized HSD, peripheral HSD, localized HSD and historical HSD according to the Beighton score, 5-point questionnaire and distribution of JH.

- **Skin/soft tissues/internal organs**: skin fragility, delayed wound healing (comprising surgical complications), fragility/ruptures of internal organs.
- **Craniofacial**: specific eye anomalies (e.g. lens dislocation, vitreal and retinal features, myopia), occipitoatlantoaxial instability, Chiari malformation, temporomandibular joint dysfunction/disorder, deafness, retrognathia/malocclusion, gingival retractions/fragility.

Quality of life of patients with JHRDs is also strongly influenced by the 'so-called' **JH-related co-morbidities** (point 3 manifestations), whose presence and severity should be screened and assessed in all individuals affected by these disorders. They mostly include:

- **Psychological distress** (e.g. anxiety, depression).
- **Bladder/pelvic dysfunctions** (e.g. underactive/overactive bladder, pelvic prolapse, chronic pelvic pain, dyspareunia).
- **Cardiovascular dysautonomia** (neuromediated hypotension, postural orthostatic tachycardia, ortostatic hypotension, orthostatic intolerance).
- Various **gastrointestinal functional disorders**.

All patients should be assessed for these major issues with prioritization of the cure/prevention according to the overall health status and clinical-molecular diagnosis. Accurate phenotypic classification guides the clinician in focusing attention and tracing the more adequate follow-up. For example, OI and skeletal dysplasias are dominated by bone/orthopedic and craniofacial manifestations, while musculoskeletal, cardiovascular and respiratory, skin/soft tissue/internal organs are usually less severe or absent. Conversely, MFS, TGFβ-pathway disorders and vascular EDS are distinguished by prominent cardiovascular and respiratory manifestations, while musculoskeletal and skin/soft tissue/internal organs features characterize EDS and related disorders (other variants). Finally, patients with HSD have problems mostly limited to the musculoskeletal system.

According to the above listed medical issues by clinical domain, potentially involved specialists include:

- **Musculoskeletal**: rheumatologist, specialist of physical medicine and rehabilitation, physical therapist, occupational therapist.
- **Bone/orthopedic**: orthopedic surgeon, specialist of physical medicine and rehabilitation, endocrinologist.
- **Cardiovascular and respiratory (HT)**: cardiologist, hearth/thoracic surgeon, vascular surgeon, interventional radiologist, pneumologist.
- **Skin/soft tissue/internal organs**: dermatologist, plastic and reconstructive surgeon, abdominal surgeon.
- **Craniofacial**: ophthalmologist, neurologist, neurosurgeon, maxillo-facial surgeon, dentist, gnathologist, speech therapist, audiologist.
- **JH-related co-morbidities**: pertinent specialist(s) according to the type and severity of co-morbidity/ies.

Such a wide array of specialists for each domain prompts to group together the medical needs of all patients with the various JHRDs and to identify multiple professional teams distinguished by the clinical domain (e.g. bone/orthopedic), rather than a specific disorder (e.g. bone dysplasias) of interest. Such an approach reflects the principle of parsimony of healthcare strategies for the management of rare diseases with partially overlapping clinical problems. These practically oriented teams should be orchestrated by a 'case manager' or a 'case manager team' with experience in the diagnostic assessment of JHRDs and molecular testing interpretation, as well as with skills for appropriate follow-up, prioritization of healthcare issues and pediatric-adult transition. In this scenario, the clinical geneticist is emerging, perhaps, as the best candidate for this role at bridge between molecular medicine and clinical governance.

While general knowledge on rare JHRDs with a recognized molecular defect is definite by studies on relatively small, but homogeneous patients' samples, this is not the case for the much larger and protean group of patients belonging to the 'spectrum'. The 'spectrum' concept is aimed to simplify the confusing overlap between the 'old' JHS and the previous definition of hEDS. Patients put into the 'spectrum' should have undergone an expert exclusion of other JHRDs and phenocopies with possibly severe and/or life-threatening manifestations in other organs, and should present a unique or predominant involvement of the musculoskeletal system. An overall management approach to these patients is summarized in Table 2.

Table 2. Management approach to patients belonging to the 'spectrum'.

Phenotype	Status	To do
Asymptomatic, non-syndromic joint hypermobility	Healthy (unless co-morbidities)	• Nothing (?) • Refer to specialist in case of co-morbidity • Follow-up in specific cases (e.g. children) for diagnosis refinement
No overlap—check presence/absence of secondary musculoskeletal manifestations		
Hypermobility spectrum disorders	Affected (possibly transient phenotype)	• Refer to a musculoskeletal/rehabilitation team • Refer to specialist in case of co-morbidity • Follow-up in specific cases (e.g. children) for diagnosis refinement
No overlap—check presence/absence of the 2017 criteria for hEDS		
Hypermobile Ehlers-Danlos syndrome	Affected (chronic disorder)	• Refer to a musculoskeletal/rehabilitation team (in presence of musculoskeletal symptoms) • Refer to specialist in case of co-morbidity • General follow-up for monitoring/treatment of possible pleiotropic manifestations

11. Five-year view

As in most rare diseases, the field of drug innovation and hindering disease progression is a major issue in hereditary connective tissue disorders. Among their protean manifestations, CV involvement was the best investigated for pharmacologic prevention in the last decades. Studies involving complex and futuristic attempts on stem cells are still in their infancy. At the same time, modern CV medicine is getting more prone on pharmacologic trials that employ well known, characterized and already available medications. In fact, early since 2006, studies in animal models of MFS exhibited excessive activation of and signaling by the growth factor TGFβ. Constant administration of TGFβ antagonists can attenuate or prevent many pathologic manifestations in fibrillin-1-deficient mice including emphysema, skeletal muscle myopathy, myxomatous valve changes, and aortic aneurysm. Losartan, an ARB, can also decrease TGFβ signaling. Losartan has shown the ability to halt abnormal aortic root enlargement in mouse models of MFS [79]. This effect was associated with both a reduction in hemodynamic stress and antagonism of TGFβ signaling in the vessel wall. These data suggested that losartan, a drug already in clinical use in CV medicine, has the potential to prevent the major life-threatening CV manifestation of this disease.

In this sense, studies using higher dosing of ARBs and newer generation medications are ongoing. Several studies have demonstrated that the greatest benefit of β-blockers and/or ARBs will be achieved when medication is started early in the course of disease [59]. Multiple clinical trials have been undertaken or are ongoing in this category (see https://clinicaltrails.gov). Personalized dosages for medications already used in the management of CV involvement of these disorders, novel applications of known drugs and, perhaps, new molecules directly affecting key steps of disease pathogenesis are all potentials goals to be achieved in the next five years. At the same time, the increasing number of causative genes and genotype-phenotype correlations, and the still limited number of patients for selected disorders are putting the management of CV involvement of JHRDs within highly specialized settings. In this scenario, clinical research should moving toward the delineation of diagnostic and management flow-charts helping practitioners for evidence-based decision making.

Pain management is another field requesting more research. Basic science and preclinical studies are needed in order to substantiate the too fragmented data on the manifestations and natural history of pain in HSDs and EDS. Patients' narrations suggest variability within a common frame. Pain usually starts in infancy/childhood in form of 'growing pain' at knees or in association with joint dislocations and soft-tissue traumatisms. In these circumstances, it is plausible that capsule-ligamentous laxity facilitates micro-instability (→ recurrent arthralgias) of weight-bearing joints (e.g. knees) and macro-instability (→ dislocations and soft-tissue injuries) of joints with physiologically wide ranges of motion (e.g. shoulders and heels). Anyway, patients with the most restricted lives are those with chronic pain presenting with features of neuropathic pain and pain sensitization (i.e. hyperalgesia and allodynia); manifestations that are hardly explained by capsule-ligamentous laxity. Such advanced disease phase is shared with other painful, acquired connective tissue disorders, which are typically more common in females, a phenomenon equally well known in JHS and hEDS (old criteria) [80]. Hence, future research could explore the role of the extracellular matrix and sexual dimorphism in the generation of neuropathic pain and chronification of pain in JHRDs. This kind of studies could also support clinicians and molecular research in searching reliable biomarkers for the diagnosis of hEDS and subtypes of HSDs.

In conclusion, JH and JHRDs are experiencing a new era in many disciplines, including but not limited to clinical/medical genetics, pediatrics, rheumatology, physical medicine and rehabilitation, cardiology and cardiothoracic surgery. Although considered a medical curiosity for decades, they now represent common reasons of consultation in different settings. A new generation of practitioners and scientists is needed for exploring the unsolved complexities underlying the multidimensional heterogeneity of JHRDs.

Key issues

- Joint hypermobility is a common trait in most ethnicities; it is more frequently encountered in women and children.
- Joint hypermobility-related disorders is a broad term grouping together different congenital/hereditary disorders featuring joint hypermobility.
- Hereditary soft connective tissue disorders, including Ehlers-Danlos syndromes, disorders of the TGFβ-pathway, cutis laxa syndromes, arterial tortuosity syndrome and lateral meningocele syndrome, are the most common syndromic forms of joint hypermobility.
- Ehlers-Danlos syndromes is the most representative among the syndromes with joint hypermobility.
- The term 'hypermobility spectrum disorders' has been recently introduced to define individuals with joint hypermobility and secondary musculoskeletal manifestations, in the absence of a recognizable genetic syndrome.
- Medical management of joint hypermobility related disorders is still based on low-evidence data; major fields of interest include: pain, reduced bone mineralization, cardiovascular manifestations (also comprising the risk of sudden death) and soft-tissue fragility.
- Pain strongly impacts quality of life, particularly in the hypermobile Ehlers-Danlos syndrome and hypermobility spectrum disorders, and has a protean natural history; nociceptive pain, neuropathic pain, and pain sensitization are all components of this manifestation.
- Reduced bone mineralization is the leading feature of osteogenesis imperfecta, but is appreciable in many other hereditary soft connective tissue disorders, such as selected variants of the Ehlers-Danlos syndrome.
- Intravenous bisphosphonates are the gold standard for the treatment of reduced bone mineralization in osteogenesis imperfecta and cognate disorders with increased bone fragility.
- Cardiovascular manifestations are variable and mainly include thoracic aortic disease, heart valve disease, cardiomyopathy, middle arteries fragility and cardiovascular dysautonomia. Strong genotype-phenotype correlations exist.

- Multiple clinical trials have been published on the pharmacological prevention of the cardiovascular risk in the disorders of the TGFβ-pathway, but many knowledge gaps remain.
- Further research is needed for reaching a more personalized therapy impacting both quality and quantity of life in joint hypermobility-related disorders.

Funding

This paper was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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