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**The revised Ghent nosology for the Marfan syndrome.**

Bart L. Loeys<sup>1,\*</sup>, Harry C. Dietz<sup>2,\*</sup>, Alan C. Braverman<sup>3</sup>, Bert L. Callewaert<sup>1</sup>, Julie De Backer<sup>1</sup>, Richard B. Devereux<sup>4</sup>, Yvonne Hilhorst-Hofstee<sup>5</sup>, Guillaume Jondeau<sup>6</sup>, Laurence Faivre<sup>7</sup>, Dianna M. Milewicz<sup>8</sup>, Reed E. Pyeritz<sup>9</sup>, Paul D. Sponseller<sup>10</sup>, Paul Wordsworth<sup>11</sup>, Anne M. De Paepe<sup>1</sup>.

<sup>1</sup> Center for Medical Genetics, Ghent University Hospital, Ghent, Belgium, <sup>2</sup> McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University, Baltimore, USA, <sup>3</sup>Department of cardiology, Washington University School of Medicine, Saint-Louis, USA, <sup>4</sup> Weill Cornell Medical College, New York, USA, <sup>5</sup> Center for Human and Clinical Genetics, Leiden University Medical Center, Leiden, the Netherlands, <sup>6</sup> Centre de Référence pour le Syndrome de Marfan et apparentés, Hopital Bichat, Paris, France, <sup>7</sup> Center for Genetics, Children's Hospital, Dijon, France, <sup>8</sup> Department of Medical Genetics, University of Texas Medical School, Houston, USA, <sup>9</sup> Department of Medical Genetics, University of Pennsylvania, Philadelphia, USA, <sup>10</sup> Department of Orthopedics, Johns Hopkins University, Baltimore, USA <sup>11</sup> Clinical Rheumatology, Nuffield Orthopaedic Center, Oxford, United Kingdom.

\* Authors equally contributed to the manuscript

**Address for correspondence:**

Bart Loeys, MD, PhD  
Center for Medical Genetics  
Ghent University Hospital  
Building OK5  
De Pintelaan 185  
9000 Gent  
Belgium  
Phone: 32-9-332.63.43  
Fax: 32-9-332.49.70  
Email: [bart.loeys@ugent.be](mailto:bart.loeys@ugent.be)

**Abstract**

The diagnosis of Marfan syndrome (MFS) relies on defined clinical criteria (Ghent nosology), outlined by international expert opinion to facilitate accurate recognition of this genetic aneurysm syndrome and to improve patient management and counseling. These Ghent criteria, comprising a set of major and minor manifestations in different body systems, have proven to work well since with improving molecular techniques, confirmation of the diagnosis is possible in over 95% of patients. However, concerns with the current nosology are that some of the diagnostic criteria have not been sufficiently validated, or are not applicable in children or necessitate expensive and specialized investigations. The recognition of variable clinical expression and recently extended differential diagnosis are further confounding accurate diagnostic decision making. Moreover, the diagnosis of MFS - whether or not established correctly- can be stigmatizing, hamper career aspirations, restrict life-insurance opportunities and cause psychosocial burden.

An international expert panel has established a revised Ghent nosology, which puts more weight on the cardiovascular manifestations and in which aortic root aneurysm and ectopia lentis are the cardinal clinical features. In absence of any family history, the presence of these two manifestations is sufficient for the unequivocal diagnosis of MFS. In absence of any of these two, the presence of a bonafide *FBNI* mutation or a combination of systemic manifestations is required. For the latter a new scoring system has been designed. In this revised nosology, *FBNI* testing, although not mandatory, has greater weight in the diagnostic assessment. Special considerations are given to the diagnosis of MFS in children and alternative diagnoses in adults.

We anticipate that these new guidelines may delay a definitive diagnosis of MFS but will decrease the risk of premature or misdiagnosis and facilitate worldwide discussion of risk and follow-up/management guidelines.

## Introduction

Since Antoine-Bernard Marfan described the five-year-old Gabrielle with skeletal manifestations of the disease that now bears his name <sup>1</sup>, important progress has been made in the delineation of the Marfan syndrome (MFS) and recognition of associated risks. The main features of this autosomal dominant disorder include disproportionate long bone overgrowth, ectopia lentis and aortic root aneurysm. In 1955, Victor McKusick first established a classification of connective tissue disorders, which resulted in the publication of his monograph “Heritable Connective Tissue Disorders” <sup>2,3</sup>. In 1986, an international panel of experts defined a set of clinical criteria (Berlin nosology) for the diagnosis of Marfan syndrome (MFS) <sup>4</sup> with the aim of facilitating accurate communication about the condition between healthcare providers, researchers and patients. It was felt that this would improve proper patient management and effective patient counseling.

Following the identification of *FBNI* (encoding fibrillin-1) as the causal gene for MFS <sup>5</sup> it was recognized that the Berlin criteria falsely allowed a diagnosis of MFS in individuals with a positive family history of MFS, who had only nonspecific connective tissue findings themselves and who did not carry the mutation present in more typically affected family members. New diagnostic criteria were therefore put forth in 1996, referred to as the Ghent nosology <sup>6</sup>. These Ghent criteria were more stringent than the Berlin criteria, mitigating over-diagnosis of MFS and providing better guidelines to differentiate MFS from related, ‘overlapping’ conditions such as the MASS phenotype

(myopia, mitral valve prolapse, borderline and non-progressive aortic root dilatation, skeletal findings and striae) and mitral valve prolapse syndrome (MVPS).

Since physicians associate the diagnosis of “Marfan syndrome”, above all else, with risk for aortic aneurysm/dissection, it can be detrimental to diagnose MFS in patients without tangible evidence of such risk. Avoidable consequences associated with misdiagnosis of MFS include: restriction of career aspirations or access to insurance benefits; additional financial burden associated with frequent medical care; anxiety or situational depression; unfounded marital or reproductive decisions; loss of health benefits or psychosocial stigmatization associated with exercise restriction, a particularly important issue during childhood. The challenge is to balance such concerns with the paramount need to maintain good health through proper counseling and application of sound anticipatory medical practices. Toward this objective, it is also important to avoid the diagnosis of MFS when clinical or molecular observations could reveal alternative (and often more severe) diagnoses that mandate specialized counseling or management protocols.

The Ghent nosology employs a set of ‘major’ and ‘minor’ manifestations in numerous tissues including the skeletal, ocular, cardiovascular, and pulmonary systems and the dura, skin and integument<sup>6</sup>. Major manifestations include ectopia lentis, aortic root dilatation/dissection, dural ectasia or a combination of  $\geq 4$  out of 8 major skeletal criteria. The diagnosis of MFS in an index patient requires major involvement of at least 2 organ systems with minor involvement of a third organ system. In the presence of an *FBNI* mutation known to cause MFS or a first-degree relative who was unequivocally

diagnosed based upon Ghent nosology, the presence of one major and one minor manifestation in different organ systems is sufficient to make the diagnosis.

### **Current status of the Ghent nosology.**

The Ghent criteria have found worldwide application in helping physicians to diagnose MFS appropriately. New molecular techniques allow the detection of *FBNI* mutations in up to 97% of Marfan patients who fulfill the Ghent criteria <sup>7,8</sup>. This suggests that the current Ghent criteria have excellent specificity to identify patients with *FBNI* mutations. Consideration of sensitivity is highly complex due to varying definitions of the “target” population and competing clinical priorities. For example, the current criteria have been criticized for taking insufficient account of the age-dependent nature of some clinical manifestations (making the diagnosis in children more difficult) <sup>9</sup> and for including some rather nonspecific physical manifestations or poorly validated diagnostic thresholds. Although the assignment of major and minor criteria within the Ghent nosology has contributed to its utility, several of those criteria are not intuitive when considered from the perspective of the differential diagnosis or patient management. Consideration of the diagnosis of familial ectopia lentis is particularly illustrative of the prevailing issues. This diagnostic category has been widely applied for individuals and families that show lens dislocation and skeletal features of MFS but do not show aortic enlargement or dissection. *FBNI* mutations are seen in familial ectopia lentis and are not easily distinguished from those causing MFS on the basis of character or location within the gene – suggesting either occult phenotype-genotype correlations or the influence of

modifiers. The Ghent nosology clearly attempted to accommodate the fact that some people with ectopia lentis, skeletal findings and even *FBNI* mutation have less cardiovascular risk (i.e. risk to the aortic root) than seen in classic MFS, by allowing the diagnosis of familial ectopia lentis in the absence of a second major Marfan manifestation. However, inadequate data were available to evaluate the critical issue of whether cardiovascular risk could be predicted by the presence of non-cardiac features, such as dural ectasia or major versus minor skeletal involvement. At the other extreme, is it justified not to diagnose MFS in someone with typical lens dislocation and aortic root enlargement simply because they lack minor skeletal or skin findings? To address some of these issues, an international panel (see acknowledgment) of experts in the diagnosis and management of MFS was convened in Brussels, Belgium by the National Marfan Foundation (U.S.A.) and charged with considering modifications to the Ghent criteria. Other factors under consideration included the specialized nature, availability and cost of diagnostic tests for selected manifestations (e.g. dural ectasia), the need to better define certain diagnostic categories better (e.g. familial ectopia lentis, MASS phenotype<sup>10</sup> and MVPS), to define features that should trigger alternative diagnoses and a desire to complement diagnostic criteria with follow-up and management guidelines for various patient groups including children who do not yet fulfill the diagnostic criteria but may do so in the future.

**Proposal for New Nosology.**

This proposal for a revised nosology (Table 1) was based on critical review of clinical characteristics in large published patient cohorts<sup>7, 8, 11, 12</sup>, and expert opinions of the panel members with extensive experience in applying the current criteria, the differential diagnosis of MFS and the strengths and limitations of molecular genetic testing. Several guiding principles were followed: maximal use of evidence-based decision making; attention to practical (patient-centric) implications; a focus on features and criteria that distinguish MFS from other disorders and definition of purposeful thresholds for diagnosis. As a result, five major changes in the diagnostic guidelines are proposed.

First, more weight is given to two cardinal features of MFS, aortic root aneurysm/dissection and ectopia lentis. In the absence of findings that are not expected in MFS, the combination of ectopia lentis and aortic root enlargement/dissection should be sufficient to make the diagnosis. All other cardiovascular and ocular manifestations of MFS and findings in other organ systems, such as the skeleton, dura, skin and lungs, contribute to a “systemic score” (Table 2) that guides diagnosis when aortic disease is present but ectopia lentis is not.

Second, a more prominent role is assigned to molecular genetic testing of *FBNI* and other relevant genes (e.g. *TGFBR1 and 2*), as well as other genes indicated in Table 4. In practice, this does not make *FBNI* testing a formal requirement (which imposes

financial burden in some countries, and does not yet have 100% sensitivity and specificity), but allows its appropriate use when available.

Third, some of the less specific manifestations of MFS were either removed or made less influential in the diagnostic evaluation of patients. This avoids the use of obligate thresholds that lack clear validation or general availability.

Fourth, the new criteria formalize the concept that additional diagnostic considerations and testing are required if a patient has sufficient findings to satisfy the criteria for MFS but also shows unexpected findings, particularly if they segregate with disease in the family or if they are suggestive of a specific alternative diagnosis. Particular emphasis is placed on Sphrintzen-Goldberg syndrome (SGS), Loey-Dietz syndrome (LDS) and the vascular form of Ehlers-Danlos syndrome (vEDS). SGS and LDS have substantial overlap with MFS, including the potential for similar involvement of the skeleton, aortic root, skin and dura (Table 4). Occasionally, vEDS can show overlap in the vascular system, dura, skin and skeleton. It is essential to consider discriminating features (Table 4) because each of these conditions has a unique risk profile and management protocol.

Finally, this nosology should help to allay concerns regarding delayed or ambiguous diagnoses by providing context-specific recommendations for patient counseling and follow-up.

In the revised nosology, new diagnostic criteria have been defined for a sporadic patient and for an index patient with a positive family history (Table 1). In the absence of

a conclusive family history of MFS, the diagnosis can be established in four distinct scenarios:

(1) The presence of aortic root dilatation ( $Z$ -score  $\geq 2$  when standardized to age and body size) or dissection<sup>13</sup> and ectopia lentis allows the unequivocal diagnosis of MFS, irrespective of the presence or absence of systemic features except where these are indicative of SGS, LDS or vEDS (Table 4).

(2) The presence of aortic root dilatation ( $Z \geq 2$ ) or dissection and the identification of a bona fide *FBNI* mutation (Table 3) are sufficient to establish the diagnosis even when ectopia lentis is absent. An overview of criteria that enhance confidence in the pathogenetic potential for MFS of particular *FBNI* mutations is provided in Table 3. These include missense mutations that substitute or create cysteine residues, alter one of the conserved residues important for calcium binding in epidermal growth factor-like (EGF) domains, create a premature termination codon (nonsense mutations), delete or insert coding sequence, or disrupt the consensus sequence for pre-mRNA splicing. Evidence for pathogenicity of other types of missense mutations would include its absence in at least 400 ethnically-matched control chromosomes and co-segregation with disease in the family, or *de novo* occurrence in a sporadic case (with confirmation of paternity). Definitive evidence of linkage to a predisposing *FBNI* haplotype can substitute for an *FBNI* mutation for diagnostic purposes but this linkage analysis requires at least 6 informative meioses in the patient's family to confirm the MFS-associated *FBNI* allele. The absence of a mutation in the *FBNI* gene despite complete screening is possible in MFS.

(3) Where aortic root dilatation ( $Z \geq 2$ ) or dissection is present but ectopia lentis is absent and the *FBNI* status is either unknown or negative, a MFS diagnosis is confirmed by the presence of sufficient systemic findings ( $\geq 7$  points, according to a new scoring system) (table 2) confirms the diagnosis. However, features suggestive of SGS, LDS or vEDS must be excluded and appropriate alternative genetic testing (*TGFBR1/2*, collagen biochemistry, *COL3A1*, and other relevant genetic testing when indicated and available upon the discovery of other genes) should be performed.

(4) In the presence of ectopia lentis but absence of aortic root dilatation/dissection, the identification of an *FBNI* mutation previously associated with aortic disease is required before making the diagnosis of MFS. If the *FBNI* mutation is not unequivocally associated with cardiovascular disease in either a related or unrelated proband, the patient should be classified as “ectopia lentis syndrome” (see differential diagnosis).

In an individual with a positive family history of MFS (where a family member has been independently diagnosed using the above criteria), the diagnosis can be established in the presence of ectopia lentis, or a systemic score above or equal to 7 points or aortic root dilatation with  $Z \geq 2$  in adults ( $\geq 20$  years old) or  $Z \geq 3$  in individuals  $< 20$  years old.

Special consideration should be given to young individuals ( $< 20$  years old). In sporadic cases, these children may not fit in one of the four proposed scenarios. If insufficient systemic features ( $< 7$ ) and/or borderline aortic root measurements ( $Z < 3$ ) are

present (without *FBNI* mutation), we suggest to use the term “non-specific connective tissue disorder” until follow-up echocardiographic evaluation shows aortic root dilation ( $Z \geq 3$ ). If an *FBNI* mutation is identified in sporadic or familial cases but aortic root measurements are still below  $Z=3$ , we propose to use the term “potential MFS” until the aorta reaches threshold. Neonatal MFS is not considered as a separate category, but rather represents the severe end of the MFS spectrum.

In adults (>20 yrs), we define three main categories of alternative diagnoses: ectopia lentis syndrome (ELS), MASS phenotype (myopia, mitral valve prolapse, aorta, skin and skeletal findings), mitral valve prolapse syndrome (MVPS) (see differential diagnosis).

Finally, we recognize that some patients will remain difficult to classify due to overlap of phenotypes from different entities, the evolving nature of these connective tissue diseases, absence of mutation after screening of the appropriate genes or divergence between the phenotype and the genotype. However, these patients should be uncommon and will hopefully benefit from better definition of still unrecognized phenotypes in the future.

### **Organ System-Specific Considerations:**

#### **Cardiovascular Criteria**

A key diagnostic criterion in the new nosology is aortic root aneurysm or dissection. Aortic root aneurysm is defined as enlargement of the aortic root at the level of the sinuses of Valsalva. Aortic root measurements should be done parallel to the plane

of the aortic valve and perpendicular to the axis of blood flow. The largest correctly measured root diameter obtained from at least three transthoracic images should be corrected for age and body size and interpreted as a Z-score. There are varying practices regarding whether root measurements should be done in systole or diastole and whether the thickness of one aortic wall should be included (i.e. the leading edge to leading edge method). The method employed must match that used to generate the normative data for Z-scores to be valid. For echocardiographic measurements made from inner wall to inner wall during systole in individuals  $\leq 25$  years, a convenient Z-score calculator can be found at [www.marfan.org](http://www.marfan.org). For echocardiographic measurements made from leading edge to leading edge in diastole in all age groups, reference graphs and Z-score equations are available<sup>13</sup>. If transthoracic echocardiographic evaluations do not allow precise visualization of the proximal aorta, trans-esophageal echocardiography or CT or MRI imaging should be applied, with special attention to using double-oblique images to obtain correct diameter measurements and use of the same nomograms<sup>14</sup>.

Mitral valve prolapse is also a common finding in MFS and is included as a feature in the systemic score. Mitral valve prolapse should be defined by echocardiography as protrusion of one or both of the mitral valve leaflets across the plane of the mitral annulus during systole. This is best detected in parasternal long-axis or apical long-axis 3-chamber or 2-chamber views. There are no special criteria for diagnosing MVP in MFS and standard practices should be applied<sup>15</sup>.

Pulmonary artery (PA) dilation (e.g. main PA diameter above 23 mm in adults)<sup>16</sup> is often seen in MFS, but it is not specific to this diagnosis. In addition, complications of pulmonary artery disease occur rarely. PA dilation was not therefore included in the

systemic score because further research is needed regarding thresholds and the diagnostic utility of this finding.

Patients with MFS can develop aortic enlargement or dissection at segments distant from the aortic root. The frequency of this finding (particularly at the proximal descending thoracic aorta and in the abdomen) appears to be increasing with the prolonged survival due to improved management of disease at the aortic root. While descending aortic aneurysm or dissection in the absence of aortic root enlargement can occur in Marfan syndrome,<sup>17, 18</sup> this is rare and given the low specificity of this finding for MFS, this finding is not included in the diagnostic criteria. Intermittent imaging of the descending thoracic aorta is indicated in adult patients where there is a clinical suspicion of Marfan syndrome in the absence of aortic root enlargement. Widespread vascular disease is more common with other conditions in the differential diagnosis, such as vascular EDS and LDS. For example, systemic vascular imaging (head to pelvis) is recommended if there is a suspicion of Loeys-Dietz syndrome because of the high frequency of tortuosity, aneurysms and dissections throughout the vascular tree.

### **Ocular criteria**

The most prominent ocular features of MFS are myopia and ectopia lentis. The diagnosis of ectopia lentis is based on slit-lamp examination after maximal dilatation of the pupil. Ectopia lentis reflects failure of supporting structures called ciliary zonules. Dislocation of the lens in MFS is most typically upward and temporal but is not specific as deviation in any direction may occur. If lens subluxation is deemed equivocal or

minimal, manifesting only as a scalloped or ruffled lens margin at extremes of gaze, the eye exam should be repeated later before a definitive diagnosis of ectopia lentis can be made (such findings can occur outside the context of MFS, e.g. in individuals with high myopia). Increased globe length and corneal flattening are seen in MFS, but they have unclear specificity and are not routinely measured by ophthalmologists. Given that myopia is very common in MFS, is routinely monitored, and tends to show early onset, high severity and rapid progression, myopia of greater than 3 diopters contributes to the systemic score for diagnosis. However, since myopia is quite common finding in the general population we have only attributed one point to it in the systemic score.

### **Systemic criteria**

Clinical manifestations of MFS in other organ systems were critically evaluated for their specificity and diagnostic utility based on expert opinion and the available literature. Several of the “minor” criteria from the old Ghent nosology were eliminated, but the most selective systemic features were included in the “systemic score”.

Three points are assigned to the combination of wrist and thumb signs. The thumb sign is positive when the entire distal phalanx of the adducted thumb extends beyond the ulnar border of the palm with or without the assistance of the patient or examiner to achieve maximal adduction. The wrist sign is positive when the tip of the thumb covers the entire fingernail of the fifth finger when wrapped around the contralateral wrist. If either of the two signs is absent, only one point is assigned.

Two points were assigned to each of five other specific systemic manifestations including anterior chest deformity, hindfoot deformity, spontaneous pneumothorax, dural

ectasia and acetabular protrusion. Pectus carinatum is believed to be more specific for MFS than pectus excavatum and is assigned two points. Subjective qualifiers in the original Ghent criteria such as “requiring surgery” have been eliminated but the examiner should be confident that a positive finding (pectus excavatum or chest wall asymmetry) extends beyond normal variation of chest contour in the general population before assigning one point. Hindfoot valgus<sup>19</sup> (two points) in combination with forefoot abduction and lowering of the midfoot (previously referred to as medial rotation of the medial malleolus) should be evaluated from anterior and posterior view. The examiner should distinguish this from the more common “flat foot” (one point) without significant hindfoot valgus. As in the past, any spontaneously-occurring pneumothorax remains a diagnostic feature. For the detection of lumbosacral dural ectasia, no preferred method (CT or MRI) or uniformly accepted cut-offs have emerged from the literature<sup>20-23</sup> and local standards should apply. Dural ectasia is a sensitive but not a specific sign of MFS and, as such, is no longer considered on equal footing with lens dislocation or aortic root enlargement. It is commonly seen in Loeys-Dietz syndrome and has been described in mutation-proven vEDS. Finally, an additional technical exam for detection of acetabular protrusion<sup>24</sup> can be helpful but is not mandatory: classical X-ray, CT or MRI can be used. On an X-ray anterior-posterior pelvis angle, the medial protrusion of the acetabulum above 3 mm beyond the ilio-ischial (Kohler) line is diagnostic. Criteria on CT or MRI are not precisely defined but involve loss of the normal oval shape of the pelvic inlet at the level of the acetabulum.

One point is assigned to eight other manifestations, one cardiovascular (mitral valve prolapse), one ocular (myopia,  $\geq 3$  diopters) and six features from other organ

systems. These are considered less specific features for MFS and can be observed in other connective tissue disorders or as normal variation in the general population<sup>18</sup>.

The combined presence of reduced upper to lower segment ratio (for white adults <0.85; <0.78 in black adults; no data have been assessed in Asians) and increased armspan to height ratio (for adults >1.05) in the absence of significant scoliosis contributes one point to the systemic score. In Asians the incidence of an enlarged armspan to height ratio in Marfan patients was noted to be lower<sup>25</sup> and prior studies of Asian (and also Afro-Caribbean) populations demonstrated different distributions of armspan and height, so one should consider these ethnic differences when using cut-off values<sup>26</sup>. For the US/LS ratio in children, abnormal ratios are US/LS < 1 (for age 0-5 yrs), US/LS < 0.95 (for 6-7 yrs), US/LS < 0.9 (8-9 yrs old) and < 0.85 (above age 10 yrs). The lower segment is defined as the distance from the top of the symphysis pubis to the floor in the standing position and the upper segment is the height minus the lower segment. Importantly, neither of these ratios provides an accurate measurement of bone overgrowth in the presence of severe scoliosis or kyphosis. Scoliosis<sup>27</sup> can be diagnosed either clinically if, upon bending forward, a vertical difference of least 1.5 cm between the ribs of the left and right hemithorax is observed or if a Cobb's angle (angle between a line drawn along the superior end plate of the superior end vertebra and a second line drawn along the inferior end plate of the inferior end vertebra of the scoliosis measured on anterior-posterior view of the spine) of at least 20° is seen on radiographs. In the absence of scoliosis, one point can be contributed by the presence of an exaggerated thoracolumbar kyphosis. Elbow extension is considered reduced if the angle between the upper and lower arm measures 170 degrees or less upon full extension. One point can be

assigned based upon facial characteristics if the patient shows at least three of the five typical facial characteristics including dolichocephaly, downward slanting palpebral fissures, enophthalmos, retrognathia and malar hypoplasia. Striae atrophicae are considered significant as a diagnostic feature if they are not associated with marked weight changes (or pregnancy) and if they have an uncommon location such as the mid-back, lumbar region, the upper arm, axillary region or thigh.

The following criteria were removed from the current nosology because of lack of perceived specificity: joint hypermobility, highly arched palate, and recurrent or incisional herniae<sup>18</sup>.

### **Differential diagnosis**

Several conditions have been recognised which present overlapping clinical manifestations with MFS in the cardiovascular, ocular or skeletal systems. These include conditions with aortic aneurysms (Loeys-Dietz syndrome, bicuspid aortic valve, familial thoracic aortic aneurysm, vascular Ehlers-Danlos syndrome, arterial tortuosity syndrome), ectopia lentis (ectopia lentis syndrome, Weil-Marchesani syndrome, homocystinuria, Stickler syndrome) or systemic manifestations of MFS (Shprintzen-Goldberg syndrome, congenital contractural arachnodactyly, Loeys-Dietz syndrome, MASS phenotype (myopia, mitral valve prolapse, aorta, skin and skeletal findings) and MVPS (mitral valve prolapse syndrome) (Table 4).

### **Conditions with cardiovascular features of MFS**

Historically the terms MASS phenotype and MVPS (mitral valve prolapse syndrome) have been used but several issues about the use of these terms have arisen. First, the definition of the MASS phenotype is not unequivocally applicable as it required at least two, but preferably three of the following manifestations: myopia, mitral valve prolapse, borderline aortic root enlargement, skin and minor skeletal features (insufficient to fulfill the major skeletal criterion of the original Ghent nosology)<sup>6</sup>. This definition indirectly also assumes a non-progressive nature of the aortic root dilatation but it is currently unknown to what proportion of patients this applies. Thirdly, *FBNI* mutations have been found occasionally in MASS phenotype patients<sup>18,28</sup> but the precise risk for the development of aortic aneurysm and progression for these patients is poorly studied. Analogous to the ectopia lentis syndrome, the spirit of the definition of **MASS phenotype** aims to avoid the diagnosis of MFS without documented risk for aortic root aneurysm development. The diagnosis of MASS is made in individuals with an aortic root size below  $Z=2$ , at least one skeletal feature and a systemic score  $\geq 5$ . The presence of ectopia lentis precludes this diagnosis. If an *FBNI* mutation is identified in a MASS patient, this patient has the potential to evolve into MFS but it is currently unknown how often and which factors predict this transition over time.

Alternatively, when mitral valve prolapse is present in association with limited systemic features (score  $< 5$ ), we suggest to use the term **mitral valve prolapse syndrome (MVPS)**. MVPS is a common condition usually inherited in autosomal dominant mode<sup>29</sup> with several candidate gene loci<sup>30</sup> but with evidence for rare X-linked inheritance<sup>31</sup> which affects ~1.5% of the population. In addition to prolapse of the mitral

leaflets, MVPS commonly includes pectus excavatum, scoliosis and mild arachnodactyly<sup>32</sup>. However, aortic enlargement and ectopia lentis preclude this diagnosis.

**Loeys-Dietz syndrome (LDS)** is an autosomal dominant aortic aneurysm syndrome characterized by the triad of hypertelorism, bifid uvula/cleft palate, and/or arterial tortuosity with ascending aortic aneurysm/dissection. It is caused by heterozygous mutations in the genes encoding the type 1 or 2 subunit of the transforming growth factor-beta receptor (*TGFBR1* or *TGFBR2*)<sup>33</sup>. Other more variable clinical features that distinguish LDS from MFS include craniosynostosis, Chiari malformation, club foot deformity, congenital heart disease, cervical spine instability, easy bruising, dystrophic scarring, translucent skin and, most importantly, a high risk of aneurysm and dissection throughout the arterial tree. Patients with LDS are not typically inappropriately tall and do not exhibit disproportionately long extremities, although arachnodactyly is observed. Some patients with *TGFBR1/2* mutations lack overt craniofacial features despite an equal or greater severity of vascular or systemic findings. Importantly, the natural history of patients with LDS tends to be more aggressive than those with MFS or vEDS. In LDS, aortic dissections often occur at a younger age or at smaller aortic dimensions (<40mm) compared to MFS, and the incidence of pregnancy-related complications is particularly high<sup>34</sup>. As with *FBNI* mutations, the phenotype associated with *TGFBR1/2* mutations can be variable, even within families, and can be associated with skeletal features of MFS leading to overlapping phenotypes in the old Ghent nosology<sup>35-37</sup>. In order to avoid persistent ambiguity even under the proposed criteria, molecular testing should be strongly considered because it influences the clinical management<sup>34</sup>. It has been proposed that patients with *TGFBR1/2* mutations that lack outward discriminating

features of LDS should be designated LDS2, highlighting the potential for more aggressive vascular disease than seen in Marfan syndrome (MIM 190181 and 190182).

With a population prevalence of up to 1%<sup>38,39</sup>, **bicuspid aortic valve (BAV)** is the most common congenital cardiac malformation. A subset of individuals with BAV present with ascending aortic aneurysm, however such patients usually lack ocular or other systemic findings that contribute strongly to MFS diagnosis. Skeletal findings such as pectus deformity and scoliosis can be observed in these families. Bicuspid aortic valve and aortic aneurysm can occur together in some family members but independently in others indicating that they can be variably penetrant consequences of a common underlying genetic defect<sup>40,41</sup>. Unlike MFS this condition commonly shows maximal or exclusive dilatation in the ascending aorta above the sinotubular junction<sup>42</sup>. Mutations have been identified in the *NOTCH1* and *KCNJ2* genes, but these account for only a small fraction of BAV patients, who may have prominent valve calcification or associated forms of congenital heart disease. Linkage analysis reveals genetic heterogeneity with putative loci on chromosomes 18q, 5q and 13q<sup>43</sup>.

**Familial thoracic aortic aneurysm syndrome dissection syndrome (FTAAD)** is a clinically and genetically heterogeneous group of disorders where thoracic aortic disease predominates. The age of onset and rate of progression of aortic dilatation is highly variable and conditions that include variable or subtle systemic manifestations of a connective tissue disorder have been included in this designation. It is anticipated that future stratification of patients by genetic etiology will help to refine phenotypic descriptions and inform patient counseling and management. To date, there are 5 genes and 2 additional loci<sup>44,45</sup> associated with FTAAD. Mutations have been identified in

*FBN1*, *TGFBR1/2*, *MYH11*, and *ACTA2*, the latter two encoding components in the smooth muscle cell contractile apparatus. Mutations in *MYH11* associate aortic root aneurysms with patent ductus arteriosus (PDA) <sup>46</sup>. Mutations in *ACTA2*, accounting for up to 16% of FTAAD, associate aortic aneurysm with other variable features including iris flocculi, livedo reticularis, cerebral aneurysm, bicuspid aortic valve and PDA <sup>47</sup>. In addition to thoracic aortic aneurysms and dissections, patients with *ACTA2* mutations can present with vascular disease in the cerebrovascular system (premature ischemic strokes, Moyamoya disease and cerebral aneurysms) or premature coronary artery disease <sup>48</sup>

The **vascular type of EDS** (previously EDS IV), is caused by mutations in *COL3A1*, the gene encoding type III collagen; it is characterized by vascular and tissue fragility. Cardinal features distinguishing vEDS from MFS include translucent skin, easy bruising, dystrophic scarring and a tendency for intestinal or uterine rupture. Typically, dissection or rupture occurs in medium-sized arteries in vEDS although aortic involvement is sometimes observed. There is no particular predisposition at the aortic root. About half of the aneurysms/dissections occur in thoracic or abdominal branch arteries; arteries of the head, neck and limbs are less frequently involved <sup>49</sup>.

Three other rare types of Ehlers-Danlos syndrome have been associated with vascular problems. The **kyphoscoliotic type** (previously type VI EDS) is characterized by kyphoscoliosis, joint laxity, and muscle hypotonia. This autosomal recessive condition is caused by defects in the enzymatic activity of lysyl hydroxylase, encoded by the *PLOD1* gene. Aortic dilation/dissection and rupture of medium-sized arteries have been observed <sup>50</sup>. Patients with the so-called “**cardiac valvular subtype of EDS**”, which associates severe cardiac valvular problems and features of the classic type of EDS

(atrophic scars, skin hyperelasticity and joint hypermobility), were found to have a complete deficiency of the pro $\alpha$ 2-chain of type I collagen (*COL1A2*)<sup>51</sup>. Most recently, patients with arginine to cysteine substitutions in the pro $\alpha$ 1-chain of type I collagen (*COL1A1*) displayed classic EDS but evolved to a vascular EDS-like phenotype later in life, with increased risk for spontaneous arterial rupture, most prominently affecting the femoral and iliac arteries<sup>52</sup>.

**Arterial tortuosity syndrome (ATS)** is a rare autosomal recessive connective tissue disorder, characterized by severe tortuosity, stenosis, and aneurysms of the aorta and medium-sized arteries<sup>53</sup>. Skeletal and skin involvement is common. The underlying genetic defect is homozygosity or compound heterozygosity for loss-of-function mutations in *SLC2A10*, the gene encoding the facilitative glucose transporter GLUT10<sup>54</sup>. The condition is lethal in infancy in a subset of patients but some survive into adulthood and seem to do well<sup>55</sup>.

### **Conditions with ectopia lentis**

Patients with **familial ectopia lentis** typically have some skeletal features of MFS and an *FBNI* mutation. While lack of aortic disease is a defining feature of this condition, it may be difficult to distinguish from emerging MFS in the absence of other affected family members or at a young age. Even within extended pedigrees with familial ectopia lentis, later onset aortic aneurysm may be observed. In order to highlight the systemic nature of this condition better and to emphasize the need for assessment of features outside the ocular system, we propose the designation **ectopia lentis syndrome (ELS)**. The presence of a personal or family history of aortic aneurysm or the identification of an

*FBNI* mutation previously associated with aortic aneurysm would be sufficient to transition the diagnosis to MFS, independently of the number or distribution of systemic features. To ensure that adequate vigilance of other organ systems is maintained, the diagnosis of ELS cannot be formally invoked before the age of 20 years. The disorder is genetically heterogeneous, with autosomal dominant inheritance caused by *FBNI* mutations<sup>56</sup> and recessive forms caused by *LTBP2* and *ADAMTSLA* mutations<sup>57, 58</sup>. Importantly, in ELS patients with *FBNI* mutations, cardiovascular follow-up by imaging should be maintained throughout life.

Ectopia lentis can be present as a component of other rare conditions. **Ectopia lentis et pupillae** is an autosomal recessive condition in which remnants of the pupillary membrane are present. However, it is not associated with cardiovascular or skeletal features of MFS.

In contrast to **Weill-Marchesani syndrome (WMS)**, the lens dislocation is typically associated with microspherophakia (small, rounded and thickened crystalline lens) and a shallow anterior eye chamber. WMS patients are short with brachydactyly and joint stiffness. Both autosomal dominant and recessive forms of WMS have been described and are caused by *FBNI* mutations<sup>59, 60</sup> and mutations in the *ADAMTSL10* gene<sup>61</sup>, respectively. **Homocystinuria** is often easily differentiated from MFS by the presence of mental retardation and thrombosis, and can be excluded by urine amino acid analysis in the absence of pyridoxine supplementation. In homocystinuria, the lens usually dislocates downward due to complete loss of support by ciliary zonules. In **Stickler syndrome**, patients can present with a Marfanoid habitus. Typical ocular signs include retinal detachment, myopia and open-angle glaucoma. Early cataracts are common, but

lens subluxation is not. Other potential discriminating features from MFS include cleft palate, hearing loss and epiphyseal changes of the bones.

### **Conditions with overlapping systemic features**

**Shprintzen-Goldberg syndrome (SGS)** is a rare craniosynostosis syndrome characterized by some of the systemic features found in MFS (pectus abnormalities, scoliosis, arachnodactyly), craniofacial dysmorphism (exophthalmos, hypertelorism, downslanting palpebral fissures, maxillary and mandibular hypoplasia, high arched palate and low set ears) and developmental delay. So far, only two SGS patients have shown an *FBNI* mutation<sup>62, 63</sup>. Another patient reported by Kosaki et al.<sup>63</sup> as SGS was felt to have LDS based on arterial tortuosity and the presence of a bifid uvula<sup>64</sup>. Other important distinguishing features between SGS and either LDS or MFS are the high incidence of cognitive impairment and the low frequency of vascular disease in the former.

**Congenital contractural arachnodactyly (CCA)** is an autosomal dominant disorder characterized by a Marfan-like body habitus and arachnodactyly<sup>65</sup>. Most affected individuals have "crumpled" ears that present as a folded upper helix and contractures of major joints (knees and ankles) at birth. The proximal interphalangeal joints of the fingers and toes have flexion contractures (camptodactyly). Kyphosis/scoliosis is present in about half of affected individuals. Mild enlargement of the sinuses of Valsalva has been reported, but there is no evidence that the aortic dilatation progresses to dissection or rupture<sup>66</sup>. CCA is caused by mutations in *FBN2*, the gene encoding the extracellular matrix microfibril fibrillin-2<sup>67</sup>.

## **Management**

### **Management guidelines for MFS patients**

Aortic root dilatation in MFS is usually progressive. Therefore absence of aortic root enlargement on initial clinical examination does not necessarily exclude the diagnosis, even in adulthood.

All individuals who meet the criteria for MFS should initially have at least yearly echocardiograms. More frequent imaging should be performed if the aortic diameter is approaching a surgical threshold ( $\geq 4.5$  cm in adults; less well defined in children) or shows rapid change ( $\geq 0.5$  cm/year) or with concerns regarding heart or valve function. Individuals under age 20 with systemic findings suggestive of MFS but no cardiovascular involvement should have annual echocardiograms due to the potential for rapid evolution of the phenotype. Adults with repeatedly normal aortic root measurements can be seen at intervals of 2-3 years.

Although several alternative medical treatments have been proposed (ACE-inhibitors, calcium channel antagonists), the standard of care in most centers for the prevention of aortic complications in MFS remains beta-blockade<sup>68</sup>. More data are required before ACE inhibitor-therapy can be considered standard treatment<sup>69</sup>. Beta-blockade should be considered in all patients with MFS, including children and those with aortic root diameters of less than 4 cm, unless contraindicated. The beta-blocker should be titrated to maximum effect, aimed at a heart rate after submaximal exercise (eg. running up and down two flights of stairs) less than 100 beats per minute in individuals over 5 years of age. Angiotensin receptor blockers (ARBs) have shown the ability to

prevent aortic enlargement in a mouse model of Marfan syndrome<sup>70</sup>, and encouraging results were observed in a pilot experience in children with severe MFS<sup>71</sup>. Several multicenter trials of losartan versus or on top of atenolol in MFS are currently underway<sup>72</sup>. If beta-blockers are contraindicated or not tolerated, other classes of antihypertensive agents can be used, but there is not definitive evidence that they will afford protection in people with MFS.

Management of acute dissection of the ascending aorta (type A dissection) is emergency surgery. Consideration of prophylactic surgery is recommended when the diameter at the sinuses of Valsalva approaches 5.0 cm. Other factors that inform the timing of surgery include a family history of early dissection, the rate of aortic root growth, the severity of aortic valve regurgitation, associated mitral valve disease, ventricular dysfunction, pregnancy planning in women, and the desire for a valve sparing operation.

Type B dissection (originating in the thoracic descending aorta) accounts for about 10% of all dissections in MFS. Possible indications for surgery include intractable pain, limb or organ ischemia, an aortic diameter exceeding 5.5 cm or a rapid increase in the aortic diameter. Open surgery is still preferred as experience with intravascular stenting in MFS is very limited, and the pressure endovascular stents need to apply against the wall of adjacent normal-sized aortic segments to remain well-seated may not be tolerated by weakened connective tissue, or the adjacent aorta may also be dilated. Regular imaging of the entire aorta is encouraged after root surgery and in adulthood.

Mitral valve repair or replacement is advised for severe mitral valve regurgitation with associated symptoms or progressive left ventricular dilatation or dysfunction. Repair

should be considered, especially in patients undergoing aortic valve-sparing root replacement. If a mechanical aortic valve prosthesis is chosen, mitral valve replacement may be considered, although preservation of left ventricular function may be better with mitral valve repair. After isolated mitral valve repair, one should carefully monitor aortic root size as increased rates of enlargement have been observed.

Decisions regarding exercise restriction should always be made on an individual basis. Recommendations from the National Marfan Foundation ([www.marfan.org](http://www.marfan.org)) and guidelines from the American Heart Association/American College of Cardiology task forces<sup>73</sup> are useful templates. In general, patients with MFS should avoid contact sports, exercise to exhaustion and especially isometric activities involving a Valsalva manoeuvre. Most patients can and should participate in aerobic activities performed in moderation.

Pregnancy in MFS women is associated with increased cardiovascular risk, with the majority of aortic complications (progressive dilatation and dissection) occurring in the third trimester or in the early postpartum period. The risk of aortic root complication is increased when the aortic root diameter is above 4.0 cm at the start of the pregnancy<sup>74</sup>.

Annual ophthalmological evaluation for the detection of ectopia lentis, cataract, glaucoma and retinal detachment is essential. Early monitoring and aggressive refraction is required for children with MFS to prevent amblyopia. Indications for surgical lens extraction include lens opacity with poor visual function, anisometropia or refractive error amenable to optical correction, impending complete luxation and lens-induced glaucoma or uveitis.

Skeletal manifestations such as scoliosis and pectus deformity should be treated according to standard orthopedic management rules.

**Management guidelines for related conditions**

Regular follow-up including annual cardiovascular imaging and ophthalmological evaluation is advised in MASS, MVPS and ELS to monitor aortic size, and the degree of mitral regurgitation, over time. Counseling for patients with either ELS or MASS phenotype should include the risk of a more severe presentation in their offspring, including aortic enlargement.

Careful cardiovascular and ophthalmological follow-up is of course strongly indicated in children with potential MFS or non-specific connective tissue disorders.

**Conclusion**

The diagnostic evaluation for MFS is unavoidably complex due to the highly variable presentation of affected individuals, the age-dependent nature of many of its manifestations, the absence of gold standards and its extensive differential diagnosis. While diagnostic criteria should emphasize simplicity of use and the desire for early diagnosis, accuracy receives highest priority in order to avoid the deleterious and often irreversible consequences of ungrounded or erroneous assignment. While the increased focus on vascular disease for the diagnosis of MFS in this proposal will likely prove controversial, it is responsive to the practical burden faced both by patients and physicians and does not represent a true departure from the spirit of prior diagnostic guidelines. Ongoing concerns about delayed diagnosis and/or the use of diagnostic categories that may prove provisional should be offset by additional discussion of ongoing risk and the definition of follow-up and management principles. A comparative analysis on different retrospective datasets has shown ~90% concordance between the old

and revised Ghent nosology. The 10% discordance was generally beneficial by facilitating earlier diagnosis in young children with a convincing clinical phenotype and delayed diagnosis in individuals without clear cardiovascular risk. The current proposal will benefit from a prospective analysis, leading to further refinement. A web-based diagnostic tool for the application of these criteria can be accessed at [www.marfan.org](http://www.marfan.org).

**Table 1. Revised Ghent criteria for Diagnosis of Marfan syndrome and Related conditions.****In the absence of family history:**

- (1) Ao ( $Z \geq 2$ ) AND EL = MFS
- (2) Ao ( $Z \geq 2$ ) AND *FBNI* = MFS
- (3) Ao ( $Z \geq 2$ ) AND Syst ( $\geq 7$ pts) = MFS\*
- (4) EL AND *FBNI* with known Ao = MFS

EL with or without Syst AND with an *FBNI* not known with Ao or no *FBNI* = ELS

Ao ( $Z < 2$ ) AND Syst ( $\geq 5$ ) without EL = MASS

MVP AND Ao ( $Z < 2$ ) AND Syst ( $< 5$ ) without EL = MVPS

**In the presence of family history:**

- (5) EL AND FH of MFS (as defined above) = MFS
- (6) Syst ( $\geq 7$  pts) AND FH of MFS (as defined above) = MFS\*
- (7) Ao ( $Z \geq 2$  above 20 yrs old,  $\geq 3$  below 20 yrs) + FH of MFS (as defined above) = MFS\*

Ao= aortic diameter at the sinuses of valsalva above indicated Z-score or aortic root dissection, Z = Z-score, EL=ectopia lentis, Syst = systemic score (see table 2), *FBNI*= fibrillin-1 mutation (as defined in table 3), *FBNI* with known Ao = *FBNI* mutation that has been identified in an individual with aortic aneurysm, *FBNI* not known with Ao = *FBNI* mutation that has not previously been associated aortic root aneurysm/dissection, ELS = ectopia lentis syndrome, MASS = myopia, mitral valve prolapse, aortic root dilatation, striae, skeletal findings, aortic aneurysm syndrome, MVPS = mitral valve prolapse syndrome, MFS = Marfan syndrome.

\* Caveat: Without discriminating features of SGS, LDS or vEDS (as defined in table 4)

- AND after *TGFBR1/2*, collagen biochemistry, *COL3A1* testing if indicated
- other conditions/genes will emerge with time

**Table 2. Scoring of systemic features.**

- Wrist AND thumb sign – **3** (Wrist OR thumb sign – **1**)
- Pectus carinatum deformity – **2** (pectus excavatum or chest asymmetry – **1**)
- Hindfoot deformity – **2** (plain pes planus – **1**)
- Pneumothorax – **2**
- Dural ectasia – **2**
- Protrusio acetabuli – **2**
  
- Reduced US/LS AND increased arm/height AND no severe scoliosis – **1**
- Scoliosis or thoracolumbar kyphosis – **1**
- Reduced elbow extension – **1**
- Facial features (3/5) – **1** (dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia)
- Skin striae – **1**
- Myopia > 3 diopters - **1**
- Mitral valve prolapse (all types) – **1**

**Maximum total: 20 points; score  $\geq 7$  indicates systemic involvement**

**Table 3. Criteria for causal *FBNI* mutation.**

- Mutation previously shown to segregate in Marfan family
- De novo (with proven paternity and absence of disease in parents) mutation (one of the five following categories)
- Nonsense mutation
- Inframe and out of frame deletion/insertion
- Splice site mutations affecting canonical splice sequence or shown to alter splicing on mRNA/cDNA level
- Missense affecting/creating cysteine residues
- Missense affecting conserved residues of the EGF consensus sequence ((D/N)X(D/N)(E/Q)X<sub>m</sub>(D/N)X<sub>n</sub>(Y/F) with m and n representing variable number of residues; D aspartic acid, N asparagine, E glutamic acid, Q glutamine, Y tyrosine, F phenylalanine)
- Other missense mutations: segregation in family if possible + absence in 400 ethnically matched control chromosomes, if no family history absence in 400 ethnically matched control chromosomes
- Linkage of haplotype for  $n \geq 6$  meioses to the *FBNI* locus

**Table 4. Features of differential diagnosis.**

<b>Differential diagnosis</b>	<b>Gene</b>	<b>Discriminating features</b>
Loeys-Dietz syndrome (LDS)	<i>TGFBR1/2</i>	bifid uvula/cleft palate, arterial tortuosity, hypertelorism, diffuse aortic and arterial aneurysms, craniosynostosis, club foot, cervical spine instability, thin and velvety skin, easy bruising
Shprintzen-Goldberg syndrome (SGS)	<i>FBNI</i> and other	craniosynostosis, mental retardation
Congenital arachnodactyly syndrome (CCA)	<i>FBN2</i>	crumpled ears, scoliosis, contractures
Weill-Marchesani syndrome (WMS)	<i>FBNI</i> and <i>ADAMTS10</i>	microspherophakia, brachydactyly, joint stiffness
Ectopia lentis syndrome (ELS)	<i>FBNI</i> <i>LTBP2</i> <i>ADAMTSL4</i>	Marfanoid skeletal features
Homocystinuria	<i>CBS</i>	thrombosis, mental retardation
Familial thoracic aortic aneurysm syndrome (FTAA) FTAA with bicuspid aortic valve (BAV) FTAA with patent ductus arteriosus (PDA)	<i>TGFBR1/2</i> , <i>ACTA2</i> <i>MYH11</i>	Marfanoid skeletal features, levido reticularis, iris flocculi
Arterial tortuosity syndrome (ATS)	<i>SLC2A10</i>	Generalized arterial tortuosity, arterial stenosis, facial dysmorphism
Ehlers-Danlos syndromes (vascular, valvular, kyphoscoliotic type)	<i>COL3A1</i> , <i>COL1A2</i> , <i>PLOD1</i>	middle sized artery aneurysm, valvular insufficiency, translucent skin, dystrophic scars, scoliosis, facial characteristics

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