

Perspectives on the revised Ghent criteria for the diagnosis of Marfan syndrome

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Abstract: Three international nosologies have been proposed for the diagnosis of Marfan syndrome (MFS): the Berlin nosology in 1988; the Ghent nosology in 1996 (Ghent-1); and the revised Ghent nosology in 2010 (Ghent-2). We reviewed the literature and discussed the challenges and concepts of diagnosing MFS in adults. Ghent-1 proposed more stringent clinical criteria, which led to the confirmation of MFS in only 32%–53% of patients formerly diagnosed with MFS according to the Berlin nosology. Conversely, both the Ghent-1 and Ghent-2 nosologies diagnosed MFS, and both yielded similar frequencies of MFS in persons with a causative *FBNI* mutation (90% for Ghent-1 versus 92% for Ghent-2) and in persons not having a causative *FBNI* mutation (15% versus 13%). Quality criteria for diagnostic methods include objectivity, reliability, and validity. However, the nosology-based diagnosis of MFS lacks a diagnostic reference standard and, hence, quality criteria such as sensitivity, specificity, or accuracy cannot be assessed. Medical utility of diagnosis implies congruency with the historical criteria of MFS, as well as with information about the etiology, pathogenesis, diagnostic triggers, prognostic triggers, and potential complications of MFS. In addition, social and psychological utilities of diagnostic criteria include acceptance by patients, patient organizations, clinicians and scientists, practicability, costs, and the reduction of anxiety. Since the utility of a diagnosis or exclusion of MFS is context-dependent, prioritization of utilities is a strategic decision in the process of nosology development. Screening tests for MFS should be used to identify persons with MFS. To confirm the diagnosis of MFS, Ghent-1 and Ghent-2 perform similarly, but Ghent-2 is easier to use. To maximize the utility of the diagnostic criteria of MFS, a fair and transparent process of nosology development is essential.

Keywords: Marfan syndrome, Ghent nosology, diagnosis, *FBNI*, mutation, aorta

Introduction

Marfan syndrome (MFS) is a disorder of the connective tissue that is inherited in an autosomal dominant fashion and is caused by mutations in the gene coding for fibrillin-1 (*FBNI*). MFS has a low prevalence with similar frequency in both sexes and in all countries and races. MFS is a severe, chronic, and life-threatening disease with multiorgan involvement without availability of a curative therapy.¹ MFS is associated with chronic fatigue and pain, as well as with psychological despair that compromises the quality of life and imposes restrictions on the autonomy of affected persons.^{2–7}

A classical study of life expectancy from the era prior to the availability of therapy documented poor survival of persons with MFS in the early 1970s.¹ The study documented 74 deaths in 257 affected persons with 50% of men and women dead at the age of 40 years and 48 years, respectively, which corresponded to a reduction of life

expectancy by 30%–40% when compared to the normal population. The mean age of death was 32 years, whereby fatalities resulted from rupture of aortic aneurysm in 12 (16%) patients, dissection of aortic aneurysm in eight (11%), surgical death at attempted repair of the aorta in four (5%), insufficiency of the aortic valve in 14 (19%), congestive heart failure in eight (11%), bacterial endocarditis in two (3%), ventricular fibrillation after orthopedic surgery in one (1%), sudden unexplained death in three (5%), and suicide in one (1%) person, whereas the remaining patients died of miscellaneous reasons or of unknown causes.¹

The evolution of aortic surgery offered life-saving therapy for patients with acute aortic rupture and dissection, as well as prophylactic treatment to prevent patients with aortic root aneurysm from developing aortic rupture or dissection.⁸ The various modifications of the technique of Bentall and De Bono, with complete replacement of the aortic root, became the operation of choice starting in the early 1970s.^{9–11} In addition, a classical open-label randomized trial of propranolol in adolescents and adults with MFS showed that prophylactic beta-adrenergic blockade (BAB) was effective in slowing the rate of aortic dilatation and reducing the development of aortic complications in some MFS patients.¹² Subsequently, a retrospective multicenter study documented that the life expectancy of patients with MFS had increased by over 25% since 1972, where benefits were documented from both cardiovascular surgery and medical therapy including BAB.¹³ Since this study, the introduction of valve-sparing techniques for the replacement of the aortic root has resulted in a major improvement of life quality by obviating the risk for coagulation, where the technique of David yielded the best results.^{14–17} Alternatives for BAB have been tested in numerous, mostly small nonrandomized trials. These studies used angiotensin-converting enzyme inhibitors, calcium channel blockers, or angiotensin-receptor blockers.^{18–22} Results from these studies were conflicting. Very recently, a randomized double-blind trial in young patients with MFS showed equally beneficial effects with atenolol as compared to losartan, with no differences with regards to side effects, giving us the opportunity to choose either option.^{23–25}

Once the diagnosis of MFS is suspected, care for patients should be coordinated in specialized centers. With the help of such centers, along with the support of regional Marfan patient organizations, affected persons can have a normal life expectancy with an acceptable quality of life.^{26,27} In this article, we review the literature and discuss the challenges and concepts of diagnosing MFS in adults.

Prevalence of MFS

A number of studies have assessed the prevalence of MFS. The earliest study comes from Northern Ireland and it reports 1.5 affected persons per 100,000 of the population, with a gene frequency of 0.729 per 100,000.²⁸ A second study that screened 29,067 children from 18 provinces and cities of the People's Republic of China from 1951 to 1987 reported five children with MFS, giving a prevalence of 17.2 per 100,000 of the population, with a gene frequency of 8.61 per 100,000 inhabitants, and a penetrance of 71.69%.²⁹ A study of the population of Tayside and northeast Scotland identified 30 patients with MFS alive on prevalence day June 30, 1991, corresponding to an estimated prevalence of 1:14,691 or 6.81 per 100,000 inhabitants.³⁰ Based on 239 persons (122 males, 117 females) with MFS who were alive and living in Denmark by January 1, 1993, a fourth nation-wide study from Denmark identified a prevalence of 4.6 persons with MFS per 100,000 of the Danish population with an estimated average birth rate of 0.96 per 10,000 live born.³¹ Our study of adults with MFS identified a prevalence of seven in 100,000 adults in the Hamburg metropolitan area.³² Finally, a national cohort study from Taiwan identified 2,329 persons with MFS in a study period from 2000 to 2012 and calculated an average prevalence of 10.2 persons with MFS (95% confidence interval [CI]: 9.8–10.7) per 100,000 persons of the Taiwanese population, with a minimal birth rate incidence (estimated among those aged 20–29 years) of 23.3 per 100,000 (95% CI: 21.7–23.3) individuals.³³ Table 1 provides an overview of the existing studies on the prevalence of MFS.

Taken together, all studies provide lower prevalence rates than do the widely cited estimate of one per 5,000 individuals.³⁴ Interestingly, these studies document a wide range from 1.5–17.2 per 100,000, or 0.075–0.86 per 5,000 individuals in the general population.^{28–33} However, all reported prevalence rates are far less than one in 2,000 citizens, and hence MFS complies with the European definition of a rare disease.³⁵ The wide range of the reported prevalence in the different studies reflects the usage of different diagnostic criteria of MFS, but it also seems likely that the medical workup in the different countries has led to the different estimates of population frequency. In fact, there is increasing evidence for the under-diagnosis of MFS in the general population, where the search for the “needle in the haystack” may pose a major diagnostic dilemma of MFS (Figure 1A).

For instance, there is a marked delay in the diagnosis of MFS. The European Organisation for Rare Diseases (EURORDIS) performed a survey of patients with rare diseases in 18 European countries, where 682 families affected

Table 1 Studies on the prevalence of MFS in the general population

Author	Population	Number of patients with MFS, size of population	Prevalence of MFS per total population
Lynas ²⁸	Population of Northern Ireland	MFS: 20 Population: 1,370,921	1.5 per 100,000
Sun et al ²⁹	Children from 18 provinces and cities of the People's Republic of China	Children with MFS: 5 Children from population: 29,067	17.2 per 100,000
Gray et al ³⁰	Population of Scotland	MFS: 30 Population of Tayside and northeast Fife: 441,000	6.8 per 100,000
Fuchs ³¹	Population of Denmark	MFS: 239 Population: 5,180,614	4.6 per 100,000
Rybczynski et al ³²	Adult population of the Hamburg, Germany, metropolitan area	Adults with MFS and MFS-like syndromes: 207 Adult population: 3.5 million	7 per 100,000
Chiu et al ³³	Population of Taiwan	Population: 22,765,535 MFS: 2,329	10.2 per 100,000

Abbreviation: MFS, Marfan syndrome.

by MFS were included.³⁶ The time between the first clinical manifestations and diagnosis was 2 years for half of the patients with MFS, but it was as long as 4.5 years for 25% of patients. During the quest for diagnosis, more than five physicians were consulted by 38% of families and more than 20 physicians by 7% of families. Prior to obtaining the correct diagnosis of MFS, another diagnosis was given to 25% of patients, resulting in delayed diagnosis and inappropriate treatment in 81% of the patients. For 72% of families, the delay in diagnosis was considered responsible for deleterious consequences.³⁶ Similarly, a cohort study of all hospitalized patients with a diagnosis of MFS and related disorders in England still documents a high rate of cardiovascular events.³⁷ This study documents 159 patients with aortic dissection, 101 with stroke, and eleven with rupture of an abdominal aortic aneurysm in a total of 4,468 hospitalized MFS patients over a mean follow-up of 6.9 years.³⁷ Moreover, current data from autopsy studies suggest that the rate of MFS patients who die from aortic dissection outside the hospital is still as high as 7.8%.³⁸

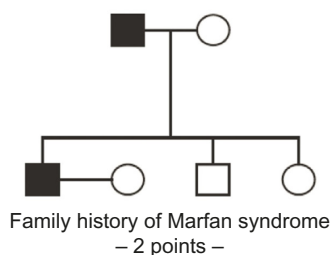
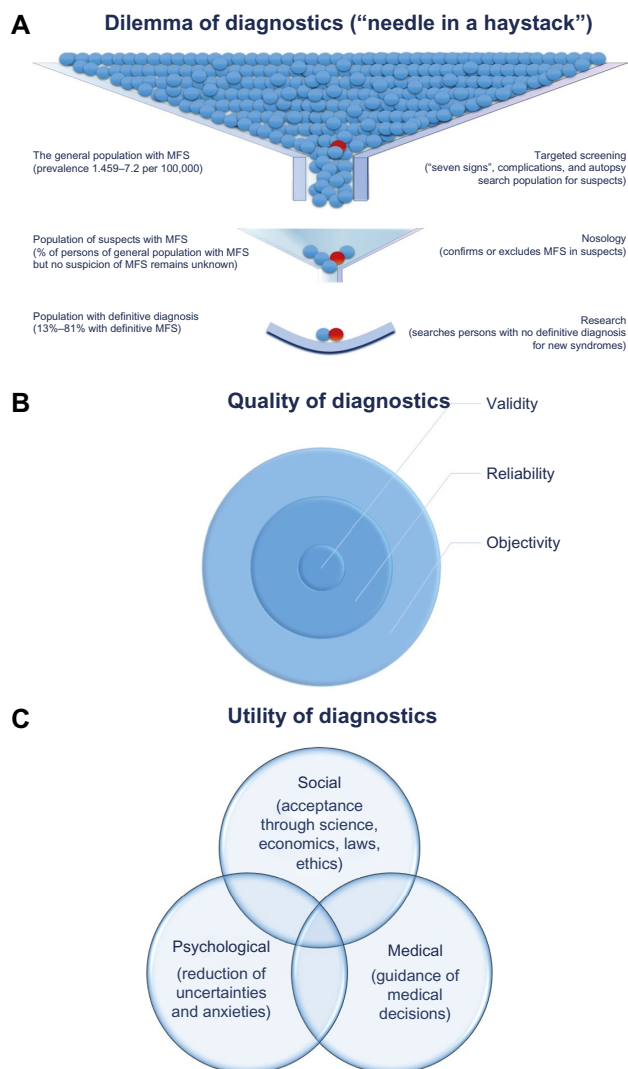
Based on administrative data from 389 patients with MFS, Roll³⁹ documented a negative linear relationship between the density of physicians in a given region and the probability of an immediate diagnosis of MFS, whereby a higher number of visits to physicians was associated with a significantly decreased probability of immediate diagnosis. Moreover, they found that the distance to medical health care centers was not a predictor of an immediate diagnosis.³⁹ The authors argue that diagnostic errors rarely occur because of a lack of knowledge about a rare disease, but rather because of cognitive errors in the process of gathering the right information about the patient, and in putting together heterogeneous information about the disease.⁴⁰ More importantly, they see structural deficiencies as a major cause of the delay in the

diagnosis of MFS, and they discuss factors such as asymmetry of information among physicians, a behavioral pattern of “organized irresponsibility”, which might be facilitated through the availability of more physicians, a lack of long-term and sustained physician–patient relationships, and the lack of networking between physicians.^{39,41–44}

In summary, the identification of persons with MFS in the general population remains a diagnostic dilemma because it is not realistic to screen the entire population for a rare disease, and there is no simple way to define a target population. However, whenever a risk for MFS may be identified, targeted screening may be performed with tests like the “seven-signs” screening tool (Figures 1 and 2).^{45–48} In addition, young patients with aortic dissection, or family members of a person who died at a young age from aortic dissection, should also be considered for diagnostic testing for MFS.⁴⁹

Manifestations of MFS

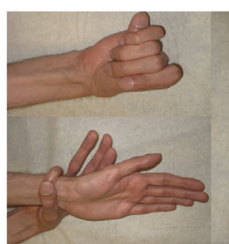
MFS is a multiorgan disease affecting the skeleton, the cardiovascular system, the eyes, the lungs, the skin, and the nervous system.^{50,51} Individuals who have MFS do not exhibit all manifestations of MFS, and nosologies for diagnosing MFS select those manifestations as diagnostic criteria that are considered relevant. In this review, we propose five types of diagnostic contents, which together define the relevance of each sign, manifestation, or criterion of MFS (Table 2). The first is history: changes of diagnostic criteria should avoid large shifts in the population of people already labeled as having or not having MFS. Accordingly, the criteria of MFS should be largely congruent with the picture of MFS that evolved throughout the history of the syndrome. The second type of information is etiology and pathogenesis: demonstration of a causative *FBNI* mutation or of pathogenetic changes



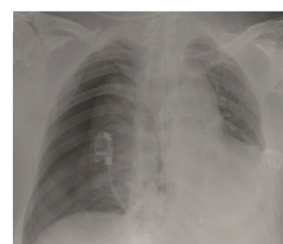
Previous thoracic aortic surgery – 1 point –



Pectus excavatum – 1 point –



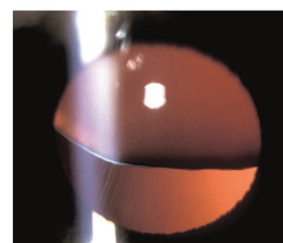
Wrist and thumb sign – 1 point –



History of pneumothorax – 1 point –



Skin striae – 1 point –



Ectopia lentis – 4 points –

Figure 1 Dilemma, quality and utility of diagnosis of Marfan syndrome.
Notes: (A) The rarity of MFS poses a dilemma, where an unknown fraction of persons with MFS may not be suspected of having MFS, or he or she may only be identified by major complications or at necropsy. (B) Criteria to estimate the quality of diagnostic criteria, such as the Ghent nosologies, comprise objectivity, reliability, and validity, where objectivity is a prerequisite for reliability, and reliability a prerequisite for validity. When a diagnosis is reliable, then all three qualities should converge. (C) The utility of diagnostic criteria includes medical, social, and psychological dimensions, which depend on context and may diverge. To maximize the overlap of all three dimensions, negotiation, compromise, and consensus are useful for developing diagnostic criteria.
Abbreviation: MFS, Marfan syndrome.

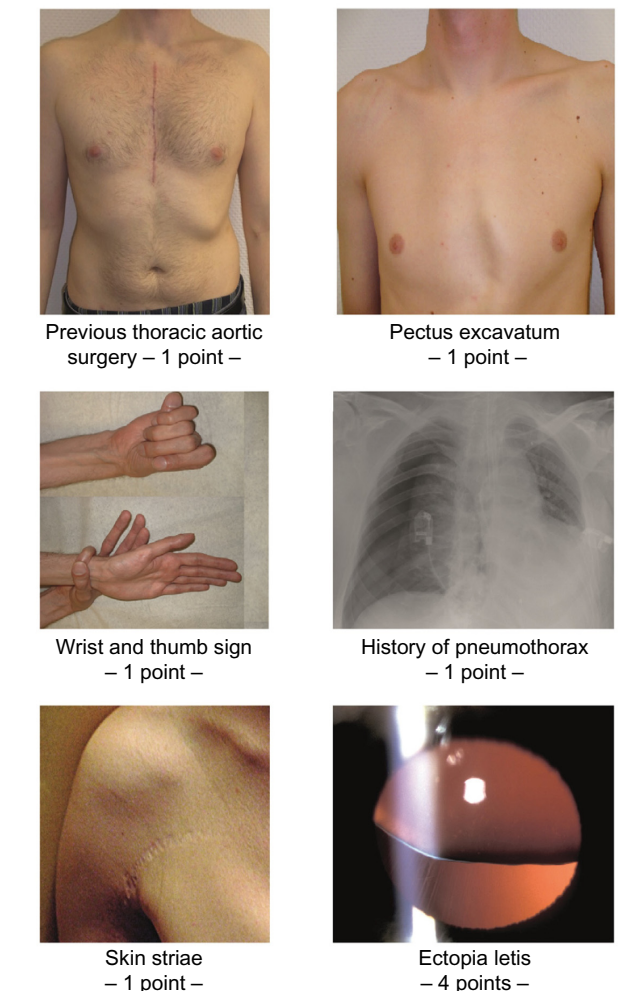


Figure 2 “Seven-signs” of Marfan syndrome may be used for targeted screening of Marfan syndrome in adults of the general population.
Notes: The screening tool assigns four score points to ectopia lentis, two points to a family history of Marfan syndrome, and one point to previous thoracic aortic surgery, to pectus excavatum, to a wrist and thumb sign, to previous pneumothorax, and to skin striae. According to the total score, the pretest probability of Marfan syndrome may be assessed as low (≤ 1 point), moderate ($> 1-3.5$ points), or high (> 3.5 points).⁴⁸

that indicate progressive organ disease, such as increased transforming growth factor (TGF- β 1) serum levels or aortic medial degeneration, can reduce diagnostic and prognostic uncertainty. Third, diagnostic triggers are manifestations that prompt suspicion of MFS in formerly undiagnosed subjects. Fourth, prognostic triggers are manifestations such as aortic dilatation or mitral valve prolapse that, fifth, may give rise to complications such as aortic dissection or mitral valve regurgitation (Table 2).

History

Table 3 provides a brief history of the initial descriptions of frequent or typical manifestations of MFS. This tabulation of their initial descriptions may be somewhat arbitrary, because the criteria used for defining both MFS and manifestations have varied since the initial description of the disease and,

Table 2 Diagnostic content of various signs, manifestations, or criteria of MFS

Type of information	Sign, manifestation, or criterion – or their combination – is frequent and typical of MFS		
	High	Moderate	Low
History	MFS as a heritable triad of skeletal, ocular, and cardiovascular manifestations ⁷⁴	Dilatation and dissection of the descending aorta, MVP, PAD, Pneu, skin striae, DE	Calcification of the mitral valve annulus
Etiology and pathogenesis	Autosomal dominant inheritance, <i>FBNI</i> mutation as an exclusive cause of MFS ⁵⁵	Alteration of TGF- β 1 signaling ^{70–72,107}	CMN ^{108–110}
Diagnostic triggers	Wrist and thumb sign, ^{45,46} EL, FH of MFS, previous thoracic aortic surgery, pectus excavatum, history of Pneu, skin striae ^{48,111}	Body height in males \geq 1.90 m and in females \geq 1.78 m; previous surgery of the lens or of the spinal column ⁴⁸	MVP, PAD, joint hypermobility, hernia, ^{32,83} skeletal muscle myopathy, ¹¹² DE, ^{89,113,114} liver cysts, renal cysts, cholelithiasis ¹¹⁵
Prognostic triggers	AoDD ⁵	Thoracic/abdominal aortic dilatation, ¹¹⁶ MVP, ^{90,117} SDB, ^{20,21} myocardial dysfunction including increased NT-proBNP levels, ^{118–123} EL, myopia, apical pulmonary blebs ^{124,125}	PAD ¹²⁶ , skeletal malformations, ¹²⁷ osteopenia, ¹²⁸ DE ⁸⁹
Complications	Dissection or rupture of the ascending aorta, AR	Thoracic/abdominal aortic dissection or rupture, ^{129,130} MVR, ^{91,131} IE, HF, ¹³² SCD, ^{122,123,133} retinal detachment, glaucoma, amaurosis, ⁵¹ Pneu ¹³⁴	Rupture or dissection of MPA, ^{126,135} restrictive ventilatory defect, ¹³⁶ impaired cardiorespiratory function, ¹³⁷ lumbar or sacral radiculopathy, ¹³⁸ atlantoaxial or lumbar subluxation, ^{139,140} bone fractures, ¹²⁸ intrapelvic meningocele, ¹⁴¹ dural leak with postural headache, ¹⁴² bronchiectasis, ¹⁴³ recurrent or incisional hernia ^{32,144}

Abbreviations: MFS, Marfan syndrome; MVP, mitral valve prolapse; PAD, pulmonary artery dilatation; Pneu, pneumothorax; DE, dural ectasia; TGF- β 1, transforming growth factor-beta 1; CMN, cystic media necrosis; EL, ectopia lentis; FH, family history; AoDD, aortic diameter at the sinuses of Valsalva dilatation; SDB, sleep-disordered breathing; NT-proBNP, N-terminal probrain natriuretic peptide; AR, aortic valve regurgitation; MVR, mitral valve regurgitation; IE, infective endocarditis; HF, heart failure; SCD, sudden cardiac death; MPA, main pulmonary artery.

accordingly, descriptions of the history of MFS keep varying between authors. Nonetheless, some important lessons on the diagnosis of MFS may be derived from the analysis of history. First, initial descriptions of the syndrome relied on signs that can easily be observed, such as “spider-like” fingers and toes, chest wall deformities, and scoliosis. Accordingly, the syndrome was initially named after obvious presenting signs in the skeleton and musculature. Second, an essential step in the description of MFS was the description of major complications. Ironically, all early reports of such complications described atrial septal defects, patent ductus arteriosus, and aortic coarctation as congenital cardiovascular malformations of MFS, none of which are considered typical manifestations of MFS today. Third, ocular abnormalities, such as ectopic lenses, have been considered essential to the syndrome since their first description in 1912.^{52,53} Maumenee⁵⁴ even speculated that the ophthalmologist E Williams might have provided the first description of MFS with his report of familial occurrence of dislocated lenses as early as June 1875. Ectopia lentis might be a classical example for a diagnostic sign that is both specific for MFS and clinically relevant because it can restrict the quality of life and the autonomy of patients. Finally, the heredity of the syndrome was recognized relatively soon after its discovery, which underpins

the importance of the nature of a disease that affects whole families rather than isolated individuals.

Etiology and pathogenesis

Mutations in the *FBNI* gene are today considered the exclusive cause of MFS.⁵⁵ Mutations in other genes were excluded as causes of MFS. Nonetheless, *FBNI* mutation analysis has diagnostic limitations. First, a small portion of *FBNI* mutations remains undetected in persons with MFS, most likely because of technical limitations.⁵⁶ Second, databases identify more than 1,500 different disease-causative *FBNI* mutations, but there is no single *FBNI* genotype feature that qualifies as a reliable predictor of disease evolution.^{57,58} Third, in some rare circumstances, mutations can present with phenotypes that do not fulfill clinical criteria of MFS, such as children with a purely skeletal phenotype, Shprintzen–Goldberg syndrome, or Weill–Marchesani syndrome.^{56,59–61} Finally, an increasing number of nucleotide variants of the *FBNI* gene have uncertain clinical significance and these introduce new uncertainties.^{62,63}

FBNI mutations initiate pathogenetic cascades that result in various manifestations and complications of MFS. One pathogenetic mechanism is structural weakness of the tissue, which presents as marked and premature degeneration of the medial layer of the aortic wall.⁶⁴ However, these changes are not specific

Table 3 Historical perspective on advances in the diagnosis of MFS

Author	Year of publication	Feature	Comments
Initial description of the important features of MFS			
Marfan ^{145,146}	1896	New syndrome, “dolichosténomelié”	Description of a 5-year-old girl with multiple joint contractures, thoracolumbar kyphoscoliosis, and long, thin limbs and fingers and toes, which he called “spider-like”. Marfan termed the syndrome “dolichosténomelié”. As Behan noted, Marfan considered muscle involvement to be integral, with the small muscles “recalling atrophy”. ¹¹²
Achard ¹⁴⁷	1902	“Dolichosténomelié” renamed as “arachnodactyly”	Description of a patient with loose-jointedness of the hands, hypognathia, and dolichostenomelia. Achard described excessively slender and hypermobile fingers of normal length, which he called “arachnodactyly”.
Salle ¹⁴⁸	1912	Syndrome with	Salle described a 1.5-month-old patient with pulmonary systolic murmur, an enlarged heart, and persistent foramen ovale at autopsy. Piper and Irvine-Jones described a 1.75-year-old patient with arachnodactyly presenting with systolic thrill and patent foramen primum at autopsy. Apert described patent ductus arteriosus in a patient with MFS, and McKusick reported aortic coarctation in MFS.
Piper and Irvine-Jones ¹⁴⁹	1926	“congenital cardiovascular disease”	
Apert ¹⁵⁰	1938		
McKusick ¹⁵¹	1955		
Börger ⁵²	1914	Ectopia lentis and	Description of a 1-year-old female with dolichostenomelic habitus who exhibited luxation of the lenses, iridodonesis with enlarged cornea, and hydrophthalmos. According to Rados, ⁷⁴ Börger and von Pfaundler published the same patient. Börger reported a second patient, a 9-year-old boy with dolichostenomelic habitus who presented with severe iridodonesis and high-grade myopia (–16 diopters and –20 diopters).
von Pfaundler ⁵³	1914	high-grade myopia	
Weve ¹⁵²	1931	Autosomal dominant trait	Weve described the heritable nature of the condition and the primary involvement of tissue derived from embryonic mesoderm. He also associated Marfan’s name with the phenotype for the first time, and suggested the term “Dystrophia mesodermalis congenital, Typus Marfan”.
Jéquier ¹⁵³	1943	Pneumothorax	Description of a 38-year-old Marfan patient with spontaneous pneumothorax as a consequence of the rupture of a pulmonary cyst.
Baer et al ¹⁵⁴	1943	Aortic dilatation	Description of a 14-year-old and a 26-year-old arachnodactylic adult with sudden death who both exhibited aneurysm of the aorta at autopsy.
Etter and Glover ¹⁵⁵	1943	Aortic dissection	Description of a 21-year old man with ectopia lentis and arachnodactyly presenting with systolic and diastolic aortic murmur showing dissecting aneurysm with rupture into the pericardial sac, as well as aortic valve insufficiency at autopsy.
Tung and Liebow ¹⁵⁶	1952	Dilatation of the pulmonary artery	Description of idiopathic congenital dilatation of the pulmonary artery in an infant with MFS.
McKusick ¹⁵¹	1955	MFS as disorder of connective tissue	The initial description of MFS as a heritable disorder of connective tissue. This comprehensive description is today considered the first nosology of MFS.
Nelson ¹⁵⁷	1958	Widening of the spinal canal	Description of widening of the spinal canal with posterior scalloping of the vertebral bodies in four patients with MFS.
Kachele ¹⁵⁸	1960	Striae distensae	Description of striations in a Marfan patient as typical striae distensae elasticae. McKusick ¹⁵⁹ pointed out that the initial description of striae in MFS dates back to 1936.
Bowden et al ¹⁶⁰	1965	Mitral valve prolapse	Description of the patulous nature of the mitral valve and elongated chordae as the likely mechanics of mitral regurgitation where the elongated chordae may allow for prolapse of the valve leaflets into the left atrium in a Marfan patient.
Beals and Hecht ^{161,162}	1971	Congenital contractural arachnodactyly syndrome	Beals and Hecht described the congenital contractural arachnodactyly syndrome and proposed that this was the condition affecting Marfan’s original patient.
Dietz et al ¹⁵⁵	1991	Etiology of MFS	Description of a mutation in the <i>FBN1</i> gene as the cause of MFS.
History of targeted screening for MFS			
Steinberg ⁴⁵	1966	Thumb sign	Steinberg proposed the thumb sign as a simple, quick screening test to “truly distinguish lanky, thin persons who have spidery fingers, wear thick-lensed glasses, and who appear prematurely old” from those with MFS.
Walker and Murdoch ⁴⁶	1970	Wrist sign	Walker and Murdoch proposed the wrist sign as a complement to the thumb sign, which “when used together at the bedside provide useful confirmation of the skeletal disproportion which occurs in patients with the Marfan syndrome”. ⁴⁶
Mueller et al ⁴⁷	2013	The Kid-Short Marfan Score (Kid-SMS)	A simple clinical model to estimate the probability of MFS in children.
Sheikhzadeh et al ⁴⁸	2012	The “seven-signs” screening instrument for adults with MFS	A simple clinical model to estimate the probability of MFS in adults.

(Continued)

Table 3 (Continued)

Author	Year of publication	Feature	Comments
Early systematic reviews and international nosologies of MFS			
Rados ⁷⁴	1942	Review of Marfan patients published until 1940	Extensive case by case review and tabulation of Marfan patients published until 1940. The review includes a statistical survey of the literature, which includes 204 patients (101 males, 103 females) with detailed clinical information including manifestations and outcomes.
McKusick ¹⁶³	1956	Review of MFS phenotype	First report that might be considered an early nosology of MFS.
Beighton et al ¹⁶⁴	1988	First international nosology	The so-called Berlin nosology was the first international nosology of heritable disorders of the connective tissues.
De Paepe et al ⁷⁶	1996	Second international nosology	The so-called Ghent nosology was the revision of the Berlin nosology of heritable disorders of connective tissue. This nosology was the first to consider genetic data as diagnostic criteria.
Loeys et al ⁷⁹	2010	Third international nosology	The so-called revised Ghent nosology was the revision of the initial Ghent nosology for MFS.

Abbreviation: MFS, Marfan syndrome.

to MFS and in clinical practice, they can only be diagnosed with invasive methods.⁶⁵ Indirect measurements of arterial stiffness parameters like pulse wave velocity or augmentation index can predict progression of aortic disease in MFS, but again this is not specific for MFS.^{66–69} Another major pathogenetic mechanism is the dysregulation of TGF- β 1 that has a causal role in the evolution of various features of the Marfan. The causal role of TGF- β 1 for the phenotypic features of MFS was identified in a mouse model, and humans with MFS exhibit increased serum levels of TGF- β 1, which decrease with successful treatment of aortic disease with BAB, angiotensin-receptor blockers, or angiotensin-converting enzyme inhibitors.^{18,70–72} However, such increases of TGF- β 1 levels are not specific for aortic disease, but rather relate to the cumulative severity of organ involvement in MFS.⁷³ Moreover, increased TGF- β 1 serum levels are not specific to MFS, but they also occur in bicuspid aortic valve disease or Loeys–Dietz syndrome.⁷³ In summary, exclusive *FBNI* mutations currently qualify as the sensitive and specific causative or pathogenetic criteria of MFS.

Diagnostic triggers

In a series of 329 adults, general practitioners gave the following signs and manifestations as reasons for referral for diagnostic clarification of suspected MFS: a family history of Marfan features in 24%, aortic aneurysm or dissection both in 24%; skeletal features in 22%; MFS diagnosed in childhood in 10%; eye manifestations in 9%; miscellaneous reasons in 4%; nonaortic cardiovascular findings in 3%; and a history of pneumothorax, tissue weakness, and hypermobility in 2%. These reasons for referral reflect the perception of MFS as a familial disease of the aorta, which can be recognized

through the presence of skeletal features and typical eye manifestations. Indeed, this perception is in accord with the time-honored historical descriptions of MFS. Interestingly, however, the percentage of confirmation of MFS was highest in persons who were referred for MFS already diagnosed in childhood (88%), for eye manifestations (83%), for a family history of Marfan features (52%), and for aortic aneurysm or dissection (50%). Conversely, the percentage of confirmation of MFS was low in persons who were referred for pneumothorax (43%), skeletal features (30%), tissue weakness and hypermobility (14%), and nonaortic cardiovascular findings in none.⁴⁸ In particular, tall stature, scoliosis, or joint hypermobility seem to be perceived as typical features of MFS. However, MFS was rarely confirmed in persons in whom MFS was suspected because of the presence of these signs.⁴⁸

Table 3 highlights that very early in the history of MFS, clinicians felt the need to find methods that helped to rapidly and specifically identify persons with MFS in the general population. In 1966, Steinberg was the first to propose the thumb sign as a simple, quick screening test – as he put it – to truly distinguish lanky, thin persons who have spidery fingers, wear thick-lensed glasses, and appear prematurely old from those with MFS.⁴⁵ Since then, three other tools for targeted screening have been proposed to rapidly identify suspects of MFS based on a simple history and clinical signs (Figure 2).^{45–48}

Finally, Table 3 provides a brief history of early systematic reviews and nosologies of MFS that had a major impact on the diagnosis and recognition of the syndrome. It is remarkable that as early as 1942, Rados⁷⁴ performed a

systematic review of 204 patients published in the literature (101 males, 103 females), in which he described MFS as a heritable disease with a triad of skeletal, ocular, and cardiovascular manifestations. Since then, it has not been possible to identify a single definitive criterion to prove or refute MFS. Rather, common efforts were necessary to define an international consensus on the rules of how to diagnose MFS.

Prognostic triggers and complications

The risk for aortic dissection and rupture increases with growth of the aortic diameter, and hence the dilatation of the aortic root is a highly important prognostic trigger in MFS.⁷⁵ However, other manifestations of MFS can also trigger complications: dilatation of the thoracic or abdominal aorta and sleep-disordered breathing can lead to dissection or rupture; mitral valve prolapse to severe insufficiency or infective endocarditis; myocardial dysfunction to heart failure or sudden cardiac death; ectopia lentis or myopia to retinal detachment, glaucoma, or amaurosis; and apical pulmonary blebs to pneumothorax. Similarly, in some rare instances, dilatation of the main pulmonary artery can lead to dissection or rupture; skeletal malformations to impaired cardiorespiratory function, radiculopathy, or atlantoaxial or lumbal subluxation; osteopenia to fractures; and dural ectasia to intrapelvic meningocele and to dural leak with postural headache (Table 2).

The Ghent nosology (Ghent-1)

The first Ghent nosology was introduced in 1996 (Ghent-1), and it presented the revision of the criteria of the first international nosology, the so-called Berlin nosology (Table 4). In essence, Ghent-1 was the response to the new insights gained from the discovery of *FBNI* gene mutations as the etiology of MFS.⁷⁶ The authors of the Ghent-1 nosology specified as reasons for their new nosology that the Berlin nosology relied completely on clinical criteria, and that the MFS phenotype had to be better separated from normal variation and from mild connective tissue phenotypes, 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).⁷⁶ Of greatest concern were the misdiagnoses of relatives that arose by relying solely on the Berlin nosology after unequivocal diagnosis in a first-degree relative. Molecular evidence had shown that the criterion of a positive family history could produce a bias in favor of overdiagnosis. Accordingly, the authors stated as the most notable revisions the formulation of more stringent

requirements for the diagnosis of MFS in relatives of an unequivocally affected individual; greater diagnostic weight on skeletal involvement, which constituted a major criterion if at least four of eight typical skeletal manifestations were present; contribution of molecular analysis, which the authors wanted neither to ignore nor to overemphasize; and delineation of the initial criteria for the diagnosis of other heritable conditions with partially overlapping phenotypes. The authors identified the diagnostic relevance of molecular data, especially in situations where clinical information concerning a relevant first-degree relative was unavailable, and both clinical and genotype data were available on a second-degree or more distant relative(s). On the other hand, they argued that since methods for the characterization of mutations in *FBNI* were not entirely sensitive, and that the possibility of locus heterogeneity could not be completely ruled out, the inability to define an *FBNI* mutation or the stringent documentation of recombination between *FBNI* and the MFS phenotype did not constitute exclusion criteria.

Table 4 provides the entire list of criteria of MFS according to the Berlin and Ghent-1 nosologies. Ghent-1 mentions six organ systems with diagnostic relevance for MFS. For each of these organ systems, the nosology provides lists of manifestations that alone or in combination constitute major or minor criteria for MFS. In each organ system, the nosology distinguished between fulfillment of a major criterion, fulfillment of a minor criterion, and involvement of an organ system, where the combination of manifestations from the list of major criteria and from the list of minor criteria, or only from one of both lists was required. In addition, in the list of minor criteria of the skeletal system, three of five facial signs had to be present to fulfill one item in the list of minor criteria. For a final diagnosis, Ghent-1 distinguished between two diagnostic scenarios. First, for the index case: if the family or genetic history was not contributory, major criteria in at least two different organ systems and involvement of a third organ system were required for the diagnosis. If an *FBNI* mutation known to cause MFS in others was detected, one major criterion in one organ system and involvement of a second organ system were required. Second, for a relative of an index case: The presence of a major criterion in the family history and one major criterion in an organ system, as well as involvement of a second organ system were required (Table 4).⁷⁶

Two studies compared the diagnostic performance of the Berlin and Ghent-1 nosology. The first study was only published as an abstract, and it found that 60 of 104 (58%) patients evaluated for suspected MFS were diagnosed as

Table 4 Comparison of the diagnostic criteria of MFS according to the Berlin versus Ghent-I nosology

Berlin nosology	Ghent-I nosology
Skeletal manifestations	Skeletal system – major criterion (≥ 4 of the major criteria from the following list):
Anterior chest deformity, especially asymmetric pectus excavatum/carinatum	Pectus carinatum
Dolichostenomelia not due to scoliosis or tall stature, especially when compared to unaffected first-degree relatives	Pectus excavatum that requires surgery
Arachnodactyly	Upper-to-lower-segment ratio < 0.85 or arm span-to-height ratio > 1.05
Vertebral column deformity: scoliosis; thoracic lordosis; or reduced thoracic kyphosis	Positive wrist and thumb sign
Protrusio acetabulae	Medial displacement of the medial malleolus causing pes planus
	Scoliosis $> 20^\circ$ or spondylolisthesis
	Extension at elbows $< 170^\circ$
	Protrusio acetabuli of any degree
	Skeletal system – minor criteria (skeletal involvement with two of the major criteria or one of the major and two of the minor criteria)
	Pectus excavatum not requiring surgery
	Joint hypermobility
Abnormal appendicular joint mobility: congenital flexion contractures; hypermobility	High-arched palate with crowding of teeth
High, narrowly arched palate and dental crowding	Facial features (3/5): dolichocephaly; enophthalmos; downslanting palpebral fissures; malar hypoplasia; retrognathia
Ocular manifestations	Ocular system – major criterion
Ectopia lentis*	Ectopia lentis of any degree
	Ocular system – minor criteria (ocular involvement with ≥ 2 minor criteria):
Flat cornea	Flat cornea
Elongated globe, retinal detachment, myopia	Increased axial length of the globe (> 23.5 mm)
	Hypoplastic ciliary muscle causing decreased miosis
Cardiovascular manifestations	Cardiovascular system – major criteria
Dilatation of the ascending aorta*	Aneurysm of the ascending aorta involving at least the sinuses of Valsalva
Aortic dissection,* aortic regurgitation	Dissection of the ascending aorta
	Cardiovascular system – minor criteria (cardiovascular involvement with one major or ≥ 1 minor criterion)
Mitral regurgitation due to mitral valve prolapse, mitral valve prolapse	Mitral valve prolapse (irrespective of mitral regurgitation)
	Dilatation of the main pulmonary artery < 40 years of age (unassociated with pulmonic stenosis)
Calcification of the mitral annulus	Calcification of the mitral annulus < 40 years of age
Abdominal aortic aneurysm; dysrhythmia; endocarditis	Dilatation or dissection of the descending thoracic or abdominal aorta < 50 years of age
Pulmonary manifestations	Pulmonary system – minor criteria (pulmonary involvement with ≥ 1 minor criteria)
Spontaneous pneumothorax	Spontaneous pneumothorax
Apical bleb	Apical blebs (radiography)
Skin and integument	Skin and integument – minor criteria (skin and integumental involvement with ≥ 1 minor criteria)
Striae distensae	Striae distensae
Inguinal hernia, other hernia (umbilical, diaphragmatic, incisional)	Recurrent or incisional hernia
Central nervous system manifestations	Dura: major criterion
Dural ectasia,* lumbosacral meningocele, dilated cisterna magna, learning disability (verbal performance discrepancy), hyperactivity with or without attention deficit disorder	Lumbosacral dural ectasia
Genetics	Family and genetic history (present with ≥ 1 major criterion)
Autosomal dominant inheritance	First-degree relative who independently meets the Marfan criteria
25%–30% of cases are sporadic; paternal age effect	Mutation in <i>FBNI</i> known to cause MFS
	Haplotype around the <i>FBNI</i> locus inherited via descent and is unequivocally associated with a diagnosed Marfan in the family

(Continued)

Table 4 (Continued)

Requirements for diagnosis	Requirements for diagnosis
In the absence of an unequivocally affected first-degree relative: involvement of the skeleton and at least two other systems; at least one major manifestation. In the presence of at least one unequivocally affected first-degree relative: involvement of at least two systems; at least one major manifestation preferred, but this will depend somewhat on the family's phenotype.	For the index case: if the family/genetic history is not contributory, then major criteria in at least two different organ systems and involvement of a third organ system. If a mutation known to cause MFS in others is detected, then one major criterion in an organ system and involvement of a second organ system. For a relative of an index case: the presence of a major criterion in the family history, as well as one major criterion in an organ system and involvement of a second organ system.

Notes: Berlin nosology: *major diagnostic manifestations. Data from Beighton et al.¹⁶⁴ Ghent-1 nosology: distinction between a major criterion and the organ system "being involved", which is less important than a major criterion. Data from De Paepe et al.⁷⁶

Abbreviation: MFS, Marfan syndrome.

having MFS according to the Berlin nosology, of whom only 33 (32%) patients were confirmed by Ghent-1.⁷⁷ The second study found that 48 of 73 (66%) patients (aged 1 month to 62 years) evaluated for suspected MFS were diagnosed as having MFS according to the Berlin nosology, of whom only 39 (53%) patients were confirmed by Ghent-1.⁷⁸ Both studies, however, did not screen for *FBNI* mutations in those 45% and 19% of patients who met the Berlin, but not the Ghent-1, criteria, respectively. The authors of the first study raised the concern that using the Ghent-1 criteria "in patient care [meant that] under-diagnosing is replacing over-diagnosing".⁷⁷ Conversely, the authors of the second study concluded that Ghent-1 appropriately excluded some patients, but that further long-term follow-up or reliable molecular diagnostic techniques were necessary to establish the relative sensitivity and specificity of the Berlin and Ghent criteria.⁷⁸

In summary, Ghent-1 proposed more stringent clinical criteria that led to confirmation of MFS by Ghent-1 in only 32% and 53% of patients in the two studies available who had previously been diagnosed of MFS according to the Berlin nosology.

The revised Ghent nosology (Ghent-2)

The revised version of the Ghent nosology was introduced in 2010 (Ghent-2).⁷⁹ The authors of the Ghent-2 nosology listed the following as aims of the revision: first, identification of patients with a risk for aortic aneurysm or dissection; second, simplicity of use of diagnostic criteria; third, allowance for early diagnosis; fourth, consideration of availability and costs of diagnostic tests; fifth, better definition of entities such as familial ectopia lentis, the MASS phenotype, and MVPS; and, finally, delineation of triggers for alternative diagnoses such as Loeys–Dietz syndrome.⁷⁹ The authors

listed five major changes, which comprised the following: 1) more diagnostic weight on aortic root aneurysm or dissection and ectopia lentis; 2) a more prominent role of molecular genetic testing; 3) complete removal of some clinical criteria, such as dilatation of the main pulmonary artery, dilatation or dissection of the descending thoracic or abdominal aorta, increased axial length of the globe and abnormally flat cornea, hypoplastic iris or hypoplastic ciliary muscle causing decreased miosis, joint hypermobility, spondylolisthesis, highly arched palate, and recurrent or incisional herniae, calcification of the mitral annulus, apical blebs of the lung, or mitigation of the diagnostic relevance of dural ectasia, or adding or modifying clinical criteria such as myopia >−3 diopters, hindfoot valgus, and thoracolumbar kyphosis; 4) provision of discriminating features of alternative diagnoses such as Loeys–Dietz syndrome; and 5) provision of context-specific recommendations for patient counseling and follow-up.⁷⁹

Table 5 provides the entire list of criteria of MFS according to Ghent-2. In brief, in the absence of a family history of MFS, MFS is diagnosed in the presence of aortic root dilatation combined with ectopia lentis, or a causative *FBNI* mutation, or a systemic score ≥ 7 points, or with the combination of ectopia lentis with an *FBNI* mutation known to cause aortic dilatation. In the presence of a family history, MFS is diagnosed with the demonstration of ectopia lentis, or a systemic score ≥ 7 points, or aortic root dilatation (Z -scores ≥ 2 standard deviations [SD] above the mean with an age above 20 years, or Z -scores ≥ 3 SD above the mean with an age below 20 years).

Table 6 lists five studies that performed a direct comparison of the diagnostic performance of Ghent-1 and Ghent-2.^{80–84} Faivre et al⁸⁰ concluded that if Ghent-2 criteria were applied with common sense and flexibility, they should help and support clinicians who are less experienced with the MFS phenotype.

Table 5 Diagnostic criteria of MFS according to the Ghent-2 nosology**In the absence of family history:**

1. Aortic root diameter (Z-score ≥ 2) and ectopia lentis = MFS*
2. Aortic root diameter (Z-score ≥ 2) and causal *FBNI* mutation = MFS
3. Aortic root diameter (Z-score ≥ 2) and systemic score ≥ 7 points = MFS*
4. Ectopia lentis and causal *FBNI* mutation with known aortic root dilatation = MFS

In the presence of family history:

5. Ectopia lentis and family history of MFS (as defined above) = MFS
6. Systemic score ≥ 7 points and family history of MFS (as defined above) = MFS*
7. Aortic root diameter (Z-score ≥ 2 above 20 years old, ≥ 3 below 20 years) and family history of MFS (as defined above) = MFS*

*Caveat: without discriminating features of Shprintzen–Goldberg syndrome, Loeys–Dietz syndrome or vascular form of Ehlers–Danlos syndrome AND after *TGFBR1/2*, collagen biochemistry, *COL3A1* testing if indicated.

Scoring of systemic features of MFS

1. Wrist and thumb sign – 3 points (wrist or thumb sign – 1 point)
2. Pectus carinatum deformity – 2 points (pectus excavatum or chest asymmetry – point)
3. Hindfoot deformity – 2 points (plain pes planus – 1 point)
4. Protrusio acetabuli – 2 points
5. Reduced upper segment/lower body segment ratio and increased arm/height and no severe scoliosis – 1 point
6. Scoliosis or thoracolumbar kyphosis – 1 point
7. Reduced elbow extension – 1 point
8. Facial features (3/5) – 1 point (dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia)
9. Pneumothorax – 2 points
10. Skin striae – 1 point
11. Myopia >3 diopters – 1 point
12. Mitral valve prolapse (all types) – 1 point
13. Dural ectasia – 2 points

The systemic features number 1–13 are used for the systemic score in the Ghent-2 nosology, where a maximum total score points of 20 points can be obtained. We number the systemic features as 1–8 and address these as “skeletal score”, and the systemic features as 9–12 and address these as “non-skeletal score”.⁷³

Note: Copyright © 2010. BMJ Publishing Group Ltd. Reproduced from Loeys BL, Dietz HC, Braverman AC, et al. The revised Ghent nosology for the Marfan syndrome. *J Med Genet.* 2010;47(7):476–485.⁷⁹

Abbreviation: MFS, Marfan syndrome.

They recommended regular aortic follow-up in every patient with a diagnosis of ELS, MASS, or MVPS who does not reach the diagnosis of MFS. Radonic et al⁸¹ found that the calculation of Z-scores according to the Ghent-2 criteria underestimated aortic root dilatation, especially in patients with a large body surface area, a problem that was fixed by the subsequent publication of improved nomograms.^{85–87} Aalberts et al⁸² found that Ghent-2 led to a significant increase in the number of non-MFS diagnoses, which he found was due to lowering of the diagnostic threshold of MVPS. In addition, the authors concluded that Ghent-2 afforded a more straightforward diagnosis of MFS. Sheikhzadeh et al⁸³ found that the Ghent-1 criteria were useful when no genotyping was available, but that when gene sequencing is available, Ghent-2 could be assessed more easily and more rapidly than Ghent-1. Finally, Yang et al⁸⁴ reported that almost all the adult Korean patients who fulfilled the Ghent-1 criteria also fulfilled the Ghent-2 criteria.

Table 6 summarizes the Ghent-1 and Ghent-2 diagnoses of MFS in relation to the presence or absence of a causative *FBNI* mutation. When not considering both early studies of the Ghent criteria, which exclusively included patients with *FBNI* mutations and MFS, or with the *FBNI* mutation MFS-like

phenotype, our analysis documented that the Ghent-1 and Ghent-2 nosologies both yielded similar frequencies of MFS in persons with a causative *FBNI* mutation (90% versus 92%) and in persons not having a causative *FBNI* mutation (15% versus 13%).^{80,81} The study by Sheikhzadeh et al⁸³ documented that 245 of 300 persons with suspected MFS had an identical likelihood of exclusion or confirmation of MFS with both nosologies (82%). Table 7 illustrates the diagnostic yield of Ghent-1 and Ghent-2 in studies of patients evaluated for suspected MFS, where MFS was diagnosed in 34% versus 35%, other syndromes in 26% versus 28%, and where no definitive diagnosis could be established in 40% versus 38%. Interestingly, only the proportion of diagnoses differed across the three studies, but not the results between Ghent-1 and Ghent-2. In summary, the review of the literature illustrates a similar diagnostic performance of Ghent-1 and Ghent-2 nosologies.

Prospects for reducing the inaccurate diagnoses of MFS

Classical criteria to estimate the quality of diagnosis comprise objectivity, reliability, and validity (Figure 1B). The diagnosis of MFS will be objective when diagnostic tests

Table 6 Comparison of diagnosis of MFS according to Ghent-1 versus Ghent-2

Study	FBN1 mutation	Ghent-1		Ghent-2	
		MFS diagnosed	MFS not diagnosed	MFS diagnosed	MFS not diagnosed
Faivre et al ⁸⁰					
Design and patients	1,009 patients with <i>FBN1</i> mutation and phenotype compatible with type I fibrillinopathy, with reevaluated according to Ghent-2. A total of 54% were male, median age of 20 years (range: birth–72 years).				
Presence of <i>FBN1</i> mutation	1,009	894/1,009 (89%)	115/1,009 (11%)	842/1,009 (83%)	167/1,009 (17%)
Radonic et al ⁸¹					
Design and patients	180 adults with MFS according to Ghent-1 were reevaluated according to Ghent-2. A total of 53% were male, mean age of 37 years (range 18–62 years).				
Presence of <i>FBN1</i> mutation	180			164/180 (91%)	16/180 (9%)
Aalberts et al ⁸²					
Design and patients	343 adults with suspected MFS. A total of 51% were male, mean age of 40±14 years.				
Presence of <i>FBN1</i> mutation	45	34/45 (76%)	11/45 (24%)	36/45 (80%)	9/45 (20%)
Absence of <i>FBN1</i> mutation	95	10/95 (11%)	85/95 (89%)	9/95 (9%)	86/95 (91%)
Sheikhzadeh et al ⁸³					
Design and patients	300 adults with suspected MFS. A total of 50% were male, mean age of 35±13 years (range 16–69 years).				
Presence of <i>FBN1</i> mutation	140	126/140 (90%)	14/140 (10%)	128*/140 (89%)	12/140 (9%)
Absence of <i>FBN1</i> mutation	160	21/160 (13%)	139/160 (87%)	19/160 (12%)	141/160 (88%)
Yang et al ⁸⁴					
Design and patients	106 adults with suspected MFS, all with genetic analysis of <i>FBN1</i> . A total of 57% were male, median age of 36 years (range 20–69 years).				
Presence of <i>FBN1</i> mutation	74	74/74 (100%)	0	74/74 (100%)	0
Absence of <i>FBN1</i> mutation	32	12/32 (38%)	20/32 (63%)	10/32 (31%)	22/32 (69%)
Sum					
All <i>FBN1</i> mutations	1,268	1,128/1,268 (89%)	140/1,268 (7%)	1,082/1,268 (85%)	188/1,268 (15%)
<i>FBN1</i> mutations only in studies with suspected MFS	295	234/295 (90%)	25/295 (10%)	238/295 (92%)	21/295 (8%)
Absence of <i>FBN1</i> mutation	287	43/287 (15%)	244/287 (85%)	38/287 (13%)	249/287 (87%)

Note: *Including three patients with “potential MFS”.

Abbreviation: MFS, Marfan syndrome.

can be performed, analyzed, and interpreted in a standardized fashion that is independent of the individual clinician performing the analysis. Ghent-2 formulates diagnostic rules that are simpler and require both less diagnostic testing and less clinical expertise than Ghent-1. Similarly, Ghent-2 discards some “subjective qualifiers” of diagnostic features, and

Table 7 Diagnostic yield in suspected MFS according to Ghent-1 versus Ghent-2

Study	MFS	Other syndromes	No definitive diagnosis
Aalberts et al⁸²			
Ghent-1	44/343 (13%)	96/343 (34%)	203/343 (59%)
Ghent-2	47/343 (14%)	118/343 (34%)	178/343 (52%)
Sheikhzadeh et al⁸³			
Ghent-1	126/300 (42%)	90/300 (30%)	84/300 (28%)
Ghent-2	128/300 (43%)	80/300 (27%)	92/300 (31%)
Yang et al⁸⁴			
Ghent-1	86/106 (81%)	6/106 (6%)	14/106 (14%)
Ghent-2	84/106 (79%)	8/106 (8%)	14/106 (15%)
All studies			
Ghent-1	256/749 (34%)	192/749 (26%)	301/749 (40%)
Ghent-2	259/749 (35%)	206/749 (28%)	284/749 (38%)

Abbreviation: MFS, Marfan syndrome.

it introduces criteria for causality of *FBN1* mutations. These changes indeed are likely to enhance objectivity. In contrast, Ghent-2 does not specify which of the many criteria for mitral valve prolapse and dural ectasia should be used for diagnosing MFS.^{88–91} This may have a negative impact on objectivity when assessing these signs, especially when clinicians use different criteria in the same patient. However, mitral valve prolapse and dural ectasia are features of the systemic score that only have a minor impact on the diagnosis of MFS.⁸⁰ Altogether, therefore, the objectivity of Ghent-2 is likely to be higher than that of Ghent-1.

Clearly, objectivity is a prerequisite, but it may not necessarily lead to improved reliability. Until today, there is no study that compares intrasubject, intraobserver, and interobserver variation in the application of the Ghent-1 and Ghent-2 criteria. However, the overall diagnostic yield of MFS and alternative diagnoses is similar with both nosologies, which may argue for similar reliability (Table 7). However, there is no evidence that Ghent-2 has actually improved diagnostic reliability.

Finally, the diagnosis of MFS will be valid when MFS is correctly identified or excluded. However, to estimate

the validity of the Ghent-1 or Ghent-2 criteria, we need an external diagnostic reference standard, which determines the “true” presence or absence of MFS, and would allow the sensitivity and specificity of nosologies to be calculated.⁹² The defining criteria of a disease include etiology or clinical characteristics that allow for a clear delineation of the disease from both other diseases and the healthy population.^{56,59–61} Similarly, none of the clinical characteristics of MFS mark a clear boundary to normality or to other diseases (Table 7), and none of the clinical signs of MFS is sufficient to prove or exclude MFS with both a sufficiently high positive likelihood ratio (>10) and a sufficiently low negative likelihood ratio (<0.1).³² Thus, there is no external diagnostic reference standard of MFS and, hence, there is no stringent way to assess diagnostic validity by measuring the sensitivity, specificity, or accuracy of the Ghent-1 and Ghent-2 nosology.⁹³

In summary, the quality of diagnostic criteria of a specific nosology comprises objectivity, reliability, and validity, which have not been assessed in Ghent-1 or Ghent-2. Most notably, a nosology-based diagnosis of MFS lacks a diagnostic reference standard, and hence its sensitivity, specificity, or accuracy cannot be measured.

Perspectives from the clinic

The clinical perspective may be discussed in terms of the utility of the Ghent nosologies. In addition to objectivity, reliability, and validity, the utility of diagnostic criteria has not been described uniformly. However, the idea that all concepts have in common is to assess the usefulness of the criteria for doctors, patients, and other persons or groups. Whereas validity is an invariant and dichotomous quality of a diagnostic category, utility is gradable and context-dependent.⁹⁴ Based on the bio–social–psychological model of medicine, we will discuss the medical, social, and psychological dimension of the utility of diagnostic criteria using the example of the Ghent nosologies.⁹⁵

Medical utility

The diagnosis of MFS should provide information that is congruent with the historical criteria of MFS; and that informs about the etiology, pathogenesis, diagnostic triggers, prognostic triggers, and potential complications (Table 2). All these pieces of information together guide therapeutic decisions. Ideally, a single, easy, and quickly assessable criterion establishes the diagnosis of MFS which, at the same time, comprises all five types of information. As discussed earlier, this is not possible for MFS and, hence, diagnostic criteria compromise between feasibility and comprehensiveness. For

instance, in contrast to Ghent-1, the Ghent-2 nosology does not list all diagnostic triggers. Indeed, this may not be necessary, because tests for targeted screening for MFS are available, and these may be used for the purpose of identifying patients in the general population (Table 3 and Figure 2).^{45–48} Similarly, dural ectasia and mitral valve prolapse have a high prevalence in MFS and they may give rise to complications. However, there are many other manifestations of MFS that can also cause complications, and these prognostic triggers need monitoring once the diagnosis of MFS is established (Table 2). In conclusion, the Ghent-2 nosology focused on establishing the diagnosis of MFS easily and quickly. Accordingly, Ghent-2 lists much fewer diagnostic criteria of MFS than does Ghent-1. At the same time, the diagnostic results are astonishingly congruent with the historical Ghent-2 criteria.

Molecular analysis of the *FBNI* gene can significantly reduce diagnostic uncertainty in suspected MFS. In Table 8, we analyze how *FBNI* analysis improves the diagnosis of MFS according to Ghent-2 criteria. First, in the absence of a family history of MFS, all diagnostic scenarios (1–5) with the isolated or combined presence of aortic root dilatation, ectopia lentis, or systemic score points ≥ 7 allow one to establish the diagnosis of MFS when a causative *FBNI* mutation is present. Even in patients with a MASS phenotype or with isolated ectopia lentis, the presence of an *FBNI* mutation indicates the possibility that the phenotypes progress towards MFS during follow-up.^{32,96} Exclusion of an *FBNI* mutation also yields a significant gain of diagnostic certainty in all five scenarios, where the presence of alternative diseases becomes very likely (scenarios 1–3) or where MFS can at least be excluded with a higher degree of certainty (scenarios 4 and 5). In contrast, when the *FBNI* gene is not analyzed, all diagnostic scenarios require extensive clinical and molecular analyses of many alternative syndromes (scenarios 1–3), or these scenarios remain diagnostically uncertain (scenarios 4 and 5). Second, Ghent-2 allows for the diagnosis of MFS with the isolated presence of ectopia lentis, systemic score points ≥ 7 , or aortic root dilatation in all individuals with the presence of a family history of MFS (scenarios 6–8). However, when the *FBNI* mutation status is unknown in the entire family with MFS, then the diagnostic uncertainty about MFS may remain as illustrated in scenarios 1–5. In contrast, when an *FBNI* mutation is known, the family diagnosis of MFS is possible in all diagnostic scenarios (6–8), even without demonstrating the *FBNI* mutation known in the family. However, testing for a specific nucleotide change in the *FBNI* gene can be done with minimum of effort, time, and money,

Table 8 Analysis of how *FBNI* mutation status impacts the diagnosis of MFS according to current Ghent-2 diagnostic criteria

In the absence of FH	<i>FBNI</i> mutation present	<i>FBNI</i> unknown	<i>FBNI</i> mutation absent*
1. AoDD + EL	MFS	MFS after exclusion of SGS, LDS, vEDS	MFS after exclusion of SGS, LDS, vEDS
2. AoDD + Syst ≥ 7 points	MFS	MFS after exclusion of SGS, LDS, vEDS	
3. AoDD	MFS	MFS or other GAS	Other GAS
4. EL	MFS [†]	Uncertain	No MFS
5. Syst ≥ 7 points [‡]	MFS	Uncertain	No MFS
In the presence of FH	<i>FBNI</i> present in family and in subject	<i>FBNI</i> not assessed in family and in subject	<i>FBNI</i> present in family, but not assessed in subject
6. EL	MFS	Uncertain	MFS
7. Syst ≥ 7 points	MFS	Uncertain	MFS
8. AoDD	MFS	Uncertain	MFS if Z ≥ 2 above 20 years old, ≥ 2 below 20 years

Notes: **FBNI* gene is sequenced without showing a mutation; [†]with *FBNI* mutation known to cause AoDD; [‡]this diagnostic scenario is not addressed in the Ghent-2 nosology.

Abbreviations: MFS, Marfan syndrome; AoDD, aortic diameter at the sinuses of Valsalva dilated ≥ 2 Z-scores or aortic root dissection; EL, ectopia lentis; SGS, Shprintzen–Goldberg syndrome; LDS, Loeys–Dietz syndrome; vEDS, vascular form of Ehlers–Danlos syndrome; Syst, systemic score; GAS, genetic aortic syndrome; FH, family history of Marfan syndrome.

and these may be spent well, especially in subjects with an incomplete MFS phenotype (Table 8).

The definitive diagnosis of a specific genetic syndrome implies that there are different therapeutic approaches even to highly relevant manifestations, such as aortic root disease.^{75,93} Hence, one should avoid relying on a solely clinical diagnosis of MFS.^{97,98} Whenever MFS remains uncertain or diagnostic triggers of other diseases are observed, phenotypes should be explained by the presence of alternative syndromes, such as Loeys–Dietz syndrome. Ghent-2 clearly encourages the exclusion of related syndromes through clinical evaluation, as well as through molecular mutation analysis, and hence it may improve the guidance of therapy.⁹³

Social utility

Second, the social utility of the diagnostic criteria of MFS implies their acceptance by patients, patient organizations, the scientific community, doctors, hospital managers, and politicians. Thus, issues such as social labeling, identification with traditions, consistency with historical perceptions of MFS, scientific appropriateness, practicability, organizational needs, costs, social values, norms, and ethics come into play. Interestingly, both Ghent nosologies address most of these issues, however with a different emphasis. Ghent-2 mentions issues such as practicability and costs of diagnostics, consistency with historical perceptions of MFS, and consequences of misdiagnosis, such as restriction of career choices or access to insurance benefits, financial burden through frequent medical care, unfounded marital or reproductive decisions, and psychosocial stigmatization. The costs of clinical diagnostics based on Ghent-1 nosology for an outpatient visit in Germany are €389 per year.⁹⁹ Conversely, in Germany, the costs for conventional sequencing of the *FBNI* gene are over €4,000,

and these costs cannot be outweighed by a reduction in the clinical workup, as encouraged by Ghent-2.^{100,101}

Psychological utility

Third, for patients, the psychological utility of the diagnostic criteria of MFS may imply a reduction of uncertainty, a mitigation of anxiety related to this uncertainty, and identification with a disease that has its own history; it also offers harborage for a community of patients, researchers, and doctors.¹⁰² It may be important that the consensus process of nosology revision is a real joint effort that involves the entire community of patient organizations, researchers, and expert clinicians. In the absence of an absolute truth, the German sociologist Niklas Luhmann suggested legitimation by procedure.¹⁰³ For the quality and credibility of nosology criteria, rules of their development may be followed that are similar to those for official treatment guidelines, which may imply involvement of experts from all countries with Marfan centers, transparency of the process of expert selection, discussion, consensus, and disclosure of conflicts of interests.¹⁰⁴

In summary, in contrast to the reliability of diagnostic criteria, which is invariant and dichotomous, the utility of diagnostic criteria is graded and context-dependent. Hence, the task of optimizing the utility of diagnostic criteria can be maximized only through negotiation, compromise, and consensus (Figure 1C).^{105,106} Since utility depends on context, prioritization of the various diagnostic rules remains an issue of strategic decision making.

Conclusion

Screening tests for MFS should be used to identify persons with MFS. The Ghent-1 and Ghent-2 nosologies perform similarly, but Ghent-2 is much easier to use. Both

nosologies are formal rules that may have to be applied “with common sense and flexibility”, as Faivre et al⁸⁰ have put it. We believe that one should not rely on a purely clinical diagnosis of MFS, but rather call for a molecular confirmation of MFS or alternative diagnoses. Similarly, regular aortic follow-up may be warranted in patients with a diagnosis of ectopia lentis syndrome, MASS phenotype, or MVPS.⁸⁰ Finally, to maximize the utility of diagnostic rules, a fair and transparent process of their development is essential.

Disclosure

The authors report no conflicts of interest in this work.

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