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*Published in:*  
 American Journal of Medical Genetics. Part A

*DOI:*  
[10.1002/ajmg.a.35343](https://doi.org/10.1002/ajmg.a.35343)

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*Document Version*  
 Publisher's PDF, also known as Version of record

*Publication date:*  
 2012

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Aalberts, J. J. J., Thio, C. H. L., Schuurman, A. G., van Langen, I. M., van der Pol, B. A. E., van Tintel, J. P., & van den Berg, M. P. (2012). Diagnostic yield in adults screened at the marfan outpatient clinic using the 1996 and 2010 ghent nosologies. *American Journal of Medical Genetics. Part A*, 158A(5), 982-988. <https://doi.org/10.1002/ajmg.a.35343>

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# Diagnostic Yield in Adults Screened at the Marfan Outpatient Clinic Using the 1996 and 2010 Ghent Nosologies

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Received 28 April 2011; Accepted 12 January 2012

Marfan syndrome (MFS) is diagnosed according to the Ghent nosology, which has recently been revised. In the Netherlands, evaluation for possible MFS is performed in specialized Marfan outpatient clinics. We investigated the diagnostic yield in our clinic and the impact of the 2010 nosology. All adult patients ( $n = 343$ ) who visited our clinic between 1998 and 2008 were included. We analyzed their reasons for referral, characteristics, and established diagnoses. In addition, we applied the 2010 nosology to all patients and compared the outcomes to those obtained with the 1996 nosology. Diagnoses that were made using the 1996 and the 2010 Ghent nosology included MFS (44/343 vs. 47/343), familial thoracic aortic aneurysm and/or dissection (22/343 vs. 22/343 patients), Loeys–Dietz syndrome (4/343 vs. 4/343 patients), and (familial) mitral valve prolapse (MVPS; 5/343 vs. 28/343 patients). In both nosologies, 77% of MFS patients had an *FBN1* mutation. The 2010 nosology led to an increase in the number of diagnoses made: 4 additional cases of MFS were identified (one patient was “lost” who no longer fulfilled the criteria) and 23 additional cases of MVPS were diagnosed. The diagnostic yield of patients with aortic root dilatation was 65% using the 1996 nosology and 70% using the 2010 nosology. The change in diagnoses did not lead to a difference in clinical follow-up. We conclude that the diagnostic yield of our specialized clinic was high, in particular in patients with aortic root dilatation. Furthermore the 2010 Ghent nosology led to a significant increase in the number of diagnoses made, mainly due to lowering of the diagnostic threshold for MVPS.

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**Key words:** Marfan syndrome; Ghent nosology; diagnostic yield

## INTRODUCTION

Marfan syndrome (MFS) is an autosomal, dominantly inherited, connective tissue disorder with an estimated prevalence of approximately 1–3 in 5,000 [Gray et al., 1994] and it is usually caused by a mutation in the fibrillin-1 gene (*FBN1*) [Dietz et al., 1991]. Man-

### How to Cite this Article:

Aalberts JJJ, Thio CHL, Schuurman AG, van Langen IM, van der Pol BAE, van Tintelen JP, van den Berg MP. 2012. Diagnostic yield in adults screened at the Marfan outpatient clinic using the 1996 and 2010 Ghent nosologies.

Am J Med Genet Part A 158A:982–988.

ifestations of MFS occur in the ocular system, skeletal system, pulmonary system, skin and integument, central nervous system (CNS; dural ectasia) and in the cardiovascular system. Characteristic features of MFS include ectopia lentis (subluxation and luxation of the lens), thin body habitus and long extremities, pectus deformities and aortic root dilatation. Evaluation of possible MFS patients is usually performed in specialized Marfan outpatient clinics (MOC) and the diagnosis is established according to the Ghent nosology [De Paepe et al., 1996], which has recently been revised [Loeys et al., 2010]. The main purpose of evaluation is to confirm or exclude MFS in a patient, but it may also lead to many other, clinically relevant diagnoses, such as Loeys–Dietz syndrome (LDS), familial thoracic aortic aneurysm and/or dissection (FATAAD), familial mitral valve prolapse syndrome (MVPS), mitral valve, aorta, skeleton and skin (MASS) phenotype and Ehlers–Danlos syndrome (EDS). Establishing the correct diagnosis is important as it provides prognostic information, has implications for treatment, and also guides (genetic) counseling of family

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Published online 27 March 2012 in Wiley Online Library (wileyonlinelibrary.com).

DOI 10.1002/ajmg.a.35343

members. So far, only two studies [Hamod et al., 2003; Rybczynski et al., 2008] have reported on the outcome (diagnosis) in adult patients analyzed for possible MFS. In order to establish the diagnostic yield of our clinic, we determined the final diagnosis of all the patients referred for evaluation of MFS in a 10-year period. We were particularly interested in the diagnostic yield in patients with cardiovascular manifestations, since these carry important prognostic implications. Finally, we used the opportunity to analyze what the diagnostic yield would have been using the 2010 Ghent criteria [De Paepe et al., 1996; Loeys et al., 2010].

## PATIENTS AND METHODS

### Study Population and Diagnostic Evaluations

All adult patients (age  $\geq 18$  years) referred for evaluation for possible MFS to our clinic between 1998 and 2008 were included in our study. Every physician who suspected MFS in a certain patient was allowed to refer this patient to our MOC and there were no specific criteria patients had to meet to allow evaluation. The reason(s) for referral for all patients was routinely recorded. Evaluation of the patients was performed by a team of dedicated specialists, consisting of a clinical geneticist (JPvT), a cardiologist (MPvdB), an ophthalmologist (BAEvdP), and an orthopaedic surgeon. Inherent to this period of referral (i.e., up to 2008), the patient characteristics were collected according to the 1996 Ghent nosology [De Paepe et al., 1996]. Not all the Ghent criteria (especially no studies to detect the major criterion dural ectasia or minor criterion protrusion acetabuli) were evaluated in each patient, only when clinically relevant, that is, when necessary to

confirm or exclude MFS. All patient data, including echocardiographic data, were routinely fed into a clinical database. Mitral valve prolapse was defined as echocardiographic single or bileaflet prolapse of at least 2 mm beyond the long-axis annular plane, with or without leaflet thickening [Hayek et al., 2005]. Finally, it is important to note that patients with a bicuspid aortic valve were not evaluated at this specific clinic.

### Definitions of MFS and Other Relevant Diagnoses

The diagnoses were established using the 1996 Ghent nosology but, as part of this study, we also retrospectively applied the 2010 Ghent nosology to all patients based on their characteristics as collected at the time of referral. Other diagnoses that could be made but are not mentioned in (one) of the Ghent nosologies were also established.

The 1996 nosology for MFS distinguished major and minor criteria in different (organ) systems. MFS was present if two major (organ) systems were involved and if a third (organ) system was involved in a minor way [De Paepe et al., 1996]. To define aortic root dilatation, we used a Z-score  $\geq 2$ , in the 1996 nosology as well as in the 2010 nosology. In the 2010 nosology, there is no differentiation between major and minor criteria. Aortic root dilatation (Z-score  $\geq 2$ ) combined with one of the following characteristics establishes a diagnosis of MFS (see also Table 1): ectopia lentis, *FBN1* mutation, family history of MFS, or a systemic score  $\geq 7$ . A family history of MFS combined with ectopia lentis or a systemic score  $\geq 7$  also establishes a diagnosis of MFS [Loeys et al., 2010]. Besides defining MFS, the 2010 Ghent nosology also considers disorders that need to be differentiated from MFS. These include

TABLE I. Diagnostic Criteria for MFS in Adults According to the 2010 Ghent Nosology

In the absence of a family history of MFS:

1. Aortic root Z-score  $\geq 2$  AND ectopia lentis
2. Aortic root Z-score  $\geq 2$  AND an *FBN1* mutation
3. Aortic root Z-score  $\geq 2$  AND a systemic score\*  $\geq 7$  points
4. Ectopia lentis AND an *FBN1* mutation with known aortic pathology

In the presence of a family history of MFS (as defined above):

1. Ectopia lentis
2. Systemic score\*  $\geq 7$
3. Aortic root Z-score  $\geq 2$

\*Points for systemic score

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)

Dural ectasia = 2

Protrusio acetabula = 2

Reduced upper segment/lower segment ratio 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 = 1

MFS, Marfan syndrome.

MASS phenotype, MVPS (familial or incidental) [Hayek et al., 2005], FTAAD, EDS [Beighton et al., 1998], LDS [Loeys et al., 2006], and ectopia lentis syndrome [De Paepe et al., 1996; Loeys et al., 2010]. Definitions of these disorders have not been provided in the 1996 Ghent nosology but were added to the 2010 Ghent nosology, such as FTAAD, LDS and ectopia lentis syndrome. In the 1996 Ghent nosology, however, the MASS phenotype and MVPS are mentioned although not clearly defined. The 1996 nosology mentions the MASS phenotype as the presence of three of the following manifestations: myopia, mitral valve prolapse, borderline aortic root dilatation, striae, and minor skeletal criteria. In the 2010 nosology, a MASS phenotype is defined as borderline aortic root dilatation and a systemic score  $>5$  with at least one skeletal feature deleting the skin and eye manifestations. MVPS is mentioned in the 1996 nosology as an autosomal, dominantly inherited trait, whereas in the revised nosology, the familial occurrence is no longer required, a prolapse of the mitral valve and a systemic score  $<5$  is sufficient for the diagnosis MVPS. Benign hypermobility syndrome (BHMS) was defined according to Simpson [2006]. An aneurysm of the thoracic aorta of unknown origin (UO) was defined here as: dilatation of the thoracic aorta ( $Z$  score  $\geq 2$ ) without evidence for a systemic or familial disorder.

## Statistical Analysis

Continuous data are reported as mean  $\pm$  SD and categorical data as percentages unless stated otherwise. Differences between groups were tested using parametric or non-parametric tests, as appropriate. A  $P$ -value  $< 0.05$  was considered to indicate statistical significance. The analyses were performed using SPSS 16.0 software (SPSS, Chicago, IL).

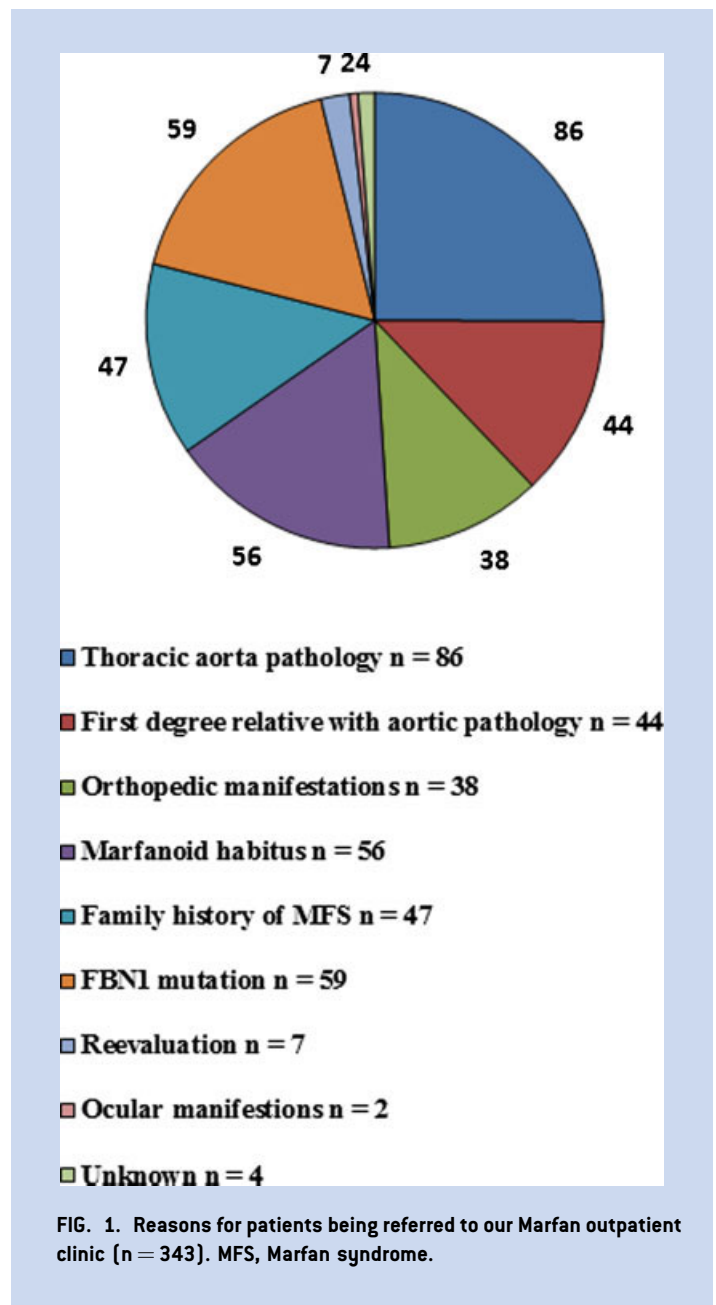
## RESULTS

### Patients

Between 1998 and 2008, 349 adult patients were referred to our clinic for evaluation of possible MFS. Six patients were excluded from analysis because of incomplete data, leaving a study group of 343 patients. Men ( $n = 174$ ) and women ( $n = 169$ ) were equally represented ( $P = 0.829$ ) and the average age was  $40 \pm 14$  years. Reasons for referral are given in Figure 1, the most common being aortic pathology (aortic dilatation or aortic dissection). More than one reason for referral was present in 113 patients.

### Patient Characteristics

In Table II and Figure 2, the characteristics of the patients according to the 1996 nosology are presented. Major cardiovascular involvement (aortic root dilatation/type A aortic dissection) was present in 28% of the patients. Ectopia lentis was present in 8% of patients and 40% of the patients had a family history of MFS and/or an *FBN1* mutation in the family. Dural ectasia was evaluated in 88/343 patients and was detected in 31 of them (35%). Major skeletal involvement was rare; it was present in only two patients.



### Diagnoses

In Table III, the diagnoses of all patients are presented, both at initial evaluation using the 1996 nosology and after re-evaluation applying the 2010 nosology. The patients were not clinically reevaluated, but the 2010 nosology was applied to the already established characteristics of the patients. In addition, diagnoses that were established but not mentioned in the Ghent nosologies are also presented. At initial evaluation, a diagnosis could be made in 41% ( $n = 140$ ) of the patients. MFS was the most common diagnosis (13%), followed by a thoracic aortic aneurysm of unknown origin (9%), FTAAD (6%) and BHMS (6%). MVPS was found in 1%. Other diagnoses are listed in Table III. No specific diagnosis could be made in 59% ( $n = 203$ ) of the patients. Thirteen of these patients without a

TABLE II. Prevalence of Characteristics in 343 Patients Evaluated at Our Clinic According to the 1996 Ghent Nosology

System	Major	Minor	None	Not evaluated
Cardiovascular	95 (28%)	42 (12%)	192 (56%)	14 <sup>a</sup> (4%)
Skeletal	2 (0.6%)	66 (19%)	246 (72%)	29 <sup>b</sup> (8%)
Ocular	29 (8%)	7 (2%)	274 (80%)	33 <sup>b</sup> (10%)
Familial/genetic	136 (40%)	n.a.	207 (60%)	—
Pulmonary	n.a.	11 (3%)	296 (86%)	36 <sup>b</sup> (10%)
Skin	n.a.	114 (33%)	197 (57%)	32 <sup>b</sup> (9%)
CNS	31 (10%)	n.a.	57 (17%)	255 <sup>b</sup> (74%)

n.a., not applicable; CNS, central nervous system.

<sup>a</sup>In these 14 cases only DNA analysis was performed because of familial MFS with a pathogenic *FBNI* mutation.

<sup>b</sup>In these cases, evaluation was deemed not relevant, since regardless of the outcome this would not have had any clinical consequences.

specific diagnosis had a high likelihood of MFS but did not (yet) fulfill the 1996 diagnostic criteria. They fulfilled one of the following profiles: (1) aortic root dilatation/type A aortic dissection combined with ectopia lentis OR an *FBNI* mutation, (2) (suspected) family history of MFS AND an *FBNI* mutation, and (3) ectopia lentis AND an *FBNI* mutation. Age did not differ significantly between patients with or without a diagnosis ( $38 \pm 14$  years vs.  $41 \pm 14$  years;  $P=0.123$ ) and distribution of gender was equal ( $P=0.274$ ).

After applying the 2010 Ghent nosology, a diagnosis could be made in 48% ( $n=165$ ) of the patients (vs. 41% using the 1996 nosology,  $P<0.001$ ). There were several changes compared to the diagnoses made at initial evaluation. The diagnosis of four patients changed from no specific diagnosis to MFS. All four of these patients belonged to the group of 13 patients with a high likelihood of MFS at initial evaluation. Two of these patients had aortic root dilatation and an *FBNI* mutation. The other two patients had

aortic root dilatation and ectopia lentis. Conversely, in one patient MFS could no longer be confirmed using the 2010 criteria (1/44 patients). This patient had a history of acute type A aortic dissection, dural ectasia, dolichocephaly, malar hypoplasia, striae, and no *FBNI* mutation. According to the 2010 nosology, this leads to a systemic score of three, which together with the type A aortic dissection was insufficient for a “revised” diagnosis of MFS. In one patient in whom initially no specific diagnosis could be made because of ectopia lentis and an *FBNI* mutation, the diagnosis changed to ectopia lentis syndrome.

There were further major changes for MVPS: according to the 1996 nosology, MVPS was diagnosed in five patients (1%) but according to the 2010 nosology MVPS was present in as many as 28 patients (8%). In three patients the diagnosis changed from MASS phenotype to “no diagnosis.” Age did not differ significantly between patients with or without a diagnosis when using the 2010 nosology ( $38 \pm 14$  years vs.  $39 \pm 14$  years;  $P=0.205$ ) and distribution of gender was equal ( $P=0.476$ ).

## FBNI Mutations

DNA analysis for *FBNI* mutations was performed in 140 patients.

Of the 44 MFS patients diagnosed using the 1996 nosology, 34 patients had an *FBNI* mutation (77%). In 11 other patients, an *FBNI* mutation was also present. They all had a high likelihood of MFS but did not (yet) fulfill the diagnostic criteria (see previous paragraph for the definition of these patients).

Of the 47 MFS patients diagnosed using the 2010 nosology, 36 patients had an *FBNI* mutation (77%). In nine other patients an *FBNI* mutation was also present. One had ELS and the other eight all had a (suspected) family history of MFS and an *FBNI* mutation.

## Aortic Root Dilatation

In 65% ( $n=52$ ) of the patients with aortic root dilatation ( $n=80$ ) a specific diagnosis could be established at initial evaluation, compared to 70% ( $n=56$ ) after applying the 2010 nosology. Figure 3 summarizes the diagnoses of the patients with aortic root dilatation using both the 1996 and 2010 Ghent nosologies.

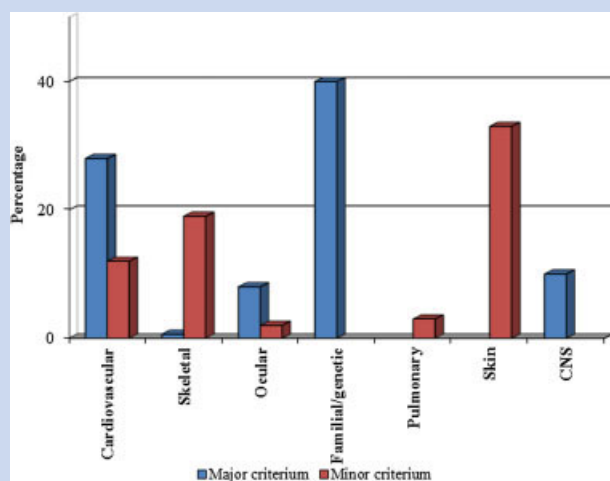


FIG. 2. Prevalence of the characteristics according to the 1996 Ghent nosology of the 343 patients evaluated at our Marfan outpatient clinic. CNS, central nervous system.



TABLE III. Diagnoses of the 343 Patients Evaluated at Our Clinic According to the 1996 and 2010 Ghent Nosologies

Diagnosis	Initial evaluation		Re-evaluation	
	Other <sup>a</sup>	1996 nosology	2010 nosology	Other <sup>b</sup>
MFS		44 [13%]	47 [14%]	
MVPS		5 [1%]	28 [8%]	
MASS phenotype		6 [2%]	3 [1%]	
EDS hypermobile type		5 [1%]	5 [1%]	
BHMS		19 [6%]	19 [6%]	
FTAAD	22 [6%]		22 [6%]	
LDS	4 [1%]		4 [1%]	
Ectopia lentis syndrome			1 [0.3%]	
Thoracic aortic aneurysm UO	30 [9%]			31 [9%]
Remaining diagnoses <sup>c</sup>	5 [1%]			5 [1%]
No diagnoses	203 [59%]		178 [52%]	
Total	343 [100%]		343 [100%]	

BHMS, benign hypermobility syndrome; EDS, Ehlers–Danlos syndrome; FTAAD, familial thoracic aortic aneurysm and/or dissection; LDS, Loeys–Dietz syndrome; MFS, Marfan syndrome; MVPS, mitral valve prolapse syndrome; UO, unknown origin.

<sup>a</sup>Diagnoses not mentioned in the 1996 Ghent nosology.

<sup>b</sup>Diagnoses not mentioned in the 2010 Ghent nosology.

<sup>c</sup>Duane syndrome, Lujan–Fryns syndrome, XYY-karyotype, dilated cardiomyopathy, congenital cataract.

## DISCUSSION

### Diagnostic Yield

Here, we have presented the diagnostic yield in our specialized MFS clinic between 1998 and 2008. We used the 1996 Ghent nosology and specific criteria for other disorders to evaluate the patients at that time. The overall diagnostic yield at initial evaluation in terms of establishing a specific diagnosis was 41%. Besides MFS (13%) many other important diagnoses were made, including FTAAD in 6%, LDS in 1% and familial MVPS in 1% of the patients. Compared to a study by Rybczynski et al. [2008], who also evaluated the diagnostic yield of patients referred for a possible diagnosis of MFS, we diagnosed MFS less frequently (13%;  $n = 44$  vs. their 50%;  $n = 138$ ). This might be due to the low threshold for referral to our center and a certain selection in the patients referred to their institution. They evaluated 279 patients in 9 years from the Hamburg metropolitan area (approximately 4.3 million inhabitants), whereas we evaluated 343 patients in 10 years from three northern provinces in the Netherlands (approximately 1.7 million inhabitants). However, Rybczynski et al. [2008] diagnosed FTAAD in 3% and MVPS in 3% of their patients, which is comparable to our results (6% and 1%, respectively) and argue against a selection in the German study. Hamod et al. [2003] reported on the diagnostic yield of 75 patients referred for a possible diagnosis of MFS and diagnosed MFS in 37% ( $n = 28$ ) of the patients. They did not report on other diagnoses that were made [Hamod et al., 2003].

The cardiovascular relevance of a timely diagnosis of MFS is obvious; MFS predisposes to aortic dissection and/or rupture causing significant morbidity and mortality. Lifelong follow-up of the aortic (root) dimensions, beta-blocker therapy, prophylactic aortic surgery (when thresholds are reached), and screening of

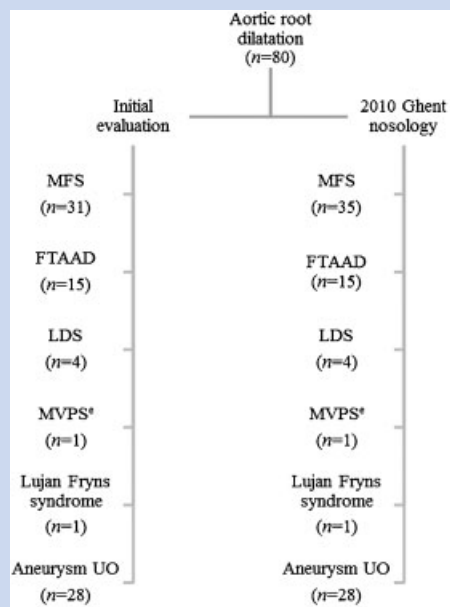


FIG. 3. Diagnostic yield of aortic root dilatation using the 1996 and 2010 Ghent nosologies. MFS, Marfan syndrome; FTAAD, familial thoracic aortic aneurysm and/or dissection; LDS, Loeys–Dietz syndrome; MVPS, mitral valve prolapse syndrome; UO, unknown origin. <sup>a</sup>This patient had familial MVPS and aortic root dilatation caused by a previously described *FLNA* mutation [Kyndt et al., 2007].

family members is indicated as soon as MFS is established [Aalberts et al., 2008a; Loeys et al., 2010].

Likewise, timely diagnosis of FTAAD and LDS is important as both are also characterized by aggressive aortic pathology [Aalberts et al., 2008b]. Family members of patients with these syndromes should also be screened. Finally, it is also preferably if familial MVPS is recognized early since it can be accompanied by serious complications, such as significant mitral regurgitation, bacterial endocarditis, thromboembolism, and sudden cardiac death [Pocock et al., 1984; Freed et al., 1999; Avierinos et al., 2002].

## Aortic Root Dilatation

The diagnostic yield in patients with aortic root dilatation was 65% at initial evaluation and 70% after applying the 2010 criteria. Diagnoses that we made in this patient category were MFS, FTAAD, LDS, familial MVPS, and Lujan–Fryns syndrome. In our opinion, all patients younger than 50 years with unexplained aortic root dilatation should be evaluated for a possible connective tissue disorder.

## Implications of the Revised Ghent Nosology

In addition to establishing the diagnostic yield of our clinic, we were also able to evaluate the implications of the recent revision of the MFS Ghent nosology. Although the 1996 nosology had a high specificity for detecting patients with *FBN1* mutations [Loeys et al., 2004] and was clinically useful, there were points of criticism, especially in children, stimulating the development of the revised nosology. In the 2010 nosology, emphasis is placed on cardiovascular manifestations, ectopia lentis and genetic evaluation. Related entities are defined in the 2010 Ghent nosology as well. Using the 2010 nosology for our study, population led to several changes compared to the outcome of the 1996 nosology. A diagnosis of MFS could be established in four additional cases. All patients had aortic root dilatation combined with an *FBN1* mutation (two cases) or ectopia lentis (two cases). These cases nicely illustrate the hallmarks and the clinical consequences of the 2010 nosology for MFS. The diagnosis is more straightforward and specific characteristics of MFS are highlighted: aortic root dilatation, ectopia lentis, and *FBN1* mutations. On the other hand, skeletal features, CNS involvement (dural ectasia), skin abnormalities, atypical cardiovascular, and ocular manifestations are given less weight in the 2010 nosology. This is illustrated by the patient who no longer fulfilled the diagnostic criteria for MFS. Although this patient no longer has MFS, this did not have any clinical consequences. Due to the type A aortic dissection, regular imaging of the entire aorta was indicated anyway, to timely discover and treat a possible post-dissection aneurysm.

The use of the 2010 nosology led to a significant increase in the number of non-MFS diagnoses made. This was due to an increase in the number of patients diagnosed with MVPS. Familial occurrence is no longer required in the 2010 nosology and therefore everyone with solely a mitral valve prolapse qualifies for MVPS. As mitral valve prolapse is a common valvular disorder (estimated prevalence 2–3%), mostly with a benign course (as opposed to certain familial forms), it is debatable whether it is useful to label all these patients as mitral valve prolapse *syndrome* [Freed et al., 1999]. It does not have clinical consequences as these patients are already well defined and

guidelines for follow-up are available [Vahanian et al., 2007]. We believe the term mitral valve prolapse is sufficient in the large majority of patients with this disorder.

At initial evaluation, a small number of patients ( $n = 13$ ) with no specific diagnosis had a high likelihood of MFS using the 1996 nosology. The 2010 nosology established definite MFS in four of these patients and one of them could be diagnosed as ectopia lentis syndrome. The remaining eight patients were all patients with a (suspected) family history of MFS and an *FBN1* mutation. They should have regular echocardiographic follow-up of aortic diameters anyway. An age limit of 50 years for follow-up appears reasonable as the chances of developing MFS are not very large if aortic diameters at that age are still normal.

Finally, the revised criteria led to a less frequent diagnosis of MASS phenotype. The criteria for this phenotype have been changed slightly, but remain rather subjective. In particular, the criterion of borderline aortic root dilatation is unsatisfying.

## Strengths and Limitations

One strength of our study is that all the patients were seen by the same team of specialists. Another is that we determined the impact of the 2010 Ghent nosology by using it on patients *suspected* of MFS who were initially evaluated by the 1996 nosology, rather than applying the new nosology to patients with *established* MFS according to the old nosology, since this would introduce a bias. In addition, we did not evaluate patients with a bicuspid aortic valve at this particular clinic, since this could introduce a bias in the outcome of the analysis. Our study is limited by the fact that not all the Ghent criteria were evaluated in each patient.

## CONCLUSION AND PRACTICAL IMPLICATIONS

The general diagnostic yield of our specialized clinic was high: at initial evaluation, a diagnosis could be made in 41% of all referrals. Besides establishing or excluding MFS, our clinic's evaluation of a patient can lead to the diagnosis of other clinically relevant connective tissue disorders, like FTAAD, LDS, and familial MVPS. Using the 2010 Ghent nosology led to a significant increase in the number of non-MFS diagnoses that were made, which was due to a lowering of the diagnostic threshold of MVPS. In addition, the 2010 nosology affords a more straightforward diagnosis of MFS in patients with aortic root dilatation, ectopia lentis and *FBN1* mutations. Finally, as the diagnostic yield in patients with aortic root dilatation was particularly high, all such patients (age <50 years) should be referred to a specialized MFS clinic to be evaluated for a possible connective tissue disorder.

## ACKNOWLEDGMENTS

We thank Jackie Senior for editing the manuscript.

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