Marfan syndrome: Getting to the root of the problem

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Diagnosis and Genetics of Marfan syndrome

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Abstract

Introduction: Marfan syndrome (MFS) is a connective tissue disorder with highly variable features in cardiovascular, ocular and skeletal systems. MFS is generally caused by one of the 2900+ described different genetic mutations in FBN1.

Areas covered: By revising the Ghent criteria in 2010, more weight has been given to genetic testing in the diagnosis of MFS. We provide an overview of correlations between different mutation-types and clinical MFS features by using the Universal Mutation Database (UMD).

Expert opinion: In this study we classified FBN1 mutations based on their action on DNA level and we found the following genotype-phenotype correlations: 1) cysteine mutations are associated with ectopia lentis; 2) introduction of a cysteine leads to less severe involvement of cardiovascular and skeletal systems; 3) whole gene deletions and premature termination codon (PTC) mutations are associated with increased skeletal and cardiovascular involvement, but lower prevalence of ectopia lentis; and 4) intronic mutations lead to MFS by exon skipping, small insertions/deletions and PTC mutations. Classification based on mutation-effect at protein level (reduced versus truncated/deformed fibrillin-1) may partly explain genotype-phenotype association and warrants further investigation for individualized prognosis and treatment.

Conclusion: Genotype-phenotype correlations can be identified in MFS and may be explained by their mutation-effect on protein level.
Chapter 5: Diagnosis and genetics

Introduction

Marfan syndrome (MFS) is a multi-system connective tissue disorder with a prevalence of 1 per 5000 individuals, generally caused by mutations in the gene encoding for fibrillin-1 (FBN1) and inherited in an autosomal dominant manner. FBN1 mutations induce abnormal or deficient fibrillin-1 protein synthesis, affecting the structural integrity of the extracellular matrix in a multitude of organs. The most feared and often lethal complication is aortic dissection, which mostly occurs after gradual dilation of the aorta. Aortic dilation is caused by degenerative features in the aortic wall, which are associated with enhanced release of transforming growth factor-β (TGF-β). Aortic dilation, especially of the aortic root, is present in the vast majority of MFS patients. The introduction of prophylactic aortic root replacement (generally at an aortic diameter of 50 mm) has led to increased life expectancy. In addition, several pharmacological drugs have been reported to slow down aortic dilation in patients with MFS. Diagnosis is based on major and minor criteria, comprising family history of MFS, mutation analysis and specific phenotypic characteristics, including ectopia lentis, dural ectasia, skeletal features, and aortic dilation or dissection (Table 1). These criteria (the so-called ‘Ghent’ criteria) have been revised in 2010 by a panel of experts in the field of MFS.

In this review, we will focus on the increased importance of genetic testing as stated in the revised Ghent criteria for diagnosis of MFS. Furthermore, we will provide 1) an overview of different mutation-types based on their effect on RNA or protein level and 2) correlations between mutation-subtypes and clinical MFS features.

Table 1. Possible combinations of major criteria leading to Marfan syndrome

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<tr>
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Abbreviations: Ao: aortic dilatation (Z≥2) or aortic dissection, EL: ectopia lentis, FBNc: FBN1 mutation, FBNa: FBN1 mutation associated with aortic pathology, FH: family member with Marfan syndrome, Syst: systemic score ≥ 7 out of 20 points

*Each line represents a possible combination leading to Marfan syndrome.*
The history of diagnosing Marfan syndrome

Antoine-Bernard Marfan was the first to describe a five-year-old patient with long slender fingers and other skeletal abnormalities in 1896. After this initial delineation, other pleiotropic and phenotypic features of MFS were recognised by Victor McKusick. Finally, the Berlin nosology was formulated in 1986; the first guidelines for the clinical diagnosis of MFS. However, some pitfalls including overdiagnosis of family members forced experts in the field to develop a new diagnostic guideline published as ‘the Ghent criteria’ in 1996. The Ghent criteria made use of a classification for the different clinical features, which were divided into major criteria with high diagnostic specificity and minor criteria. The presence of a major criterion in two different organ systems and a minor criterion in a third organ system were required to fulfil the diagnosis of MFS.

A major breakthrough in understanding the pathophysiology of MFS was the discovery of the \( FBN1 \) gene on the long arm of chromosome 15 in 1991. Mutations in this gene were shown to result in MFS in a considerable number of patients. To date, \( FBN1 \) mutations are found in approximately 90% of patients. Later, other gene mutations leading to MFS-like disease were discovered, such as mutations in the \( TGFBR1 \) and \( TGFBR2 \) genes, now considered to compose a specific entity known as Loeys-Dietz Syndrome.

A revision of the Ghent criteria has been published in 2010. These revised guidelines can be considered as a simplification of previous guidelines by giving more weight to aortic root dilation, \( FBN1 \) mutation analysis and ectopia lentis. Criteria regarding less specific manifestations of MFS were removed or became less influential in the diagnostic evaluation. Diagnosis of MFS in patients without affected family members can now be established when a patient has two major criteria: 1) aortic root dilation (Z-score ≥2); 2) ectopia lentis; 3) skeletal score ≥7 points (out of 20); and 4) pathogenic \( FBN1 \) mutation leading to aortic dilation. In patients with a MFS affected family member, only one of the four major criteria is needed to establish diagnosis of MFS (Table 1).

Reconsidering the child originally presented by Antoine Marfan, the diagnostic value of mutation analysis becomes clear. This child was probably not affected by MFS, but by congenital contractual arachnodactyly, a connective tissue disorder caused by a \( FBN2 \) mutation. These patients have more pronounced skeletal abnormalities, but rarely have aortic root dilation – the main cause of morbidity and mortality in MFS.

The \( FBN1 \) gene

Patients with MFS have a highly variable phenotype, vary in age of onset of manifestations, and vary in responsiveness to medical treatment, both between different families as within families sharing the same mutation. Currently, more than 2900 different
mutations in the \textit{FBN1} gene have been described, and over 90% of these mutations are unique to an individual or family.\textsuperscript{24}

The \textit{FBN1} gene is located on the long arm of chromosome 15 at 15q15-q21.1. It is a large gene fragmented in 65 exons, including 47 epidermal growth factor (EGF)-like domains, each containing six conserved cysteine amino acids, of which 43 EGF-domains are known to bind calcium.\textsuperscript{25} The calcium binding (cb) potential is important for the protection against proteolytic activity and for correct folding of the fibrillin-1 protein. Furthermore, the \textit{FBN1} gene contains seven domains that bear homology to latent TGF-\textbeta binding proteins (TB-domains)\textsuperscript{26}, each containing eight cysteines.\textsuperscript{26} In addition, there are two hybrid domains (the HB-domains) with homology to both EGF- and TB-domains.\textsuperscript{27} In between the 65 exons encoding the fibrillin-1 protein, the \textit{FBN1} gene also contains introns; these introns are normally removed by RNA splicing to generate the mature RNA that will be translated. Mutations leading to MFS comprise deletions of (a part of) the \textit{FBN1} gene, or minor mutations which can be located in all EGF-like domains, the TB- and HB-domains, as well as in the introns.

Location of the \textit{FBN1} mutations is of great importance. For example, \textit{FBN1} mutations located between exon 24-32 often lead to a neonatal form of MFS – a severe form of MFS usually diagnosed at birth, with lethal cardiorespiratory failure during the first weeks of life.\textsuperscript{28-31} Furthermore, mutations in the \textit{FBN1} gene may also lead to stiff skin syndrome located in exon 37, acromicric dysplasia located in exon 41-42, and Shprintzen-Goldberg craniosynostosis syndrome located in exon 29.\textsuperscript{31-34} Thus, the position of the \textit{FBN1} mutation determines the resulting phenotype, which is not exclusively MFS. In this review we give an overview of MFS phenotypes correlated to the different \textit{FBN1} mutations.

\textbf{Overview of literature}

We reviewed all articles reported in the Universal Mutation Database (UMD). We included all patients from the UMD, registered until March 2014, with (partially) described phenotypes.\textsuperscript{35} We carefully monitored duplicate mutations to avoid the description of a patient more than once. We scored the following clinical features: gender, age, cardiac involvement (including aortic aneurysm or aortic dissection as ‘major’, and mitral valve prolapse as ‘minor’), ocular involvement (including ectopia lentis as ‘major’, or one of the minor ocular features as ‘minor’) and skeletal involvement. The definition of ‘major involvement of the skeletal system’ in this manuscript comprised patients with major skeletal involvement according to the Ghent criteria of 1996, or/and patients with \textgeq 7 points according to the Ghent criteria of 2010. Minor skeletal involvement was defined as at least one of the known skeletal features present in MFS.
In total, we reviewed 143 articles and included 1511 patients with a pathogenic FBN1 mutation with (partially) known MFS phenotype. In these patients a missense mutation was present in 846 patients (56%) in whom a cysteine amino acid was involved in 555 patients (66%). A premature termination codon (PTC) was present in 442 patients (29%), a deletion or insertion of (a part of) the FBN1 gene was present in 116 patients (8%) and an intron mutation was present in 161 patients (11%). Finally, two patients had a homozygous mutation and 7 patients carried two different FBN1 mutations.

Mean age of the total cohort was 30 years, with 48% females and 80% prevalence of cardiac involvement (aortic aneurysm 71%, aortic dissection 22%, and mitral valve prolapse 51%). Furthermore, ectopia lentis was present in 52% of the patients and 29% had major involvement of the skeletal system (Table 2). All test were performed by two-sided Fisher’s exacts tests.

**Different types of FBN1 mutations**

**Cysteine mutation**

A cysteine mutation is a missense mutation substituting the amino acid cysteine for another amino acid, or introducing a cysteine at a new position. A cysteine substitution is the most common mutation type among all pathogenic FBN1 mutations. Cysteines are essential in forming disulphide bridges to establish the ternary structure of a protein. In fibrillin-1 there are more than 360 cysteines present, which is an exceptional large number for a single protein. The substitution of a cysteine by glycine is responsible for the development of a MFS phenotype in a well-known MFS mouse model (p.C1039G).36 Most cysteine substitutions involve a cb-EGF-like domain; this calcium-binding property is important for correct folding of fibrillin-1. The cb-EGF-like domains are highly conserved and contain 6 cysteine amino acids per domain, forming three disulphide bridges.37 Cysteine substitutions disrupt one of these three disulphide bridges, which has a predictable detrimental effect on the domain itself as well as on the cb-property of the domain.

We affirmed that a correlation between cysteine mutations and increased prevalence of ectopia lentis exists, compared to the total cohort of patients with a (partially) known phenotype and a pathological FBN1 mutation (71% versus 52%, p<0.001). We summarized these results and other clinical features in Table 2.32,34,38-85 Interestingly, there was a difference in MFS phenotype between cysteine substitutions and cysteine introductions, with a higher prevalence of aortic aneurysms and mitral valve prolapse in patients with a cysteine substitution compared to patients with a cysteine introduction (aneurysm: 78% versus 52%, p<0.001; mitral valve prolapse: 61% versus 27%, p<0.001, respectively). As noted previously, it seems that the disappearance of a conserved cys-
Non-cysteine missense mutations

Another large group of FBN1 mutations comprise missense mutations substituting an amino acid by another amino acid (without involvement of a cysteine). Interestingly, patients with a non-cysteine missense mutation had a more severely affected cardiovascular system (aneurysms: 65% versus 52%, p=0.031; mitral valve prolapse: 44% versus 27%, p=0.023), as well as skeletal system (skeletal involvement 86% versus 63%, p<0.001), compared to patients with a missense mutation where a cysteine was introduced. However, the non-cysteine missense group did not significantly differ from the cysteine substitution group (Table 2). We did not find an explanation for these unexpected results. Missense FBN1 mutations are traditionally thought to cause a ‘dominant negative effect’, leading to disturbed folding of the protein or disturbed interactions with fibrillin-1 or other extracellular matrix proteins, hence a disorganized tissue matrix. Apparently, there seems to be more distinction between these different missense mutation groups, which deserves further investigation.

Intron mutations and other mutations leading to minor in frame deletions or insertions

In approximately 90% of the MFS patients a FBN1 mutation is found. Recently, Gillis E et al. suggested that deep intronic mutations may cause MFS in patients without a
discovered pathogenic FBN1 mutation upon exon sequencing. Intron mutations leading to MFS were present in 8% of the patients with a known MFS phenotype. These intron mutations may lead to splice site disturbances and subsequently exon skipping or activation of a cryptic splice site causing partial exon deletion or a (partial) intron insertion. In the UMD, an intron mutation was found in 161 patients, but the mutation-effect was not tested in 85 patients (53%). In patients with an intronic mutation with a confirmed effect, the mutation led to exon skipping (n=29, 38%), in frame deletion of a part of the exon (n=22, 29%), a frameshift leading to a PTC (n=22, 29%), and in 3 patients it resulted in a small in frame insertion (4%). The intron mutations leading to PTC are described in paragraph 5.5.

In total, 96 patients had a mutation resulting in a minor in frame deletion or insertion, of whom 55 patients had one exon deletion, 14 patients had less than one exon deletion, 14 patients had more than one exon deletion, and in 13 patients the mutation resulted in a minor in frame insertion.

Minor in frame deletions or insertions in exons, leading to altered fibrillin-1 protein may also be caused by deletion of a nucleotide(s) (n=25), insertion/duplication of a nucleotide(s) (n=9), missense mutation (n=1), or an unknown cause (n=7). There were no significant differences in cardiovascular and systemic involvement, between the patients with a mutation leading to at least 1 exon skipping, in frame deletion or insertion, and intron mutations with unknown effect. Remarkably, patients with a small in-frame deletion or insertion had a more severely affected ocular system compared to patients with at least 1 exon deletion (Fisher exact tests: ectopia lentis: 85% versus 49%, p=0.003). In Table 3, we described the phenotypes of patients with a deletion of one or more exons, and the combination of minor deletion or minor insertion, and intron mutations with unknown effect.

Whole gene deletions, deletion of the exon 1 or exon 65

Besides mutations leading to deformed fibrillin-1, another type of mutation exists, leading to a reduced amount of normal fibrillin-1 protein. This condition is known as ‘haploinsufficiency’. In the minority of these mutations, deletion of the entire gene on one allele is the cause of MFS. In MFS mice with a centrally deleted FBN1 allele (Fbn1<sup>mg∆/mg∆</sup>), an excessive amount of active TGF-β is liberated from the matrix, which is considered to be the cause of the clinical MFS manifestations in this MFS mouse model. It is currently unknown whether excessive TGF-β signalling is also the cause of the MFS phenotype in humans with an allelic deletion of the FBN1 gene. Haploinsufficiency, due to deletion of the whole gene has been shown to result in a great variety of MFS manifestations, from mild to severe. In addition to whole gene deletions, no transcript will be produced when at least the first exon is deleted, sometimes accompanied by a deletion upstream of FBN1, deleting also the regulatory and promoter regions of FBN1. In addition, deletion.
of the last exon (exon 65) will result in extended transcription due to the disappearance of the termination codon, and the abnormal protein will be degraded subsequently. There was one patient with a deletion of exon 65 in the database, revealing mainly eye and skeletal symptoms, but no cardiovascular involvement (Table 4). Patients with a whole gene deletion had significantly lower prevalence of ectopia lentis compared to the total cohort (Fisher’s exact test: 28% versus 52%, p=0.006) and increased skeletal involvement (100% versus 84%, p=0.049). We summarized the clinical features of patients with deletions of the whole FBN1 gene or deletions of at least the first exon in Table 4. Large differences were seen between studies, possibly caused by extended deletions beyond the FBN1 gene, which suggests that the function of genes upstream of the FBN1 gene on chromosome 15, including SLC24A5, MYEF2, CTXN2, SLC12A1 and DUT may be involved in these phenotypes as well. In conclusion, haploinsufficiency results in a high prevalence of cardiovascular involvement (95%), and a 100% involvement of the skeletal system (Table 4). 66,87,130,133,134

**Premature Termination Codon mutations**

In DNA, triplets of nucleotides (codon), encode for amino acids. From the generated mRNA, translation starts at the start codon and stops after passing the termination codon (nucleotide sequence UAG, UAA or UGA). In patients with mutations leading to a PTC, a novel termination codon is built into the transcribed mRNA, which will overrule the ‘normal’ termination codon and thus terminates the translation prematurely. In MFS, 29% of the FBN1 mutations in the database were PTC mutations. PTCs were caused

<table>
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<th>Table 3. Mutations in introns, small insertions and deletions</th>
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<td>n = 1511</td>
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<td>Gender (female)</td>
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<td>Age (years)</td>
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<td>Cardiac involvement</td>
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<td>Skeletal involvement</td>
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<td>Major involvement</td>
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<td>Minor involvement</td>
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Fisher’s test demonstrated significant differences between the total cohort and subgroups marked with a symbol.

Abbreviations: del: deletion, ins: insertion, * = p<0.01
by 1) nonsense mutations and 2) frameshift mutations. Nonsense mutations are point mutations directly leading to a novel termination codon. Deletions or insertions of one or more nucleotides (not a multiple of three) change the reading frame, and introduce novel termination codons. In addition, intron mutations sometimes lead to a PTC. Schrijver, et al., revealed by FBN1 mRNA quantitation that mutant transcript levels were decreased, which suggests that mutant mRNA is preferentially degraded by a nonsense-mediated mRNA decay mechanism. In Table 4 we summarized the clinical features of patients with a PTC and known phenotype. In line with the results of whole gene deletions, Fisher’s exact tests revealed that MFS patients with PTCs led more often to major involvement of the skeletal system (82% versus 65%, p<0.001, respectively), but less frequently to ectopia lentis (29% versus 41%, p<0.001, respectively) compared to the total cohort, suggesting that most PTCs result in a haploinsufficient MFS phenotype.

Homozygous mutations and patients carrying two different FBN1 mutations

MFS is mostly an autosomal dominant inheritable connective tissue disorder. However, index cases with a confirmed homozygous mutation in the FBN1 gene exist, and thus MFS rarely inherit recessively. In 2007 de Vries et al. were the first to confirm a recessive mutation in the FBN1 gene. The homozygous mutations in two sibs, affected with classical MFS, were located in exon 11 of the FBN1 gene (c.1453C>T, p.R485C). All four blood-related parents, with mild signs of MFS, were heterozygous for the c.1453C>T FBN1 mutation. One other sibling, without clinical features of MFS was tested positive as carrier of the mutation. In 2010 another recessive family was described, in whom a heterozygous mutation did not exert an important effect, but the homozygous patient was affected with the classical clinical MFS phenotype.

A second rare phenomenon within the spectrum of MFS is the presence of two different FBN1 mutations in one individual. In total 7 patients had two different FBN1 mutations, with in general a more severely affected MFS phenotype (Table 4). For example, one child carried the maternal intronic mutation (c.2728+3A>G) in combination with the paternal (p.Q454P) mutation, and demonstrated a more severe cardiovascular phenotype compared to his brother with only the maternal mutation. The father only showed mild aortic dilation, while the mother showed classical MFS.

Conclusion

In conclusion, MFS is mostly an autosomal dominant heritable connective tissue disorder with a heterogeneous expression of clinical features ranging from mild skeletal abnormalities to fatal aortic dissections. Associations between different genotypic mutation-
types and their phenotype lead to the following interesting results: 1) cysteine missense mutations lead more often to ectopia lentis; 2) introduction of a cysteine mutation leads to a less severe cardiovascular and skeletal phenotype than other missense mutations; 3) whole gene deletions lead to a 95% cardiovascular involvement and a 100% skeletal involvement which is the highest of all mutation-types, but a much lower prevalence of ectopia lentis (28%); 4) Furthermore, we found that patients with a PTC mutation (leading to reduced amounts of normal fibrillin-1 protein) have a similar phenotype compared to patients with a whole gene deletion (summarized in Figure 1).

**Expert opinion**

Since the first presentation of a patient with long slender fingers by Antoine Marfan, MFS has evolved into a worldwide known syndrome in which the diagnosis can be established according to clear guidelines. The introduction of mutation analysis catalysed the knowledge of different connective tissue disorders. Currently, the presence of a pathogenic FBN1 mutation has a prominent role in the diagnosis of MFS. However, significant uncertainties, including the large heterogeneity in phenotype and treatment response, still remain in 2014.
In this review we attempt to categorize the genetic mutations in \textit{FBN1} and we give an overview of the phenotypes associated with these different types of mutations. The limitations of this review include the large differences in data presented by different authors, differences in used guidelines for diagnosing MFS, and the exclusion of \textit{FBN1} mutations where no phenotype is reported. However, since we included all patients with (partially) known phenotype, we expect that these differences are normally distributed over all mutation-types.

Our analysis of the existing data revealed a number of interesting findings. Remarkably, patients with a PTC mutation had a similar phenotype compared to patients with a whole gene deletion. Probably, because a PTC leads to nonsense mediated decay and thus a reduced amount of normal fibrillin-1 protein, known as ‘haploinsufficiency’. This

\textbf{Figure 1.} An overview of different \textit{FBN1} mutation types. Missense mutations, exon skipping and minor in frame insertions or deletions will lead to a mutant fibrillin-1 protein interfering with normal fibrillin-1. Whole gene deletions and premature termination codons (including frameshifts and nonsense mutations) will lead to less normal fibrillin-1 protein. The symbols identify significant differences between the mutation type and the total cohort of 1511 patients minus the patients of the mutation type.
phenomenon, of a reduced amount of normal fibrillin-1 leading to MFS, has already been described by Schrijver, et al in 2002. Reduced prevalence of ectopia lentis and increased prevalence of cardiovascular involvement in patients with a PTC mutation are novel findings in our study. Absence of ectopia lentis may delay MFS diagnosis, yet these patients are at higher risk for aortic dissection. Furthermore, the pathogenesis of patients with a PTC mutation is different compared to patients with a missense mutation. Rapid nonsense mediated decay of mutant transcripts leads to a loss-of-function phenotype, and thus this phenotype resembles patients with a whole gene deletion. In contrast, missense mutations or mutations leading to exon skipping result in the synthesis of truncated or deformed fibrillin-1. Truncated or deformed fibrillin-1 may have a dominant negative effect for some phenotypic features, such as ectopia lentis. On the other hand, deformed or truncated fibrillin-1 protein may have a partially normal function, leading to a less severe mutation-effect on skeletal features and aortic aneurysms compared to patients with reduced amounts of normal fibrillin-1.

Our data suggest that mutation effect at protein level partly explains differences in the development of clinical features. However, even in the group leading to truncated or deformed fibrillin-1, differences in phenotype exist. For example, ectopia lentis was more frequently present in patients with a cysteine missense mutation compared to patients with a missense mutation not involving a cysteine amino acid. Thus, the structure of the mutated fibrillin-1 protein is clearly important in the development of ectopia lentis. It could be speculated that the modification of fibrillin-1 also changes the fibrillin-1 function, and subsequently alters TGF-β signaling. However, more preclinical research is needed to confirm or reject this hypothesis and to create more consensus about the role of TGF-β in the pathogenesis of MFS. In our opinion, increased TGF-β level in MFS is rather a readout of the disease state of the aorta than the initiator of damage/clinical features.

Key questions that warrant further investigation include the role of mutations in treatment effects of beta-blockers and losartan on aortic dilation rates and aortic dissections. Currently, there are no studies investigating the treatment effects between different mutation-types. A classification in patients with a reduced amount of fibrillin-1 and patients with expression of mutated or truncated protein may result in a different response to treatment, and thus may reveal the first step in individualized prognosis and treatment in MFS.

The highly variable phenotype of MFS patients may be based on mutation effect at protein level (reduced versus truncated/deformed fibrillin-1). Further investigation at this level is needed for individualized prognosis and treatment.
Declaration of interest

This work is supported by Interuniversity Cardiology Institute of the Netherlands. The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reference List


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