CLINICAL REPORT Guidance for the Clinician in Rendering Pediatric Care

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Health Supervision for Children and Adolescents With Marfan Syndrome

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Marfan syndrome is a heritable connective tissue disorder that affects many different organ systems. In some cases, features of Marfan syndrome can be recognized at birth, but the majority will have manifestations that emerge throughout childhood and into adulthood. Significant morbidity and mortality are associated with this syndrome, and its features are best managed using a multidisciplinary approach. This clinical report is designed to assist the pediatrician in recognizing the features of Marfan syndrome as well as caring for the individual with Marfan syndrome to maximize their health and quality of life.

INTRODUCTION

Marfan syndrome is a heritable, multisystem disorder of connective tissue with extensive clinical variability. It is a relatively common condition with approximately 1 in 5000 to 15 000 people affected.[1,2] Cardinal features involve the ocular, musculoskeletal, and cardiovascular systems, including the risk of aortic aneurysms or dissections. Because of the high degree of variability of this disorder, the clinical features may be present at birth or manifest later in childhood or even adulthood.

Marfan syndrome is an autosomal dominant disorder caused by a defect in the gene that encodes fibrillin-1, *FBN1*.[3] Previously, Marfan syndrome type 2 was used to describe a similar phenotype now known to be caused by pathogenic variants in *TGFBR1* and *TGFBR2*.[4] This phenotype is now recognized as Loeys-Dietz syndrome; therefore, *FBN1* is the only gene associated with Marfan syndrome. Pathogenic variants in *FBN1* are associated with a wide phenotypic spectrum ranging from classic features of Marfan syndrome presenting in childhood and early adulthood to severe neonatal presentation with rapidly progressive disease. At the other end of the spectrum, isolated phenotypic features, such as ectopia lentis, dilated aortic root, or skeletal manifestations, alone may be the only presenting signs. Mutations in *FBN1* are found in nearly all of those meeting diagnostic criteria.[3,5–7] The protein, fibrillin-1, is involved in the

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formation of extracellular microfibrils and can regulate the bioavailability of transforming growth factor (TGF) β1, a proinflammatory cytokine.[8] Altered TGFβ signaling is considered the major contributor to the underlying pathology of this disorder.[9]

The diagnosis of classic Marfan syndrome is clinically based using well-defined criteria (revised Ghent diagnostic criteria) (Tables 1A and 1B) and does not include the whole spectrum of *FBN1*-related disorders, especially the milder, isolated features.[10] As many of the more specific clinical features are age-dependent (eg, ectopia lentis, aortic dilatation, dural ectasia, and protrusio acetabulae), children and adolescents may not fulfill formal diagnostic criteria and are often described as having "potential" Marfan.[10] Younger patients at risk for Marfan syndrome based on clinical features or a positive family history should be evaluated periodically until their growth is complete or preferably undergo appropriate genetic testing.

There have been more than 3000 different pathogenic variants reported in *FBN1*, and genetic testing in Marfan syndrome has become an important part of the diagnosis and management of the condition. However, the genotype-phenotype correlation in these pathogenic variants has been less clear.[11,12] The earliest correlations made were between the pathogenic variants in the middle region of the *FBN1* gene (exons 24–32), which appear to be linked to a more severe presentation with an earlier onset, previously called "neonatal Marfan syndrome." This severe early-onset form includes not only the skeletal findings but also having cardiac findings such as arterial aneurysms and/or multivalvular disease in the newborn period. However, some patients with the severe neonatal presentation have pathogenic variants outside the exons 24 to 32, and some patients with Marfan syndrome who present in childhood or adolescence with classic features have pathogenic variants within exons 24 to 32. There is also a correlation between missense pathogenic variants, particularly those that affect cysteine residues, and ectopia lentis.[13] Beyond these correlations, the evidence is less clear. Pathogenic variants in *FBN1* can be classified as being associated with haploinsufficiency, that is, a lack of protein production, or with a dominant negative effect, that is, an abnormal protein is formed. There is evidence in studies that show that the haploinsufficient pathogenic variants may be associated with an increased risk for cardiovascular death and aortic dissection.[14–16] However, the wide intrafamilial variability continues to confound the attempts at making conclusions about genotype-phenotype correlations in Marfan syndrome.

Many features of Marfan syndrome are seen in isolation as well as in other genetic syndromes (Table 2).[17,18] Diagnosis should be clearly established when possible in each case. For those suspected to have Marfan syndrome on clinical grounds after physical, cardiac, and ophthalmic evaluation but who may not meet full clinical criteria, one should consider *FBN1* testing.[13] Furthermore, there is extensive overlap in clinical manifestations among the different connective tissue disorders, and individuals with Loeys-Dietz syndrome can meet Ghent criteria. Documenting the causative gene is important because it affects the extent of diagnostic evaluation and management. Patients who fit clinical criteria for Marfan syndrome in whom no pathogenic variant is found in the *FBN1* gene should continue to be followed according to the health supervision for Marfan syndrome. In addition, broader genomic testing should be considered in these individuals.

Approximately one-fourth of cases arise by new mutation with the remainder inherited from an affected parent. Because of the broad phenotypic variability, some parents will not be readily recognized as having Marfan syndrome.[19] When a new diagnosis of Marfan syndrome is made in a child or adolescent, both parents and at-risk first-degree relatives should have physical, ophthalmologic, and cardiac evaluations as well as consideration of genetic testing. Similarly, when a new diagnosis of Marfan syndrome is made in a parent, all children should be screened for manifestations of Marfan syndrome.

TABLE 1A Revised Ghent Diagnostic Criteria for Marfan Syndrome

Diagnosis of Definitive Marfan Syndrome (*any of the following*)
• Aortic root ≥+2 z-score and ectopia lentis
• Aortic root ≥+2 z-score and *FBN1* mutation known to be associated with Marfan syndrome
• Aortic root ≥+2 z-score and systemic score ≥7
• Ectopia lentis and *FBN1* mutation known to be associated with Marfan syndrome
• Positive family history of Marfan syndrome and ectopia lentis
• Positive family history of Marfan syndrome and systemic score ≥7
• Positive family history of Marfan syndrome and aortic root ≥+3 z-score in those <20 y of age OR ≥ +2 z-score in those >20 y of age
Diagnosis of potential Marfan syndrome
• *FBN1* pathogenic mutation not previously known to be associated with Marfan syndrome and aortic root with a z-score of <+3

GROWTH AND DEVELOPMENT

Overall growth is characterized by excessive linear growth of the long bones. Typically, individuals with Marfan syndrome are tall for age (Figs 1 and 2), but it is important to note that not all affected individuals

TABLE 1B Systemic Scoring System of the Newly Revised Ghent Criteria (Adapted From Loeys et al 2010)

Feature	Value
Wrist and Thumb sign	3
Wrist or Thumb sign	1
Pectus carinatum	2
Pectus excavatum or chest asymmetry[a]	1
Hindfoot deformity (eg, heel valgus)[b]	2
Pes planus	1
Pneumothorax	2
Dural ectasia	2
Protrusio acetabulae	2
Reduced upper-to-lower segment ratio and increased arm span-to-height	1
Scoliosis or thoracolumbar kyphosis	1
Reduced elbow extension	1
Craniofacial features: 3 of the following: dolichocephaly, downward-slanting palpebral fissures, enophthalmos, retrognathia, and malar hypoplasia	1
Skin striae	1
Myopia	1
Mitral valve prolapse	1

[a] In the presence of pectus carinatum, no additional points can be given for excavatum or chest asymmetry.
[b] Hindfoot valgus is often associated with pes planovalgus and no additional point can be given for pes planus when heel valgus present.

are tall by population standards; they are typically taller than predicted for family (excluding others with Marfan syndrome).[20] Average final height for males was 191.3±9 cm (75 in) and 175.4±8.2 cm (69 in) for females.[20]

The linear growth of the tubular bones is accelerated, resulting in disproportionate features. The extremities are often disproportionately long in comparison with the trunk (dolichostenomelia), altering the upper to lower segment and the arm span to height ratios. The arm span to height ratio is relatively fixed during childhood, but the upper to lower segment ratio changes during growth. Similarly, the tubular bones of the hand and fingers are elongated, but the palm is not proportionately wider, resulting in relative arachnodactyly as measured by the thumb and wrist signs (Fig 3).

Excessive growth is attributable, in part, to a peak growth velocity, which typically occurs as much as 2 years earlier compared with the general population.[20] Hormonal therapy to limit adult height is rarely used and less often in males. Complications can include accelerated growth, early puberty, and the undesirable consequences of increased blood pressure that may result in the progression of the aortic dilatation.[21] Prepubertal females have been treated in the past with high-dose estrogen therapy and progesterone to reduce final adult height; however, this remains controversial in both its psychosocial and medical benefits.[22–24] Surgical manipulation of the growth plates (epiphysiodesis) to limit long bone growth has also been used.[20]

Lean muscle mass is also affected. Individuals with Marfan syndrome often show a paucity of muscle mass and fat stores despite adequate caloric intake. Weight is often below the 50th percentile for age before adulthood.[20]

In Marfan syndrome, cognitive ability is usually within the typical range for the general population. However, poor vision and the underlying medical problems may interfere with education-related activities. Similarly, many patients report chronic fatigue, which may affect education and manifest as inattention or poor concentration but may also affect activities of daily living.[25–27] The etiology of the fatigue is likely heterogeneous, attributable in part to the underlying chronic condition, medications such as β-blockers, sleep disturbance (eg, sleep apnea), and/or orthostatic intolerance.[28]

CARDIOVASCULAR

The cardiovascular system is the major source of morbidity and mortality in Marfan syndrome. Cardiovascular manifestations include: dilatation of the aorta, most commonly at the aortic root, aortic valve insufficiency, a predisposition for aortic tear (dissection) and rupture, mitral valve prolapse with or without regurgitation, tricuspid valve prolapse, and enlargement of the proximal pulmonary artery.[29] Marfan syndrome is the most commonly diagnosed syndrome associated with pediatric presentation of aortic dilatation.[30]

The aortic dilatation in Marfan syndrome tends to progress over time, with the vast majority presenting before the age of 18 years. The dilatation typically is at the level of the sinuses of Valsalva (the aortic root), but dilatation of any part of the aorta can be observed in these patients (Fig 4). Histologic examination reveals elastic fiber fragmentation with loss of elastin content and accumulation of amorphous matrix components in the aortic media. This "cystic medial necrosis" does not distinguish Marfan syndrome from other causes of aortic aneurysm and, therefore, is only a description, not a pathognomonic feature.

The size of the aorta can be assessed using echocardiography, MRI, or computed tomography. In growing children, it is useful to

TABLE 2 Differential Diagnoses: Syndromes With Overlapping Features of Marfan

Syndrome	Manifestations	Genetic Etiology
Mitral valve prolapse syndrome	Mitral valve prolapse; skeletal manifestations as seen in Marfan syndrome	*FBN1* (in some)
MASS phenotype	Mitral valve prolapse; myopia; nonprogressive aortic dilatation; nonspecific skin and skeletal features	*FBN1*
Familial ectopia lentis	Eye and skeletal findings of Marfan syndrome	*FBN1* (in some) *ADAMTSL4*
Shprintzen-Goldberg syndrome	Skeletal and cardiac findings of Marfan syndrome; craniosynostosis; hypertelorism; proptosis; abdominal hernias; joint laxity; developmental delay or intellectual disability	*SKI*
Weill-Marchesani (autosomal dominant form)	Ectopia lentis; short stature; brachydactyly; characteristic facial features	*FBN1*
Loeys-Dietz syndrome	Skeletal and cardiovascular features of Marfan syndrome; NO ectopia lentis; aggressive dilatation of large and medium-sized arteries; most common and unique features include hypertelorism, bifid uvula or cleft palate, blue sclerae, developmental delays, hydrocephalus, translucent skin, arterial tortuousity, and craniosynostosis	*TGFBR1; TGFBR2; SMAD3; TGFB2; TGFB3*
Congenital contractural arachnodactyly (distal arthrogryposis, type 9)	Marfan-like skeletal features; "crumpled" ears; contractures of the knees, ankles, and digits at birth; progressive kyphoscoliosis; arachnodactyly; cardiac valvular anomalies	*FBN2*
Familial thoracic aortic aneurysm	Dilatation of the aorta and dissections either at the level of the sinuses of Valsalva or the ascending thoracic aorta without the other phenotypic features of Marfan	Heterogeneous
Vascular Ehlers-Danlos syndrome	Thin skin with visible veins; easy bruising; small joint laxity; rupture of hollow organs as well as medium and large-size arteries	*COL3A1; COL3A2*
Kyphoscoliotic Ehlers-Danlos syndrome	Marfanoid body habitus; kyphoscoliosis; joint laxity; mitral valve prolapse; hypotonia; blue sclerae; ocular fragility; at risk for rupture of medium-sized arteries	*PLOD; FKBP14*
Homocystinuria	Ectopia lentis; skeletal abnormalities such as those seen in Marfan syndrome; variable cognitive impairment; tendency for thrombotic events	*CBS*
Stickler syndrome	Severe myopia; retinal detachment; hearing loss; midface hypoplasia; cleft palate; spondyloepiphyseal dysplasia	*COL2A1; COL11A1; COL11A2; COL9A1; COL9A2*
Fragile X syndrome	Often tall; long face; joint laxity; mild dilatation of the aorta; mitral valve prolapse; pectus excavatum; variable intellectual disability	*FMR1*

monitor the aortic root z-score normalized to body surface area (https://www.marfan.org/dx/zscore). The aortic z-score represents the number of standard deviations from the mean for any given aortic dimension. An aortic root z-score of 0 means the dimension is average for a given body surface area, and a z-score between −2 and +2 represents the normal range based on 95% of the general population. During childhood, the degree of dilatation generally stays relatively constant or progresses slowly. The aortic root z-score typically stays about the same or slowly increases, reflecting that the aortic root grows in proportion to somatic growth. Rapid dilatation is rare during childhood.

The age of onset and rate of progression of aortic dilatation is highly variable. As the aneurysm enlarges, the aortic annulus can dilate, leading to aortic regurgitation; however, the vast majority of children and adolescents have no significant aortic regurgitation. Aortic or mitral valve dysfunction, when present, can lead to volume overload with secondary left ventricular dilatation and heart failure. Indeed, mitral valve prolapse with congestive heart failure is the leading cause of cardiovascular morbidity and

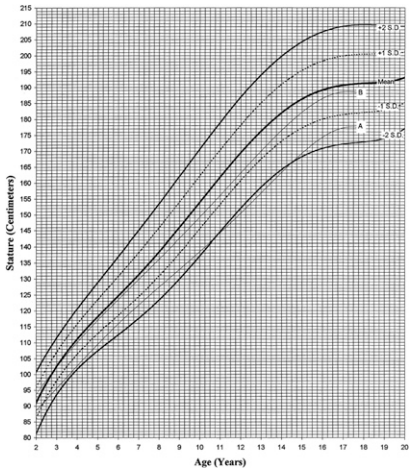

FIGURE 1
Growth curves for males in Marfan syndrome. (A) 50th percentile and (B) 95th percentile for the general population used for comparison. Reprinted with permission from Erkula G, Jones KB, Sponseller PD, Dietz HC, Pyeritz RE. Growth and maturation in Marfan syndrome. *Am J Med Genet*. 2002;109(2):104.[20]

mortality in young children with the severe neonatal presentation of Marfan syndrome.[31]

The risk of aortic dissection or rupture increases with the aortic dimension, and prophylactic surgical replacement of the aortic root is generally recommended when the maximal aortic dimension reaches or exceeds 5.0 cm in adults and older teenagers. However, approximately 15% of patients with Marfan syndrome suffer aortic dissection at an aortic dimension less than 5.0 cm, and dissection at 4.5 cm has been documented among women with Marfan syndrome.[32,33] Fortunately, aortic dissection is exceedingly rare in childhood or adolescence. Acute aortic dissection usually presents as severe chest pain but can also include respiratory distress, pallor, pulselessness, asymmetric blood pressures, paresthesia, and paralysis.

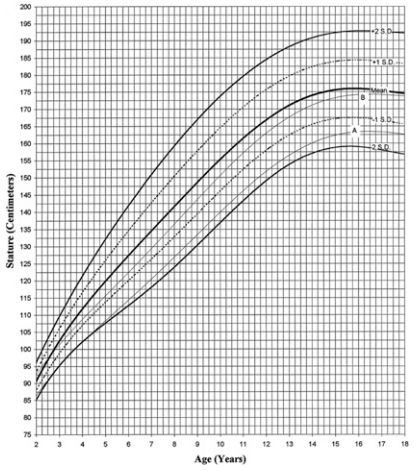

FIGURE 2
Growth curves for females in Marfan syndrome. (A) 50th percentile and (B) 95th percentile for the general population used for comparison. Reprinted with permission from Erkula G, Jones KB, Sponseller PD, Dietz HC, Pyeritz RE. Growth and maturation in Marfan syndrome. *Am J Med Genet*. 2002;109(2):104.[20]

All individuals with a diagnosis of Marfan syndrome should be followed by a cardiologist familiar with Marfan syndrome. An echocardiogram should be obtained at diagnosis.[33] A subsequent echocardiogram is often desired in 6 months to assess the rate of progression. The frequency of subsequent echocardiograms in children depends on the z-score. For most children, an annual echocardiogram is sufficient. If the aortic root is severely dilated (z-score $>+5$ or z-score increasing), more frequent echocardiograms may be indicated. If the aortic root is normal or minimally dilated (z-score $<+2.5$), the echocardiograms can be performed every 1 to 2 years. In adults, yearly echocardiograms are sufficient when aortic dimensions are small to moderate (<4.5 cm in adults) and rates of aortic dilatation are low (<0.5 cm per year). More frequent evaluations are indicated when the aortic root diameter exceeds 4.5 cm in adults, when the rate of aortic dilatation exceeds 0.5 cm per year, or with the onset of significant valvular or ventricular dysfunction. If not clearly demonstrated by echocardiography, aortic root dimensions can also be determined using computed tomography (CT) or magnetic resonance angiography (MRA) and potentially have the benefit of evaluating beyond the aortic root. MRA is recommended for serial studies because of the radiation associated with CT. CT is best when there is a question of dissection. Because aortic dilatation can occur at any age, lifelong monitoring is warranted.

Medications that reduce hemodynamic stress on the aortic wall, such as β blockers or angiotensin receptor blockers, are often prescribed.[33] In early animal studies, the angiotensin receptor blocker losartan showed remarkable promise in reversing the aortic pathology in mice with Marfan syndrome.[34] In a small series of children with severe Marfan syndrome, the combination of β-blocker and losartan showed better suppression of aortic root enlargement.[35] These early studies stimulated a series of clinical trials over the last decade that evaluated the efficacy of β blockers (mainly atenolol) and angiotensin receptor blockers (mainly losartan) in slowing the growth of the aorta in children, adolescents, and adults with Marfan syndrome. Some trials have directly compared atenolol against losartan without a placebo arm.[36–38]

The Pediatric Heart Network (PHN) Marfan Trial, funded by the National Institutes of Health, is the largest pharmacologic Marfan trial completed to date. In this large multicenter study of losartan versus atenolol in children, adolescents, and young adults with Marfan syndrome (age range at enrollment, 6 months to 25 years) with aortic root dilatation (z-score $>+3$), losartan and atenolol demonstrated similar efficacy in slowing the aortic root dilatation progression over a 3-year period.[37] However, losartan was dosed at the standard dosing (1.0–1.4 mg/kg per day), whereas atenolol was used at unusually high

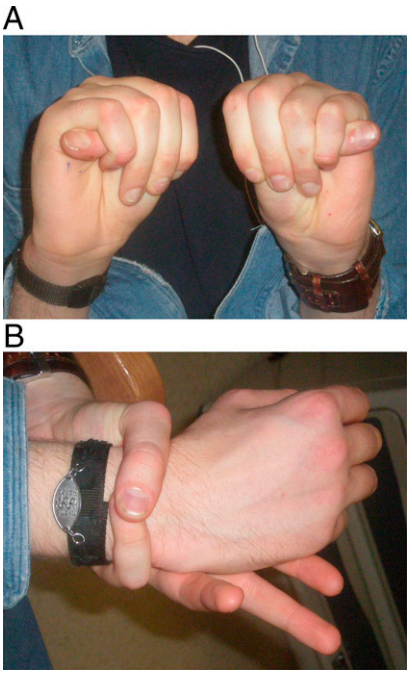

FIGURE 3
Positive thumb sign (A) with the thumbnail extending past the ulnar side of the hand and positive wrist sign with the overlap of the nailbeds of the thumb and fifth finger (B).

doses (1–4 mg/kg per day) to achieve maximal β-blockade. Of note, in the PHN trial, the magnitude of the benefit for β blockers as well as angiotensin receptor blockers in terms of reduction in aortic root

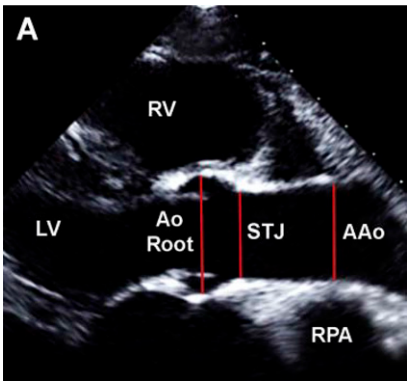

FIGURE 4
In Marfan syndrome, dilatation is typically at the level of the aortic root (sinuses of Valsalva). Measurements are taken during systole. LV, left ventricle; RV, right ventricle; Ao Root, aortic root (sinuses of Valsalva); STJ, sinotubular junction; AAo, ascending aorta. Reprinted with permission from *J Am Soc Echocardiogr.* 2010;23(5):485; doi:10.1016/j.echo.2010.03.019.[116]

z-score was greater in younger patients, supporting the idea of initiating medical therapy in very young patients with aortic dilatation. Finally, both drugs were safe and well tolerated.

Other trials compared the combination of an angiotensin receptor blocker and a β blocker to monotherapy with a β blocker. Some, but not all, of these trials were randomized and placebo controlled. The results of these trials have been mixed. Some trials showed a benefit of the combination therapy,[39,40] but others did not.[41,42] However, an individual patient data meta-analysis supported the use of dual therapy.[43]

The Aortic Irbesartan Marfan Syndrome trial in the United Kingdom, a multicenter, double-blind, placebo-controlled randomized trial of irbesartan, an angiotensin receptor blocker, versus placebo added to prior therapy (generally β blocker or no therapy) showed a benefit of irbesartan in slowing the rate of growth of the aortic root.[44] Irbesartan has the theoretical advantage over losartan in the potential for higher dosing with comparable safety and tolerance profiles. However, none of these trials were powered to determine whether drug therapy affected the rate of aortic surgery, aortic dissection, or death, because such a trial would require huge resources over a long period of time.

Treatment with either a β blocker or an angiotensin receptor blocker is recommended for a patient diagnosed with Marfan syndrome with aortic root dilatation. Some clinicians prefer to treat all patients, even those without aortic root dilatation, but it is reasonable to follow closely without treatment if there is no significant root dilatation. When using a β blocker, care should be given to achieving a reduction in resting and exercise heart rate compared with baseline, because the magnitude of the benefit may depend on the efficacy of β blockade. When using losartan, doses of 1.0 to 1.4 mg/kg per day were used in the PHN Marfan Trial; however, doses as high as 2.0 mg/kg per day are now routinely used in patients with Marfan syndrome in clinical settings. Combination therapy with a β blocker and an angiotensin receptor blocker can be considered in patients with severe and/or progressive aortic root dilatation. Irbesartan may be superior to losartan because of the potential for higher dosing without compromising safety or tolerance; however, there is currently much less experience with irbesartan in the setting of Marfan syndrome. Angiotensin receptor blockers in females of childbearing age should be used with caution, given their teratogenic effect. Angiotensin receptor blockers are contraindicated in pregnancy. Data suggest calcium channel blockers may increase the risk of aortic events and, therefore, are relatively contraindicated.[45] Angiotensin-converting enzyme (ACE) inhibitors have not been studied as extensively in humans with Marfan syndrome. Data from a mouse model of Marfan syndrome suggest that angiotensin receptor blockers are superior to ACE inhibitors in attenuating aortic aneurysms.[46]

Timely surgical replacement of the aortic root has resulted in markedly improved life expectancy in people with Marfan syndrome. Surgical replacement of the aorta is indicated once: (1) the maximal aortic root measurement exceeds 5.0 cm; (2) the rate of increase of the aortic diameter approaches >0.5 cm per year; or (3) there is progressive aortic regurgitation.[33] More

aggressive therapy may be indicated in individuals with a family history of early aortic dissection and those contemplating pregnancy. Many individuals can receive a valve-sparing procedure that precludes the need for chronic anticoagulation therapy[33,47] and is considered safe and appropriate in children and adolescents.[48] Although most young children with Marfan syndrome will not require cardiac surgical intervention, those children who do undergo their first operation before the age of 10 years have a high risk of requiring repeated cardiac operations, such as valve replacement.[49] These young children generally have the severe neonatal Marfan presentation rather than a classic Marfan presentation. Overall, cardiac complications are rare in young patients with classic Marfan syndrome receiving medical therapy and close follow-up. There is a small risk of sudden death related to arrhythmias, which is not well characterized but appears to be more common in patients with dilated left ventricle.[50]

Aortic dilatation can also be seen in the descending aorta, although typically at later ages. All individuals with Marfan syndrome should begin intermittent surveillance of the entire aorta with CT or MRA scans in late teen or young adult years.[33,51] Such imaging should be performed about every 3 years or more frequently if there is dilatation of the aorta beyond the aortic root. CT or MRA scans should also be performed at least annually in anyone with a history of aortic dissection or in those for whom echocardiography does not provide adequate imaging of the aortic root.

Some individuals with Marfan syndrome report orthostatic intolerance and associated fatigue. These findings are likely inherent to Marfan syndrome but can be easily exacerbated by medications such as β-blockers.[28] Patients should remain well-hydrated and be instructed on symptoms and various physical counter maneuvers that may help orthostasis.[52] Counter maneuvers can include standing up slowly, standing with one's legs crossed, squatting, and sitting in a crouched position with the legs closer to the chest. In the absence of syncope, symptoms of orthostatic intolerance can be managed by the primary care practitioner. Syncopal episodes, if they occur, should be further evaluated to exclude seizures or cardiac arrhythmia.

Agents that stimulate the cardiovascular system (tachycardia, vasoconstriction, hypertension) including routine use of triptans and decongestants should be avoided if possible. The use of psychostimulant medications for chronic fatigue or attention-deficit/hyperactivity disorder can be used with caution and be approved by the cardiologist. Stimulant-related complications are rare, and adequate management of attention-deficit/hyperactivity disorder is important for optimal quality of life.[53] Fluoroquinolone antibiotics, which may increase the risk of aortic aneurysm and dissection, should be avoided if possible.[54]

OCULAR

Myopia is the most common ocular feature, typically attributable to elongation of the globe, and often progresses rapidly during childhood.[55] Displacement of the lens (ectopia lentis) is a hallmark feature of Marfan syndrome but is only observed in 1 or both eyes in 30% to 60% of affected individuals.[56] If ectopia lentis occurs, it is often a presenting feature and commonly occurs before the age of 10 years. Ectopia lentis is very uncommon in the general population; every diagnosis of ectopia lentis warrants a genetic workup for Marfan syndrome or related conditions. This finding is most reliably diagnosed by slit-lamp examination after full pupillary dilatation, which may exhibit delayed response, especially in the pediatric population with Marfan syndrome.[57]

The cornea is often thinned and may be flat or even cone shaped (keratoconus) curvature.[56] Individuals with Marfan syndrome are at increased risk for retinal detachment, glaucoma (~30%), and early cataract formation typically in adulthood. Flashes of light (photopsias) and new floaters are symptoms of posterior vitreous detachment, which may precede retinal detachment.[57,58] Retinal detachment should be considered in any patient presenting with an acute onset of visual symptoms, and these patients should be evaluated and treated emergently. Most retinal detachments can be repaired successfully, but the key to optimum visual recovery is prompt diagnosis and treatment. Unilateral retinal detachments may occur unnoticed by a young patient, or even by an adult, because of maintenance of vision in the unaffected eye, so routine vision assessments of each eye in isolation are recommended.

Affected individuals should be monitored at least yearly by an ophthalmologist familiar with Marfan syndrome with slit-lamp examinations for lens subluxation and cataract formation, evaluations for glaucoma, and dilated fundus examinations for retinal tears or detachments. In most cases, high refractive error can be treated with corrective lenses, but young children are at risk for amblyopia and require careful refraction and close monitoring.[59]

Ectopia lentis (lens dislocation) can present a clinical challenge.

Typically, the lens will sublux superotemporally in Marfan syndrome. If the lens is subluxed but remains within the visual axis, substantial lenticular astigmatism may occur, requiring high astigmatic correction. If the lens edge is positioned at or beyond the visual axis, corrective lenses usually reserved for aphakic (lack of a lens) may be needed. If there is sufficient optical distortion from lens subluxation that cannot be corrected with spectacles or contact lenses, lensectomy (surgical removal of the lens) with or without intraocular lens placement should be considered.[60] Because of weak zonular support for the Marfan lens, intraocular lens placement (pseudophakia) is more complex, requiring additional means to affix the intraocular lens. Sutured intraocular lens placement may be performed, which is generally a safe procedure but does carry greater risks, including retinal detachment and dislocation of the intraocular lens itself, because its long-term stability and safety is largely unknown.[61] Corneal refractive surgery for myopia is generally contraindicated in individuals with Marfan syndrome because of a greater risk of ocular complications.

MUSCULOSKELETAL

The musculoskeletal features are often the presenting concerns of patients with potential Marfan syndrome. In children younger than 14 years, De Maio et al (2016) found: both wrist and thumb signs in 64%; pectus deformity or chest asymmetry in 61%; severe flatfoot in 61% with a hindfoot deformity; acetabular protrusion in 14%; reduced upper to lower segment ratio and/or increased arm span to height ratios in 39%; scoliosis $>20^{\circ}$ in 18%; and reduced elbow extension in 11%.[62]

The skeletal system involvement is characterized by bone overgrowth. Such overgrowth may be noticeable at birth or can develop in young children with a tendency to progress more rapidly during periods of rapid growth, necessitating close monitoring at such times (Table 3). Overgrowth of the limbs (dolichostenomelia) creates the tall, lanky appearance and drives the increase of the arm span to height ratio and a decrease in the age-related upper body segment to lower body segment ratio. Further, elongation of the short tubular bones of the hand without accompanying widening results in the appearance of arachnodactyly as well as the clinical "thumb" and "wrist" signs (Table 1B).

Overgrowth of the ribs can push the sternum inward (pectus excavatum) or outward (pectus carinatum). Nearly two-thirds of patients with Marfan syndrome will develop pectus deformity, including chest asymmetry, which is often perceived as a disturbing physical feature by teenagers and can contribute to issues related to self-esteem, anxiety, or depression.[63] Of those patients presenting with a pectus deformity, 5% will have Marfan syndrome, and the pectus may be the presenting feature in young children.[64] Although most patients with pectus excavatum are asymptomatic, symptoms can include breathlessness, exertional chest pain, palpitations, and exercise intolerance. The pectus deformity

TABLE 3 Anticipatory Guidance in Marfan Syndrome

	At Diagnosis	0–12 Mo	1–5 Y	6–12 Y[a]	13–18 Y[a]	19–22 Y
Cardiac examination[b]	√	Each visit	Each visit	Each visit	Yearly	Yearly
Echocardiogram	√	As indicated	Yearly	Yearly	Yearly	Yearly
Ocular (ophthalmology)	√	—	Yearly	Yearly	Yearly	Yearly
Musculoskeletal[b]						
Scoliosis: clinical exam	√	Each visit	Yearly	Every 6 mo	Every 6 mo	Yearly
Joint laxity	√	Each visit	Yearly	Every 6 mo	Every 6 mo	—
Pectus deformity	√	Each visit	Yearly	Every 6 mo	Every 6 mo	—
Bone age		—	—	√[c]	—	—
Review diagnosis	√	PRN	PRN	PRN[d]	PRN[d]	PRN[d]
Examine family members	√	PRN	PRN	PRN	PRN	PRN
Support group information	√	PRN	PRN	PRN	PRN	PRN
Genetic counseling	√	—	—	—	√[e]	√[e]
Lifestyle[f]	—	—	—	√	√	√
Transition	—	—	—	—	Discuss plans[g]	Begin transition[g]

Many systems should be reviewed regularly at developmentally appropriate stages.

[a] Periods of rapid growth may require closer supervision.

[b] If abnormal examination, refer for further evaluation. Follow-up evaluations as indicated.

[c] Bone age determination in preadolescence. If large discrepancy between bone age and height age, consider hormonal therapy.

[d] Review symptoms of potential catastrophic events such as aortic dissection, vision changes, and pneumothorax.

[e] Discuss reproductive and pregnancy risks.

[f] Review physical activity restrictions and lifestyle modifications.

[g] Topics to review include timing of transition; education and employment goals and accommodations or restrictions; self-advocacy; maintenance of a medical home in adulthood; insurance and insurability.

can be severe and, in extreme circumstances, interfere with pulmonary functioning, warranting surgical intervention.[65] Pectus excavatum may also have a detrimental effect on cardiac function, especially during submaximal exercising,[66] and is often repaired before cardiac surgery for aortic root replacement. This pectus deformity is typically present before age 10 years but may worsen during an adolescent growth spurt.

Scoliosis is present in slightly more than half of individuals with Marfan syndrome and can be mild to severe as well as more progressive than usually observed in idiopathic scoliosis.[67] Close monitoring by forward bend test at yearly intervals and management by an orthopedist is preferred as surgical stabilization of the spine may be required.[68] Bracing has low success rate if the curves are greater than 35° to 40° but may have some preventive value for smaller curves. Those with spinal curvatures <30° have an excellent long-term prognosis. Marked progression is often seen by those with curves >50°. The progression of scoliosis can occur well into adulthood.

Thoracic kyphosis is also common and can be postural or a further complication of bony overgrowth and ligamentous laxity (eg, kyphoscoliosis). Postural education and joint stabilization with core strengthening may be of benefit but are unproven for the treatment of scoliosis in this population. Untreated spinal deformities can lead to chronic back pain and restrictive lung disease. Spinal deformity correction is more prone to complications, including cerebrospinal fluid leaks, than in idiopathic deformity and should be conducted by those with some experience in treating individuals with Marfan syndrome.[69]

Cervical spine anomalies are also seen with a higher prevalence in patients with Marfan syndrome. Hobbs et al found a 16% prevalence of cervical spine kyphosis, atlantoaxial translation (54%), and basilar impression (36%). Neck pain or persistent tension-type headache may result, but proper ergonomics and physical therapy may be warranted.[70]

The acetabulum of the hip can be abnormally deep (protrusio acetabuli) in some. This can lead to pelvic or upper leg pain. This radiographic feature is seen commonly in Marfan syndrome, with peak prevalence in the pediatric age, then leveling off[67]; however, it is not unique to Marfan syndrome, being observed in a number of infectious, inflammatory, metabolic, genetic, neoplastic, and traumatic conditions.[71] In Marfan syndrome, the protrusio acetabuli is often asymptomatic and surgical intervention is rarely indicated.[67]

Some individuals will show reduced mobility of the elbow, whereas other joints may demonstrate ligamentous laxity. Joint laxity may be more significant in the young but rarely leads to motor delays. True joint dislocations are rare. Joint laxity can lead to muscle fatigue and overuse pain or injury.[72] More typically, such individuals demonstrate poor writing skills and complain of hand pain or fatigue with prolonged use. Physical and/or occupational therapy can address these joint laxity issues with joint stabilization exercises, postural support, education, alternative strategies (eg, use of a laptop for notetaking), and bracing or resting splints if necessary.

Inward rotation of the medial aspect of the ankle can result in pes planus with heel valgus (Fig 5). This may lead to foot, ankle, knee, hip, and/or low back pain. Some will benefit from the use of shoe orthoses, such as an arch support and more supportive shoes. Surgical intervention is rarely indicated or fully successful. Still, others will have highly arched feet but have little or no symptoms.

The facial features of Marfan syndrome include a long and narrow face with deeply set eyes (enophthalmos), downward slanting of the eyes, flat cheek bones (malar hypoplasia), and a small chin (micrognathia) (Fig 6). However, the facial features are often highly variable and may change with age. In addition, these facial features are not highly sensitive for the presence of Marfan syndrome.[73] The palate is often highly arched and narrowed (Fig 7).

Decreased bone density, typically osteopenia, has been documented in the lumbar and hip regions in patients with Marfan syndrome[67] but not consistently in other studies including that of children with Marfan syndrome.[74] The etiology of this bone loss remains speculative but no significant increase in bone fracture rates has been seen.[75]

PULMONARY/AIRWAY AND SLEEP

Pulmonary issues encountered in Marfan syndrome include spontaneous pneumothorax, reduced pulmonary reserve, and obstructive sleep apnea. In neonatal Marfan syndrome, an emphysematous lung disease can be

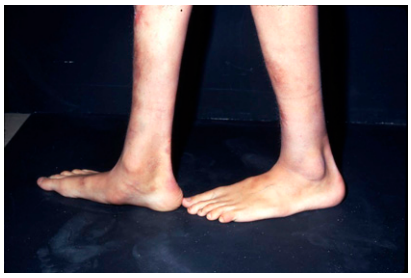

FIGURE 5
Elongated feet with collapse of the medial arch resulting in pes planus.

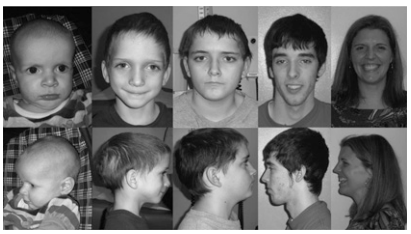

FIGURE 6
Facial features of Marfan syndrome are highly variable, ranging from subtle findings to more "classic" facial features.

present and progress rapidly; emphysema occurs in approximately 10% to 15% of those with "classic" Marfan syndrome, usually to a milder degree.[76]

Lung bullae, which develop in 4% to 15% of patients with Marfan syndrome, can develop anywhere on the surface of the lungs but especially in the upper lobes.[77] Such bullae (or blebs) can predispose to spontaneous pneumothorax. Symptoms of pneumothorax include sudden onset of chest pain, dyspnea, and/or cyanosis. Breathing against resistance (eg, playing a brass instrument), scuba diving, or high-altitude sports (eg, sky diving, mountaineering) should be avoided, especially among those with a family history of spontaneous pneumothorax. Those with recurrent pneumothorax may require chemical or surgical pleurodesis or surgical resection of pulmonary blebs.

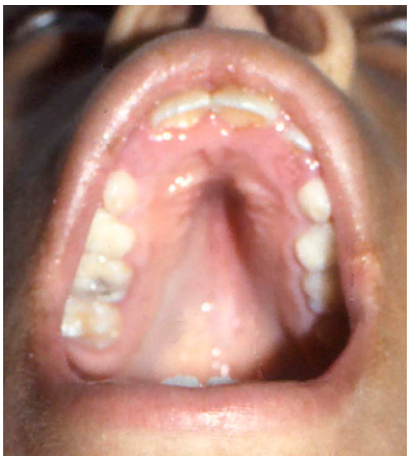

FIGURE 7
High arched ("steepled") palate.

A restrictive lung disease pattern with decreased total and residual lung volume as well as exercise intolerance is typically seen in the majority of those affected.[78] Often, this is related to pectus deformity, chest wall asymmetry, and/or scoliosis. Surgical repair of the pectus excavatum or scoliosis may improve overall pulmonary lung function. Pulmonary function tests should be performed in any patient with pulmonary complaints or significant pectus deformity or scoliosis and can be monitored after surgical repair.

Obstructive sleep apnea is present commonly in patients with Marfan syndrome.[79] Increased nasal resistance because of craniofacial abnormalities, such as a high arched palate, micrognathia with possible glossoptosis, and laryngotracheomalacia, can cause difficulty with intubation or anesthesia as well as significant upper airway resistance.[80] Sleep apnea is underappreciated among adolescents and young adults with Marfan syndrome. Studies also show the untreated sleep apnea may promote aortic dilatation[81] and elevation in pulmonary artery pressure. Symptoms commonly seen in Marfan syndrome that may be partially attributable to sleep apnea include fatigue or loss of energy as well as impaired memory and cognition ("brain fog"). Symptoms of sleep dysfunction such as fatigue, decreased sleep duration, nonrestorative sleep, and snoring should be reviewed at each visit. Formal sleep evaluation should be considered in such cases, or if there is elevation in pulmonary artery pressure.

INTEGUMENT

About two-thirds of people with Marfan syndrome develop stretch marks of the skin.[82] Often, these stretch marks are located across the lower back as well as the inguinal and axillary regions. These stretch marks are signs of rapid growth and are usually perpendicular to the axes of growth.

Because of the defect in connective tissue, those with Marfan syndrome are also at risk for hernias. Many will have inguinal herniation that will require surgical repair. However, recurrent hernias or hernias at the site of surgical incisions are a more distinctive hallmark of a connective tissue disorder such as Marfan syndrome. Primary hernia repair utilizing a synthetic mesh (or similar artificial construct) in all known or suspected cases of Marfan syndrome should be considered to minimize recurrence risk.

DURAL ECTASIA

The majority of individuals with Marfan syndrome often develop stretching of the dural sac during childhood in the dependent lumbosacral region, resulting in dural ectasia[83,84] (Fig 8). In most, the dural ectasia is asymptomatic[85]; however, dural ectasia can lead to bony erosion and nerve entrapment. Symptoms can include pain in the lower back with radiation to the hip or pelvic region and proximal leg as well as weakness and numbness above and below the knees.[86] Detection of dural ectasia can be performed using either MRI or CT, and upright imaging may be preferred.

Excessive accumulation or leakage of cerebrospinal fluid from the dural sac can cause postural hypotension and "low-pressure" headaches.[87,88] Damage of the dura from spinal taps or epidurals may not sufficiently heal, causing leakage also predisposing the patient to postural headaches. In severe cases of dural ectasia, spinal shunting

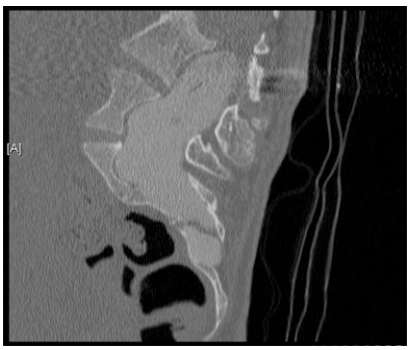

FIGURE 8
Dural ectasia of the lumbar spinal canal. MRI appearance of the dilated dural sac, which can erode the bone and entrap nerves.

and/or medication can be used. Complications following surgical repair of the dura include cerebrospinal fluid leakage and recurrence.

DENTAL

People with Marfan syndrome typically have oromaxillofacial anomalies. Most have an elongated face, malar hypoplasia, high-arched palate, and micrognathia. Often, these anomalies will cause significant dental crowding and malalignment. Routine dental care is recommended; however, many individuals with Marfan syndrome require orthodontia for proper occlusion as well as appearance. Oral maxillofacial interventions may also be indicated such as palatal expansion and/or mandibular distraction.

Subacute bacterial endocarditis prophylaxis may be indicated for dental work or other procedures expected to contaminate the bloodstream with bacteria in the presence of significant valvular insufficiency or prior valve surgery.

PAIN

Pain is not a defining feature of Marfan syndrome but is significantly underrecognized.[89] Up to 90% of adults report pain, with the majority reporting daily, unremitting pain.[90,91] Approximately one-quarter actually present with pain. Back pain is most common, and chest pain or leg pain is less common, with the quality of arthritic or a deep aching ("bone") pain.[27] Back pain does not always correlate to back pathology, such as dural ectasia, scoliosis, etc. The pain overall contributes to poor physical and mental health functioning as pain-related disability.

Headaches, including migraines and "low pressure" headaches, may also affect quality of life. Vasoconstrictive agents, such as triptans, should be used with caution for treatment of migraine headaches. Quality of life measures are decreased, at least in some part because of pain.[27] Adjunctive physical therapy, mindfulness, and cognitive behavioral techniques can be helpful in pain management.

PHYSICAL ACTIVITY

Although all children and adolescents are encouraged to participate in physical activity for overall health, skill development, coordination, musculoskeletal health, and socialization, those with Marfan syndrome are at significant risk for physical injury and medical complications. Of concern are activities including contact sports, activities involving "burst" exertion (eg, sprinting), and intense static (isometric) exertion such as weightlifting.[92] In general, patients with Marfan syndrome without aortic dilatation, significant valve regurgitation, or ventricular dysfunction are encouraged to participate in noncompetitive (recreational) activities, but this is still limited by the intensity level of the activity and the individual.[92]

Sports in which ocular trauma is likely, such as boxing or full-contact martial arts, should be discouraged. Those with aortic replacement should be instructed in low static or dynamic activities.[92] Participation in any activity should be evaluated and discussed before initiation of that activity. Although weightlifting and the most strenuous and *competitive* sports should be avoided, most individuals can participate in low-impact, low-to-moderate intensity activities, such as walking, jogging, biking, and swimming at a *recreational* level. Activities of most concern include: heavy-contact sports such as football, basketball, and hockey; body building or weightlifting, surfing, scuba diving, rock climbing, competitive running, skiing, and racquetball. More acceptable alternatives include: modest hiking, stationary cycling, bowling, golf, skating, snorkeling, and brisk walking. Caution is needed for patients with low blood pressure and orthostatic intolerance, including those on β-blocker therapy, who may be more susceptible to easy fatigue, near-syncopal or syncopal episodes, and falls.[28]

QUALITY OF LIFE

In a study of 230 teenagers and adults (average age 42 years), Rao et al revealed that the perception of health concerns was greatest for cardiac problems followed closely by spine-related issues and fatigue.[27] Many also reported depression and difficulty concentrating, which likely contribute to a decrease in work life productivity. Health-related quality of life was assessed in a large multicenter cohort of children, adolescents, and young adults participating in the Pediatric Heart Network Marfan Trial.[53] Mean quality of life scores for children and adolescents were lower compared with healthy population norms for physical and psychosocial domains. Factors associated with lower scores included frequency of patient-related symptoms, presence of a neurodevelopmental disorder,

such as learning disability or attention deficit/hyperactivity disorder, and male gender, but not treatment arm (atenolol versus losartan), aortic root z-score, or severity of Marfan syndrome-related physical findings.

In a large cohort of patients with Marfan syndrome in the GenTAC registry, health-related quality of life was also below the population norm.[93] Better quality of life was independently associated with socioeconomic factors, not factors related to general health or Marfan severity. Assessing quality of life using any of the clinically validated instruments is encouraged, but assessing all aspects of life including health burden, self-imaging, behavioral or psychological concerns, educational issues, socialization, and financial strains on the patient and family is important to be aware of and address.

PSYCHOSOCIAL

Marfan syndrome will affect each individual differently. Marfan syndrome has a significant impact on daily activities and perceived quality of life.[94,95] In 2 small series, the majority of affected individuals 13 years or older reported a positive general self-image.[96,97] However, the majority also had a negative self-image of their bodies with regard to their sexual relationships.[97] This negative body awareness can lead to social anxiety and depression.[63] Routine depression screening, especially in adolescence, may help identify individuals who need more support or intervention.[98]

Many of those affected by Marfan syndrome benefit from networking and peer relationships. The Marfan Foundation (www.marfan.org), based in the United States, is an excellent resource for connections as well as medical advice. The international organizations have been consolidated into Marfan World (http://www.marfanworld.org/).

LIFE EXPECTANCY

With timely diagnosis and proper multidisciplinary management, the life expectancy of someone with Marfan syndrome approximates that of the general population.[99,100]

TRANSITION/MEDICAL HOME

Because Marfan syndrome can affect the very young and continues throughout their lifetime, affected individuals are often followed by cardiologists, ophthalmologists, and orthopedists.[101] It is important that such individuals be recognized and a medical home be established.[102] The medical home is an important framework in the care of children and adolescents with special health care needs. The medical home provides care coordination among the medical specialties providing optimal and efficient health care for the patient and family. Just as important, the medical home should also provide coordination of other aspects, such as social, behavioral, financial, educational, and advocacy and support services.

Care needs to be coordinated among the various specialties, with a special focus on the period of transition from adolescence to adulthood. This transition planning needs to include a discussion of contraception and the cardiovascular risks associated with different methods of contraception as well as pregnancy. The transition may need to help adolescents with challenges in employment opportunities and risks, educational accommodations, insurability, self-advocacy, and health status in addition to creating or maintaining a medical home. For more insights into transitioning adolescents with special needs' medical home into adulthood, please see the joint clinical statement from the American Academy of Pediatrics, American Academy of Family Physicians, and the American College of Physicians.[103]

PREGNANCY

Pregnancy can lead to significant medical complications for women with Marfan syndrome and should be approached with careful deliberation.[104,105] Use of angiotensin receptor blockers and ACE inhibitors should be stopped, because these carry risk of fetal harm. Although there is a risk for fetal growth restriction with use of β blockers during pregnancy, β blocker therapy can generally be continued during pregnancy in women with Marfan syndrome with close monitoring of fetal growth.[106] Women with aortic dimensions greater than 4.0 cm are at significant risk for aortic complications during pregnancy and during the postpartum period, and pregnancy should be delayed if possible until after definitive treatment of the aorta has been completed.[104] Women whose aorta is greater than 4.5 cm or who previously had an aortic dissection or rupture are at substantially higher risk.[107] If already pregnant, consideration of immediate aortic replacement, early delivery, or termination of the pregnancy should be considered, given the potentially severe consequences.[104,105] The higher postpartum risk of aortic dissection may be influenced by sustained oxytocin in breastfeeding. In a mouse model of Marfan syndrome, aortic dissection postpartum was higher in those breastfeeding but reduced using oxytocin antagonists.[108] Until further clinical evidence in humans can be obtained, there is no recommendation currently about breastfeeding for mothers with Marfan syndrome.

A higher-than-expected rate of spontaneous abortion has been reported, although the etiology is unknown.[109] In addition, women with Marfan syndrome experience a higher rate of preterm deliveries, premature rupture of membranes, and increased mortality of their offspring.[109,110] Dural ectasia should be considered in any affected individual and avoidance of spinal anesthesia may be necessary. Epidural anesthesia is safe for most women with Marfan syndrome, although it may not be advised for those with moderately severe dural ectasia. General anesthesia has the benefit in avoiding complication of spinal anesthesia with dural ectasia and less stress on the aorta during delivery. Optimally, pregnancy should be considered after appropriate counseling from a geneticist or cardiologist familiar with this condition, a genetic counselor, and a perinatologist.

PRENATAL

Occasionally, the pediatrician is called on to counsel a family prenatally with regard to Marfan syndrome. Ideally, the family would already have spoken with a genetics professional but may be seeking care through the medical home. The pediatrician may have been previously involved with this family through care of siblings or 1 of the expectant parents. Families may also seek pediatric advice in the care and management of fetuses at risk. This may involve a few different scenarios.

1. The pediatrician may be asked about the risk to a child of a person with Marfan syndrome. The risk of inheriting the genetic defect in Marfan syndrome from an affected parent is 50%, consistent with autosomal dominant inheritance. Often, expectant parents are concerned about the severity of the disorder in the next generation. Variability of the Marfan phenotype is extensive but is more similar among affected family members, suggesting that the genetic defect is largely responsible for the phenotype. The vast majority of those with classic Marfan syndrome do not have children with a much more severe phenotype, such as neonatal Marfan syndrome.[111] One should also be aware of the consequences that may affect the pregnancy outcome for women with Marfan syndrome. As mentioned previously, women with aortic roots $>$4.5 cm in diameter should avoid pregnancy or undergo elective aortic grafting before becoming pregnant.[112] Aortic dissection or rupture has occurred in women with aortas $<$5.0 cm, which may result in significant morbidity and mortality of the unborn and the expectant mother.
2. The parents of a child with Marfan syndrome may ask about recurrence risk of Marfan syndrome in subsequent pregnancies. This issue may be best explained by a genetic health professional. In short, 1 of the parents may either be unrecognized as having Marfan syndrome (therefore recurrence risk is 50%) or unaffected and therefore carry only a slight chance of having a low-level of germline mosaicism (with anticipated recurrence risk of up to 2% to 3%). Because of a high occurrence of unrecognized Marfan syndrome in parents of a child with Marfan syndrome, it is advisable for both parents to undergo further evaluation to establish their own personal risk as well as the risk for subsequent pregnancies.
3. An expectant couple may have a fetus with concerning features of a severe presentation of Marfan syndrome in infancy (previously called neonatal Marfan syndrome) discovered on prenatal ultrasonography or even fetal MRI. Ultrasonographic findings may include unusually long limbs and congenital heart disease and are often detected in the third trimester.[113] Prenatal genetic testing for *FBN1* mutations may be helpful to confirm Marfan syndrome as well as reveal specific mutations in *FBN1* that may be more typically associated with this severe form and, therefore, reduced survivability. Should a diagnosis of severe presentation of Marfan syndrome in infancy be confirmed, the couple may want to deliver in a tertiary care center.

SEVERE PRESENTATION OF MARFAN SYNDROME DURING INFANCY

So-called "neonatal Marfan syndrome" is the most severe disorder resulting from a fibrillinopathy and in some cases may simply be referred to as "severe" Marfan syndrome. Features overlap significantly with classic Marfan syndrome but are more severe. Infants with the severe early presentation of Marfan syndrome are long with simple or crumpled ears, aged-appearing face, enlarged corneas, ectopia lentis, chest deformity, large feet, arachnodactyly, and contractures.[114] Respiratory insufficiency is common because of an abnormally pliant chest wall and emphysematous changes in the lungs. Cardiac abnormalities are severe and include polyvalvular dysplasia and aortic dilatation. Mortality is high within the first year of life because of cardiac failure secondary to severe mitral valve regurgitation[115]; however, some children live well beyond infancy. Almost all cases of neonatal Marfan syndrome are sporadic and are associated with mutations clustering within exons

24 through 32 of *FBN1*. Although neonatal Marfan syndrome is the most severe end of the spectrum, even among neonatal patients with Marfan syndrome, there is a range of severity, depending on the combination of features and the severity of the individual components. Often, the constellation of cardiac, pulmonary, musculoskeletal, diaphragmatic, and ocular findings heralds a very poor prognosis. Many clinicians use the terminology neonatal or infantile Marfan syndrome to describe the severe end of the clinical spectrum of Marfan syndrome, rather than considering this a discrete clinical entity. Care should be taken to avoid use of this designation simply because an infant is diagnosed with Marfan syndrome at a young age, as this might simply relate to an early evaluation because of a family history of Marfan syndrome or a particularly astute pediatrician, rather than atypically advanced disease severity.

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ABBREVIATIONS

ACE: angiotensin-converting enzyme
CT: computed tomography
MRA: magnetic resonance angiography
MRI: magnetic resonance imaging
PHN: Pediatric Heart Network
TGF: transforming growth factor

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