

# AMERICAN ACADEMY OF PEDIATRICS

## Health Supervision for Children With Marfan Syndrome

Committee on Genetics

**ABSTRACT.** This set of guidelines is designed to assist the pediatrician in caring for children with Marfan syndrome confirmed by clinical criteria. Although pediatricians usually first see children with Marfan syndrome during infancy, occasionally they will be called on to advise the pregnant woman who has been informed of the prenatal diagnosis of Marfan syndrome. Therefore, these guidelines offer advice for this situation as well.

Marfan syndrome is a heritable disorder of connective tissue characterized by autosomal dominant inheritance and variability in clinical expression. The frequency of this disorder is at least 1 in 10 000 in the United States.<sup>1</sup> Approximately one fourth of cases arise by new mutation; the rest are inherited from a parent. The gene (*FBN1*) has been mapped to chromosome 15q21.1;<sup>2</sup> the defective protein is fibrillin, an important protein in the structure of connective tissue. Specific mutations that result in defective or decreased fibrillin are being identified in persons with Marfan syndrome.<sup>3-4</sup> There is considerable heterogeneity in the known mutations.

The major clinical manifestations involve the skeletal, ocular, and cardiovascular systems and the skin.<sup>1</sup> Cardiovascular abnormalities are the most life-threatening features of Marfan syndrome, may be present at birth, manifest during childhood in about 25% of affected children,<sup>5-6</sup> and are progressive in about one third of those. The following manifestations occur in Marfan syndrome. They are divided into major and minor criteria.<sup>7</sup>

### Skeletal System

**Major Criteria.** The presence of at least four of the following manifestations: pectus carinatum; pectus excavatum requiring surgery; reduced upper-to-lower segment ratio or arm span-to-height ratio greater than 1.05; wrist and thumb signs; scoliosis of more than 20° or spondylolisthesis; reduced extension at the elbows (<170°); medial displacement of the medial malleolus causing pes planus; and pro-

trusio acetabulae of any degree (ascertained on radiographs).

**Minor Criteria.** Pectus excavatum of moderate severity; joint hypermobility; highly arched palate with crowding of teeth; and facial appearance (dolichocephaly, malar hypoplasia, enophthalmos, retrognathia, and down-slanting palpebral fissures).

### Ocular System

**Major Criterion.** Ectopia lentis.

**Minor Criteria.** Abnormally flat cornea (as measured by keratometry); increased axial length of globe (as measured by ultrasound); and hypoplastic iris or hypoplastic ciliary muscle, causing decreased miosis.

### Cardiovascular System

**Major Criterion.** Dilatation of the ascending aorta with or without aortic regurgitation and involving at least the sinuses of valsalva or dissection of the ascending aorta.

**Minor Criteria.** Mitral valve prolapse with or without mitral valve regurgitation; dilatation of the main pulmonary artery in the absence of valvular or peripheral pulmonic stenosis or any other obvious cause, occurring at younger than 40 years; calcification of the mitral annulus at younger than 40 years; and dilatation or dissection of the descending thoracic or abdominal aorta at younger than 50 years.

### Pulmonary System

**Major Criterion.** None.

**Minor Criteria.** Spontaneous pneumothorax and apical blebs (ascertained by chest radiography).

### Skin and Integument

**Major Criterion.** None.

**Minor Criteria.** Striae atrophicae (stretch marks) not associated with marked weight changes, pregnancy, or repetitive stress or recurrent or incisional hernias.

### Dura

**Major Criterion.** Lumbosacral dural ectasia seen on computed tomography or magnetic resonance imaging.

**Minor Criterion.** None.

The recommendations in this statement do not indicate an exclusive course of treatment for children with genetics disorders. They are meant to supplement anticipatory guidelines available for treating the normal child provided in the American Academy of Pediatrics publication *Guidelines for Health Supervision*. They are intended to assist the pediatrician in helping children with genetic conditions to participate fully in life. Diagnosis and treatment of genetic disorders are changing rapidly. Therefore, pediatricians are encouraged to view these guidelines in light of evolving scientific information. Clinical geneticists may be a valuable resource for the pediatrician seeking additional information or consultation.

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**Family and Genetic History**

*Major Criteria.* Having a parent, child or sibling who meets these diagnostic criteria independently; presence of a mutation in *FBN1* known to cause Marfan syndrome; and presence of a haplotype around *FBN1*, inherited by descent, known to be associated with unequivocally diagnosed Marfan syndrome in the family.

*Minor Criterion.* None.

**Requirements of the Diagnosis of Marfan Syndrome**

For the index case:

- If the family and genetic history is not contributory, major criteria in at least two different organ systems and involvement of a third organ system; and
- If a mutation known to cause Marfan syndrome in other family members is detected, one major criterion in an organ system and involvement in a second organ system.

**ROUTINE EXAMINATIONS**

Several areas require ongoing assessment throughout childhood and should be reviewed periodically at developmentally appropriate ages (Table). These

include the following:

1. Review the child's growth (Figure).
2. Review the skeletal system.
  - Assess the infant's joints for laxity and sternum for pectus deformities; evaluate the spine for scoliosis.
3. Review the cardiovascular system; cardiac manifestations can occur any time in childhood.
  - Measure the child's blood pressure.
  - Obtain an echocardiogram.
  - If abnormal cardiac findings are present, refer the infant to a pediatric cardiologist.
  - Discuss bacterial endocarditis prophylaxis if mitral valve prolapse is present<sup>8</sup>; an enlarged aortic root needs long-term follow-up by a pediatric cardiologist and discussion of prognosis and possible surgical intervention.<sup>9-13</sup> Timely medical or surgical intervention may significantly alter the prognosis for longevity. The use of  $\beta$  blockade has been shown to slow aortic dilatation and decrease risk of dissection. Initiation of therapy with  $\beta$ -blocking agents should be made in consultation with a pediatric cardiologist.<sup>14</sup>

**TABLE.** Marfan Syndrome: Guidelines for Health Supervision\*

Examination	Age†							
	Infancy, 1 mo-1 y			Early Childhood, 1-5 y		Late Childhood, 5-13 y		Adolescence to Early Adulthood, 13-21 y
	Newborn	1-6 mo	6-12 mo	1-3 y	3-5 y	5-10 y	10-15 y	15-21 y
Cardiac	○	○	○	○	○	○	○	○
Echocardiogram	●‡			●	●	●	●	●
Ocular	○	○	○	○	○	○	○	○
Skeletal								
Spine	●	●	●	●	●	●	●	●
Joints	●	●	●	●	●	●	●	●
Pectus	●	●	●	●	●	●	●	●
Measurements								
Length/height	●	●	●	●	●	●	●§	●§
Upper/lower segments	●	●	●	●	●	●	●	●
Urine/blood amino acids	●							
Bone age							●¶	●¶
Blood pressure					●	●	●	●
Anticipatory guidance								
Review diagnosis	●	S	S	S	S	S	S	S
Examine family	●#							
Support group	●	●	●	●	●	●	●	●
Review genetics	●	●**	S				●††	●††
Psychosocial	●	●	●	●	●	●	●	●
Lifestyle counsel				●‡‡	●§§	●	●¶¶	●
Reproduction							●¶¶	

\* Assume compliance with the American Academy of Pediatrics Recommendations for Preventive Pediatric Health Care.

† ● indicates to be performed; ○, objective, by standard testing; and S, subjective by history.

‡ To be performed at newborn period or before 1 year of age and yearly in the intervals at older than 3 years.

§ Review with relationship to puberty.

|| Perform once at initial evaluation.

¶ Disparity between height age and bone age should be reviewed with consideration of hormonal therapy.

# Need only be done once for each family except for children younger than 10 years.

\*\* Anxiety at first visit may have prevented full understanding.

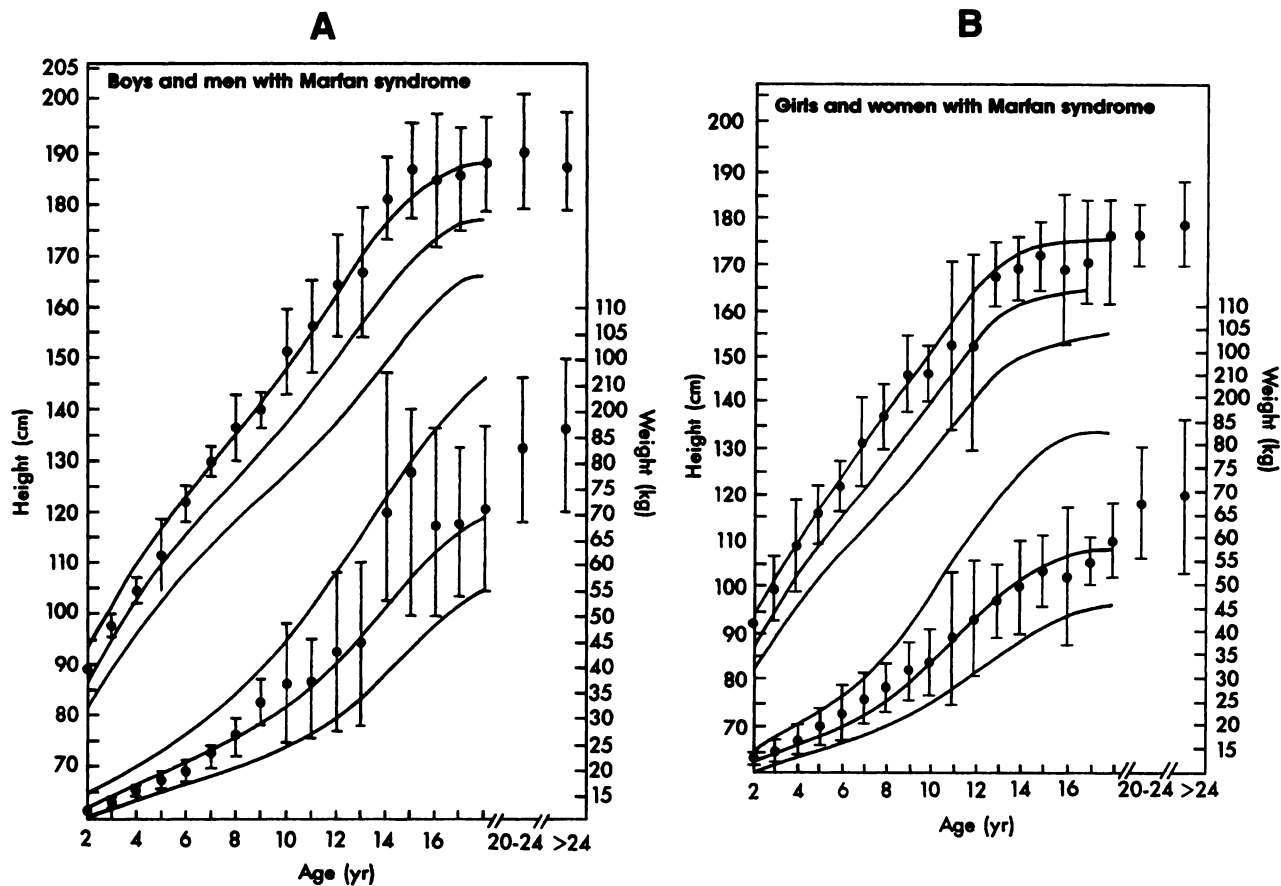
†† Review with child as well as parents.

‡‡ Begin education of parents about value of nonstrenuous and competitive sport and suggest alternatives.

§§ Reinforce use of protective eyewear; address need for visual or physical therapy.

||| Review symptoms of potential catastrophic events: aortic dissection, pneumothorax, and retinal detachment. Discuss concerns about coping with chronic condition.

¶¶ Discuss genetic risks and risks of pregnancy.



**Figure.** Growth in Marfan syndrome. Plots of height and weight versus age in boys and men (A) and girls and women (B) who did not receive treatment with hormones. Both cross-sectional and longitudinal data of approximately 200 white patients were used in construction of these preliminary curves. The points show the mean age for persons grouped in 1-year intervals, and the bars show SDs  $\pm 1$ . The curved lines show the 5th, 50th, and 95th percentiles of the unaffected population. (From Pyeritz RE. Marfan syndrome and other disorders of fibrillin. In: Rimoin DL, Connor JM, Pyeritz RE, eds. *Emery and Rimoin's Principles and Practices of Medical Genetics*. New York, NY: Churchill Livingstone; 1996:1034.)

#### 4. Evaluate the child's vision using developmentally appropriate subjective and objective criteria.

- Evaluation by a pediatric ophthalmologist should be performed, with follow-up on a regular basis to detect myopia and prevent amblyopia.

#### THE PRENATAL VISIT

Pediatricians may be called on to counsel a family in which a fetus has a genetic disorder. In some settings, the pediatrician may be the primary resource for counseling. At other times, counseling may already have been provided for the family by a clinical geneticist and/or obstetrician. Because of a previous relationship with the family, however, the pediatrician may be called on to review this information and to assist in the decision-making process. Prenatal diagnosis in Marfan syndrome is not yet routinely available. Rarely, an affected fetus has been diagnosed based on ultrasound findings.<sup>15</sup> For the most part, prenatal diagnosis will be undertaken in a family in which there is an affected parent and molecular studies have demonstrated a mutation that can be identified by DNA studies in fetal cells or in which there are multiple affected members and linkage studies are informative. If the pregnant mother is affected, she should be under the care of a physician

who is aware of the complexities of management of pregnancy in Marfan syndrome.

When appropriate, referral of the family to a clinical geneticist should be considered for a more extended discussion of recurrence rates, reproductive options, and evaluation of risks to other family members. Considerable variability exists in phenotype within and between families.

#### HEALTH SUPERVISION FROM BIRTH TO 1 MONTH: NEWBORNS

##### Examination

The following systems need to be evaluated:

##### Skeletal

- Take measurements to obtain total body length, upper and lower segments, arm span, hand and finger lengths, and leg lengths.
- Evaluate the newborn for scoliosis.
- Evaluate the joints for laxity and contractures.

##### Ocular

- Check the newborn for an abnormal red reflex or iridodonesis (uneven shimmering motion of the iris, seen best with lateral illumination as the pupil dilates and constricts). Lens dislocation usually follows years of

subluxation. Evaluation requires slit lamp examination and evaluation by a pediatric ophthalmologist.

### *Cardiovascular*

- Check the newborn for the presence of a murmur, which indicates aortic valve insufficiency, mitral valve prolapse, or mitral valve insufficiency. Cardiovascular manifestations, although unusual in the newborn, have been reported.
- Note cardiac rhythm.
- Obtain an echocardiogram. Patient referral to a pediatric cardiologist should be considered. Referral to a geneticist should be considered for confirmation of diagnosis and treatment plans.

### **Anticipatory Guidance**

1. Review the clinical manifestations.
  - If a diagnosis of Marfan syndrome is made, review the prognosis.
  - If a diagnosis of Marfan syndrome is under consideration because of an affected parent but the findings are equivocal, explain that a diagnosis cannot be confirmed or excluded, and discuss the importance of longitudinal follow-up. Consider performing molecular diagnostic studies.
2. Inform parents about support groups and available literature (see "Resources").
3. Review the genetics.
  - Because Marfan syndrome is transmitted in an autosomal dominant fashion, there is a 50% risk to the offspring of the affected individual.
  - If the parent is affected, screen other siblings for Marfan syndrome.
  - Review the recurrence risks for future children and options for prenatal diagnosis.
  - Recommend evaluation for other family members at risk; consider molecular diagnostic studies.
4. Stress the positive features of the infant, and encourage parents to treat the infant normally.

## **HEALTH SUPERVISION FROM 1 MONTH TO 1 YEAR: INFANCY**

### **Examination**

1. Review the patient's growth.
  - Assess the infant's length and obtain upper and lower segment measurements if a diagnosis is not yet certain.

### **Anticipatory Guidance**

1. Review the clinical manifestations.
2. Review whether support groups have been contacted and whether pertinent literature has been read and understood.
3. Review the genetics of the syndrome with the family, because anxiety may have prevented full understanding earlier.
  - Discuss autosomal dominant inheritance.
  - If a parent is affected, screen older siblings for Marfan syndrome and other family members at risk; this may involve molecular genetic testing.
  - Review recurrence risks for future children and options for prenatal diagnosis.
4. Stress the infant's positive features, and encourage parents to treat the infant normally.

5. Assess how parents and siblings are coping with the stress of a child with a chronic condition.

## **HEALTH SUPERVISION FROM 1 TO 5 YEARS: EARLY CHILDHOOD**

### **Examination**

1. Evaluate the child's vision using developmentally appropriate subjective and objective criteria.
  - Investigate symptoms of myopia and retinal detachment.

### **Anticipatory Guidance**

1. Discuss psychosocial concerns related to chronic illness.
2. Review recurrence risks for future children and options for prenatal diagnosis.
3. At 3 to 5 years of age, discuss lifestyle education.
  - Parents need to de-emphasize for the child the importance of strenuous exercise, contact sports, and competitive sports.
  - Emphasize alternative nonstrenuous activities and sports (eg, golf, walking, and fishing); even in the absence of cardiac disease, the risk of developing aortic dilatation is high.
4. Discuss the use of protective eyewear, and review the symptoms of retinal detachment.
5. Refer the child for services for the visually and physically handicapped if indicated. Review the need for physical therapy.
6. Discuss symptoms of pneumothorax and the need for prompt evaluation.

## **HEALTH SUPERVISION FROM 5 TO 13 YEARS: LATE CHILDHOOD**

### **Examination**

1. Review the child's growth, particularly height, in relation to pubertal status.

### **Anticipatory Guidance**

1. Discuss symptoms of aortic dissection, including chest pain and syncope. Emphasize that aortic dissection is uncommon in childhood, particularly if the aorta is only mildly to moderately dilated.
2. Consider using radiography to determine bone age, depending on the child's height and pubertal status. In some cases, discuss the use of hormones to limit height.
3. Discuss psychosocial concerns, especially physical restrictions and fears of chronic illness.
4. Begin to discuss the nature of the disease with the child, and answer questions at an age-appropriate level.
5. Discuss the school gym program, extracurricular sports, and, if appropriate, after-school jobs.
6. Review symptoms of retinal detachment. Because of the high frequency of visual problems, regular care by a pediatric ophthalmologist with annual examinations is suggested.
7. Review symptoms of pneumothorax.
8. When appropriate, discuss issues of reproduction and birth control.
9. Discuss and encourage participation in peer group activities.

## HEALTH SUPERVISION FROM 13 TO 21 YEARS OR OLDER: ADOLESCENCE TO EARLY ADULTHOOD

### Examination

1. Review the adolescent's growth and predicted final height in relation to pubertal development.
  - Consider radiographic determination of bone age and use of hormones to limit height.
2. Perform an ophthalmologic examination.
3. Obtain an echocardiogram. The pediatrician should consult a pediatric cardiologist regarding the use of  $\beta$ -adrenergic blocking agents to slow the progression of aortic dilatation.

### Anticipatory Guidance

1. Discuss the nature of the disease with the patient, and review concerns and issues related to the impact of the disease throughout adolescence.
2. Discuss issues of reproduction and birth control, including:
  - Genetic facts of autosomal dominant inheritance;
  - The risk of aortic rupture during pregnancy or at delivery<sup>16,17</sup> and the need for high-risk cardiologic and obstetric management, with risk extending through the postpartum period; and
  - Assisted reproduction. The transmission of the mutant gene can be averted by sperm or egg donation (depending on which partner is affected) followed by in vitro fertilization. Preimplantation diagnosis can also be done. These do not obviate the risk of pregnancy to the health of the affected woman. Adoption is another alternative.
3. Review psychosocial, sexual, and lifestyle concerns, such as limitations of some physical activities, occupation, and genetic risks.
4. Refer the patient for services for visual or physical disability if indicated.
5. Discuss and encourage participation in peer group activities.
6. Facilitate transition to adult medical care, if appropriate or desired.

### RESOURCES

Support groups and sources of literature are the National Marfan Foundation, 382 Main St, Port Washington, NY 11050, (516) 883-8712 or (800) 8-MARFAN; and the March of Dimes, Marfan Syndrome, Public Health Educational Information Sheet, Community Services Department, 1275 Mamoroneck Ave, White Plains, NY 10605, (914) 428-7100.

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