CLINICAL REPORT Guidance for the Clinician in Rendering Pediatric Care

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Health Care Supervision for Children With Williams Syndrome

Colleen A. Morris, MD,[a] Stephen R. Braddock, MD,[b] COUNCIL ON GENETICS

This set of recommendations is designed to assist the pediatrician in caring for children with Williams syndrome (WS) who were diagnosed by using clinical features and with chromosome 7 microdeletion confirmed by fluorescence in situ hybridization, chromosome microarray, or multiplex ligation-dependent probe amplification. The recommendations in this report reflect review of the current literature, including previously peer-reviewed and published management suggestions for WS, as well as the consensus of physicians and psychologists with expertise in the care of individuals with WS. These general recommendations for the syndrome do not replace individualized medical assessment and treatment.

Williams syndrome (WS), also known as Williams-Beuren syndrome, is caused by a deletion of part of chromosome 7 and is a multisystem disorder that was first identified as a distinct clinical entity in 1961.[1] It is present at birth with a prevalence of 1 in 7500[2] and affects boys and girls equally. Children with WS usually come to the attention of pediatricians during infancy or early childhood. WS is characterized by dysmorphic facies (100%), cardiovascular disease (80%; most commonly supravalvular aortic stenosis [SVAS]), intellectual disability (75%), a characteristic cognitive profile (90%), and idiopathic hypercalcemia (15% to 45%).[1,3–7]

The deleted portion of chromosome 7q11.23 seen in WS is 1.5 to 1.8 Mb and contains 26 to 28 genes.[3,4,8] It includes the *ELN* gene that codes for the structural protein elastin, which is an important component of the elastic fibers found in the connective tissue of many organs. The *ELN* deletion explains some of the characteristics of WS, such as some of the facial features, hoarse voice, inguinal hernia, bladder and bowel diverticula, cardiovascular disease, and orthopedic problems. The pathogenesis of other characteristics, such as intellectual disability, is likely attributable to deletion of contiguous genes in the region. Most deletions in the WS region are de novo. Affected individuals have a 50% chance of transmitting the deletion to offspring. A specific inversion

abstract

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Drs Morris and Braddock were equally responsible for writing and revising the manuscript and considering input from all reviewers and the board of directors; and both authors approved the final manuscript as submitted.

The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

All clinical reports from the American Academy of Pediatrics automatically expire 5 years after publication unless reaffirmed, revised, or retired at or before that time.

Resources for parents include the following: the Williams Syndrome Association (570 Kirts Boulevard, Suite 223, Troy, MI 48084-4156; phone: 800-806-1871 [toll free] and 248-244-2229; fax: 248-244-2230; e-mail: info@williams-syndrome.org; Web site: www.williams-syndrome.org), the Canadian Association of Williams Syndrome (PO Box 26206, Richmond, British Columbia V6Y 3V3, Canada; phone: 604-214-0132; e-mail: cawbc@yahoo.com; Web site: caws.sasktelwebhosting.com), and the US National Library of Medicine Genetics Home Reference (Web site: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC385319/).

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TABLE 1 Medical Problems in WS by Organ System and Age

Organ	System Prevalence, %	Age		
		Infancy	Childhood	Adult
Ocular and visual				
Esotropia	50	x	—	—
Hyperopia	50	—	x	x
Auditory				
Recurrent otitis media	50	x	x	—
Hypersensitivity to sound	90	x	x	x
Progressive sensorineural hearing loss	65	—	x	x
Dental				
Malocclusion	85	—	x	x
Microdontia	95	—	x	x
Cardiovascular				
Any abnormality (total)	80	x	x	x
SVAS	75	x	x	x
SVPS	25	x	x	x
PPS	50	x	—	—
Other arterial stenosis	20	—	x	x
VSD	10	x	—	—
Hypertension	50	—	x	x
Prolonged QTc	13	—	x	x
Genitourinary				
Structural anomaly	5	x	x	x
Enuresis	50	—	x	—
Nephrocalcinosis	<5	x	—	x
Bladder diverticula	50	—	x	x
Gastrointestinal				
Feeding difficulties	70	x	x	—
Constipation	50	x	x	x
Colon diverticula	30	—	x	x
Rectal prolapse	15	x	x	—
Integument				
Soft, lax skin	90	x	x	x
Inguinal hernia	40	x	—	—
Umbilical hernia	50	x	—	—
Prematurely gray hair	90	—	—	x
Musculoskeletal				
Joint hypermobility	90	x	x	—
Joint contractures	50	x	x	x
Radioulnar synostosis	20	x	x	x
Kyphosis	20	—	—	x
Scoliosis	18	—	x	x
Lordosis	40	—	x	x
Awkward gait	60	—	x	x
Calcium				
Hypercalcemia	15–40[a]	x	—	x
Hypercalciuria	30	x	x	x
Endocrine				
Hypothyroidism	5–10	x	x	x
Early puberty (but rarely true precocious puberty)	20	—	x	—
Diabetes mellitus	15	—	—	x
Obesity	30	—	x	x
Neurologic				
Hyperactive deep tendon reflexes	75	—	x	x
Chiari I malformation	10	x	x	x
Hypotonia (central)	80	x	x	—
Hypertonia (peripheral)	50	—	x	x
Cognitive				
Developmental delay	95	x	x	—
Intellectual disability	75	—	x	x
Normal intelligence	5	—	x	x
Impaired visuospatial constructive cognition	95	—	x	x
Behavioral				
ADHD	65	—	x	—
Anxiety disorder (specific phobia, generalized)	70	—	x	x
Sleep disorders	65	—	x	x

Percentages are based on the following: (1) review of rates of complications in several reports of series of patients with WS and (2) a database of 582 children and adults with WS evaluated by Colleen A. Morris, MD. PPS, peripheral pulmonary artery stenosis; SVPS, supravalvular pulmonic stenosis, VSD, ventricular septal defect; —, not applicable.

[a] Hypercalcemia prevalence was greater in those <2 y of age.

polymorphism in this area can be seen in 6% of the general population and in 25% of parents of individuals with WS, indicating that the presence of this inversion may increase the chance of having a child with WS.[9] When the deletion includes only the *ELN* gene, or if the *ELN* gene contains a mutation or pathogenic variant, the result is the autosomal, dominantly inherited condition SVAS. These individuals do not have WS. Currently, the majority of cases of WS are detected through a chromosomal microarray that is done for developmental disability. Some of these cases do not have the typical deletion seen in WS and have varying phenotypes that may lack some of the most defining features of WS. The term WS is reserved for the individuals who have typical deletions. A medical genetics evaluation is recommended to discuss the clinical manifestations, natural history, and recurrence risks for parents and other family members.

The pediatrician can use knowledge of the clinical manifestations (Table 1) and the natural history of WS to anticipate medical problems and educate the family. The characteristic facial features of WS are a broad forehead, bitemporal narrowness, periorbital fullness, a stellate and/or lacy iris pattern, a short nose with a bulbous nasal tip, a wide mouth, full lips, and mild micrognathia (Fig 1 A and B). Infants have epicanthal folds, full cheeks, and a flat facial profile, whereas older children and adults often have a narrow face and long neck. Young children typically have small, widely spaced teeth; dental malocclusion is common at all ages. Mild prenatal growth deficiency and a postnatal growth rate that is ~75% of what is normal are consistently observed. Microcephaly is present in one-third of affected individuals.[10] Growth parameters should be plotted on WS growth charts[11] (Fig 2A–2F). Children with WS typically have decreased fat stores,[12] but obesity may become a problem in teenagers and adults.[13,14] The recommendations in this report reflect review of the current literature, including previously peer-reviewed and published management suggestions for WS,[3,4,13,15] as well as the consensus of physicians and

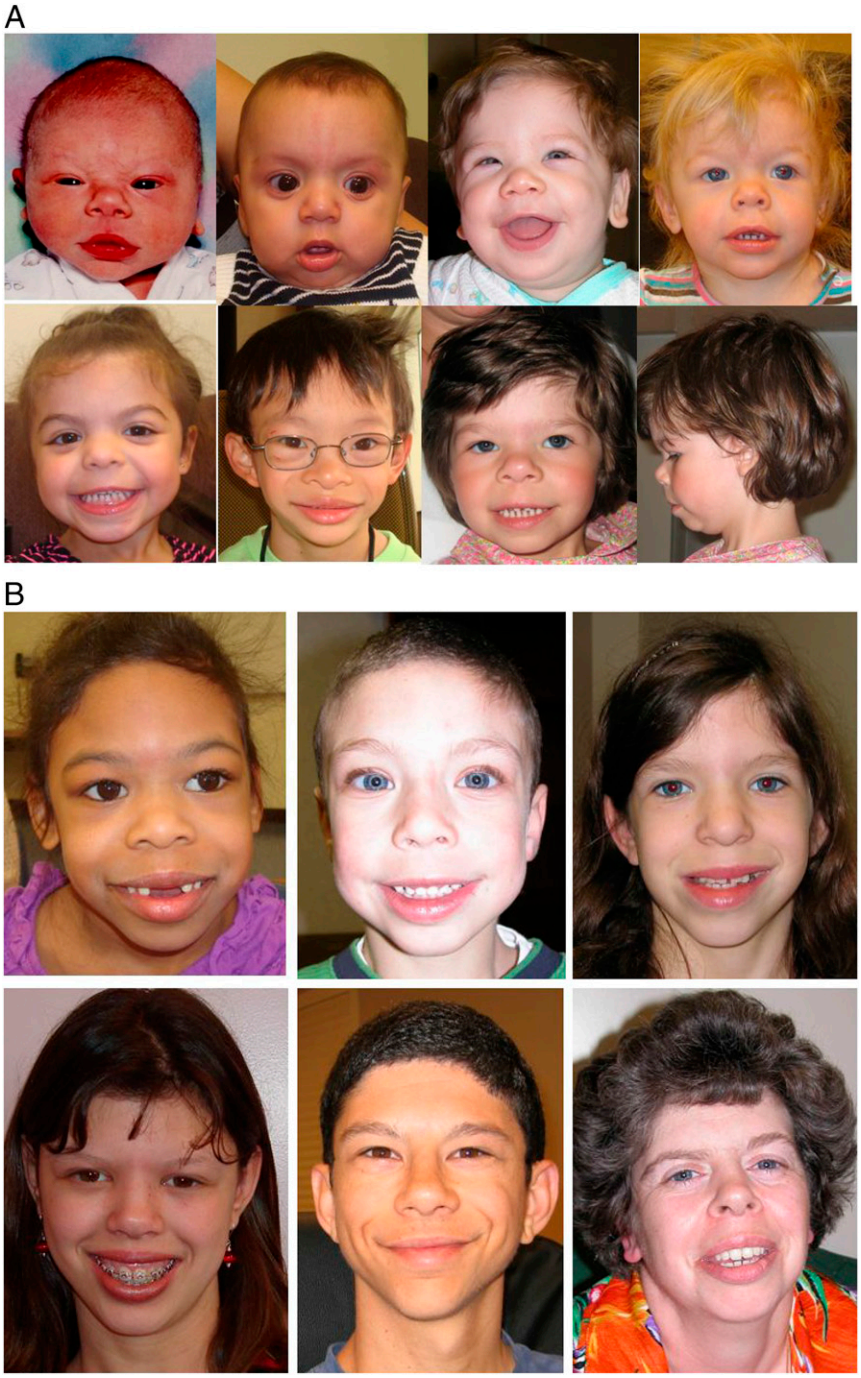

FIGURE 1

A, Infants and young children with WS. Top row (left to right) is as follows: newborn boy, 6-month-old boy, 9-month-old boy, and 1-year-old girl. Bottom row (left to right) is as follows: 2-year-old girl, 4-year-old boy, and 4-year-old girl (front view and profile). B, Children and adults with WS. Top row (left to right) is as follows: 5-year-old girl, 6-year-old boy, and 10-year-old-girl. Bottom row (left to right) is as follows: 14-year-old girl, 23-year-old man, and 34-year-old woman.

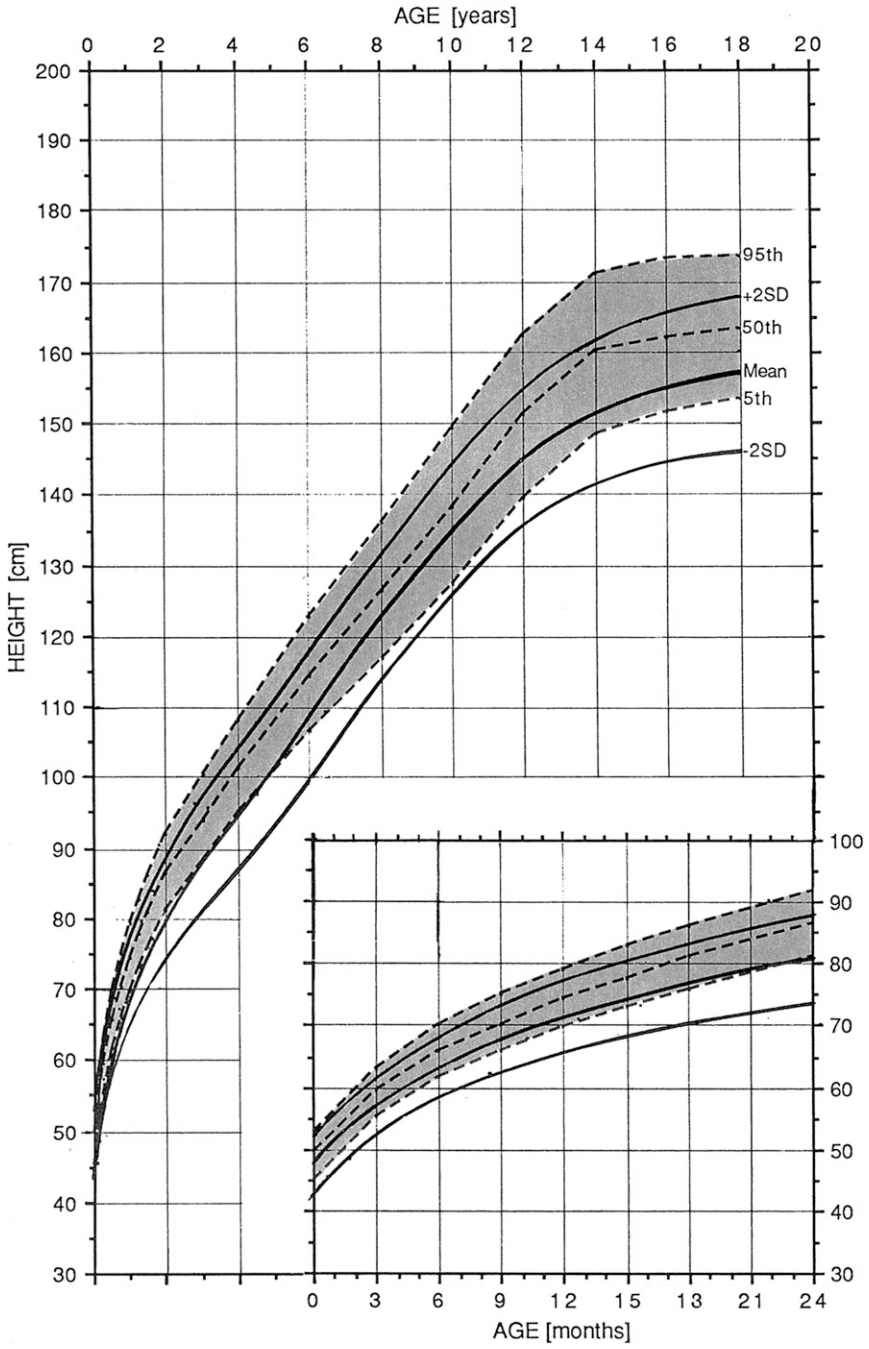

FIGURE 2A

Height for females with Williams syndrome. Normal curves = dashed lines; affected patients = solid lines. Reprinted with permission from: Saul RA, Geer JS, Seaver LH, Phelan MC, Sweet KM, Mills MS. *Growth References: Third Trimester* to Adulthood. Greenwood, SC: Greenwood Genetic Center; 1998.

psychologists with expertise in the care of individuals with WS.

CARDIOVASCULAR

The majority of children with WS have cardiovascular anomalies secondary to elastin arteriopathy, the major source of morbidity and mortality. Although any artery may be narrowed, the most common problem is SVAS, which may worsen over time, particularly in the first 5 years. Progression is more likely if the severity of the stenosis is moderate or severe and presents in infancy or early childhood.[16] SVAS is most commonly a discrete hourglass stenosis or may be a long segment stenosis (~15%).[17] Approximately 30% of children with SVAS will require surgical correction.[18] The mortality rate is 6% for cardiac surgery or catheterization.[19] Peripheral pulmonic stenosis is common in infancy but often improves over time when occurring in isolation. Mitral valve prolapse and aortic insufficiency may occur in adolescents or adults. QTc prolongation has been reported in 13% of individuals.[20]

Hypertension is present in 50% of people with WS, may occur at any age, and is occasionally associated with renal artery stenosis.[21–23] Increased vascular stiffness, which is a risk factor for stroke, is another manifestation of elastin arteriopathy found in both hypertensive and normotensive children and adults with WS.[23] Blood pressure measurement in both arms is recommended at well-child visits with use of a manual cuff at the end of the visit to minimize anxiety. Antihypertensive therapy successfully controls hypertension in most patients and also ameliorates vascular stiffness.[21,23] Consider cardiology or nephrology referral for hypertension (blood pressure >90th percentile for age and height).[24]

Patients with WS are at increased risk for myocardial ischemia, acute hemodynamic deterioration, and sudden death because of their cardiovascular anomalies, especially in the setting of sedation and anesthesia.[25] Individuals with biventricular outflow tract obstruction are at the greatest risk.[19,26] Sudden death in WS (1 per 1000 patient-years)[27] may be related to abnormalities of the coronary arteries (ostial or diffuse stenosis or dilatation)[28] or biventricular outflow

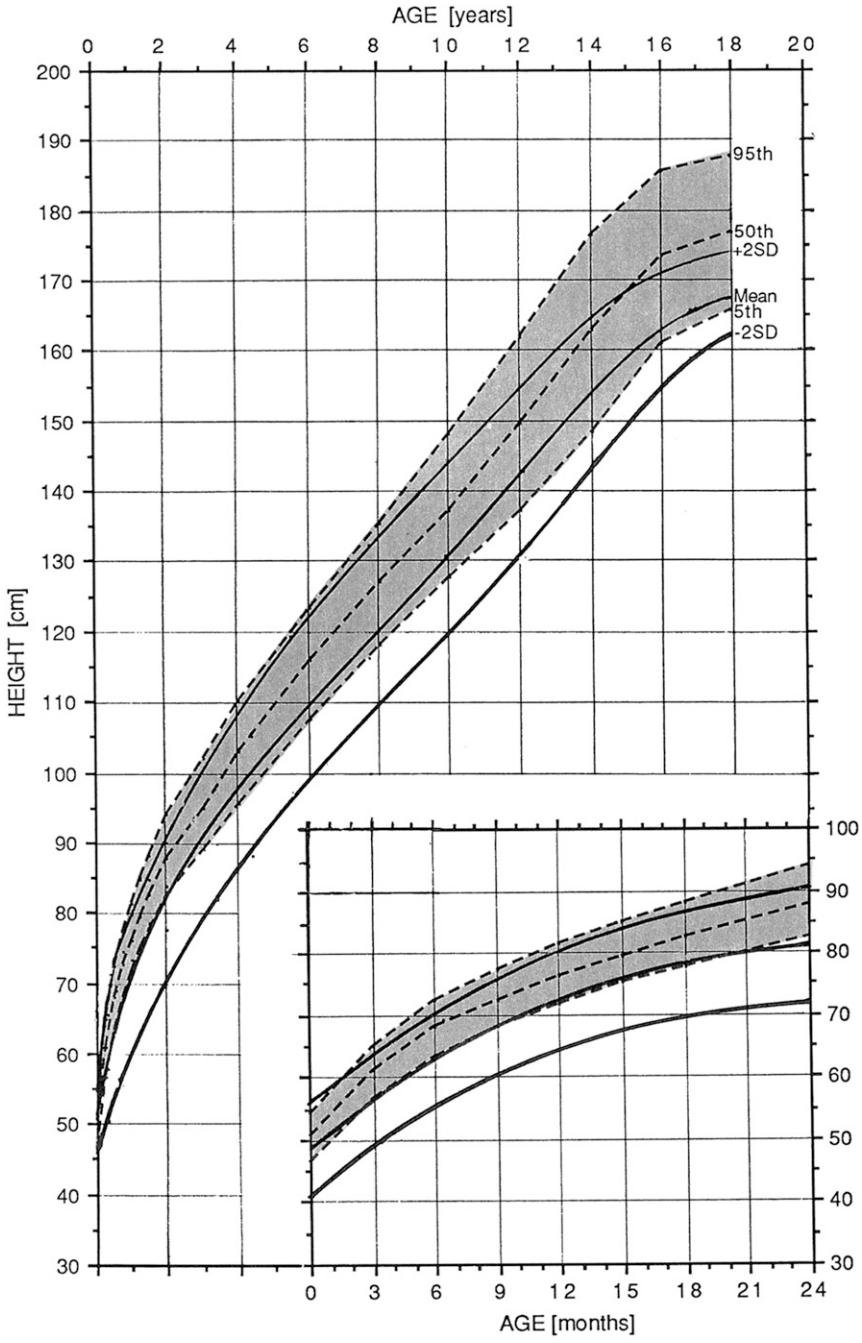

FIGURE 2B

Height for males with Williams syndrome. Normal curves = dashed lines; affected patients = solid lines. Reprinted with permission from: Saul RA, Geer JS, Seaver LH, Phelan MC, Sweet KM, Mills MS. *Growth References: Third Trimester to Adulthood.* Greenwood, SC: Greenwood Genetic Center; 1998.

tract obstruction. Because there is an increased risk of adverse events with sedation and aesthesia, recommendations have been developed for management of sedation and anesthesia in individuals with WS.[26,29,30]

Children with WS should be evaluated by a pediatric cardiologist with experience in treating WS when feasible. The initial evaluation should include 3 limb blood pressures (2 arms and 1 leg); echocardiogram, including Doppler flow studies; and electrocardiogram. Cardiology follow-up should occur frequently (every 3 months) in the first year of life and at least annually through middle childhood with subsequent intervals dictated by the nature and severity of cardiovascular disease. Children who have decreased pulses, bruits, and/or evidence of diffuse thoracic aortic stenosis will require additional cardiovascular imaging studies (computed tomography, magnetic resonance angiography, or cardiac catheterization) to define the anatomy. Because of the increased risk for serious cardiovascular complications surrounding procedures requiring anesthesia, careful perioperative planning, particularly of nonemergency procedures, is recommended with pediatric anesthesiologists who are familiar with WS and work in centers that can provide multidisciplinary support in the event of serious cardiac decompensation during sedation and anesthesia.[26,29,30]

HYPERCALCEMIA

Idiopathic infantile hypercalcemia may contribute to the presence of extreme irritability, vomiting, constipation, and muscle cramps associated with this condition.[6,31] Problems associated with hypercalcemia include dehydration, hypercalciuria, and nephrocalcinosis.[32] Symptomatic hypercalcemia is most common in the first 2 years and usually resolves during childhood,[3,33] but lifelong abnormalities of calcium and vitamin D metabolism may persist. Individuals with WS in all age groups have higher median calcium levels than controls.[32] There is increased calcium absorption from the gut; the cause of the abnormality in calcium metabolism is unknown.[14]

Serum calcium determination should be obtained every 4 to 6 months until 2 years of age, every 2 years thereafter, and when hypercalcemia is

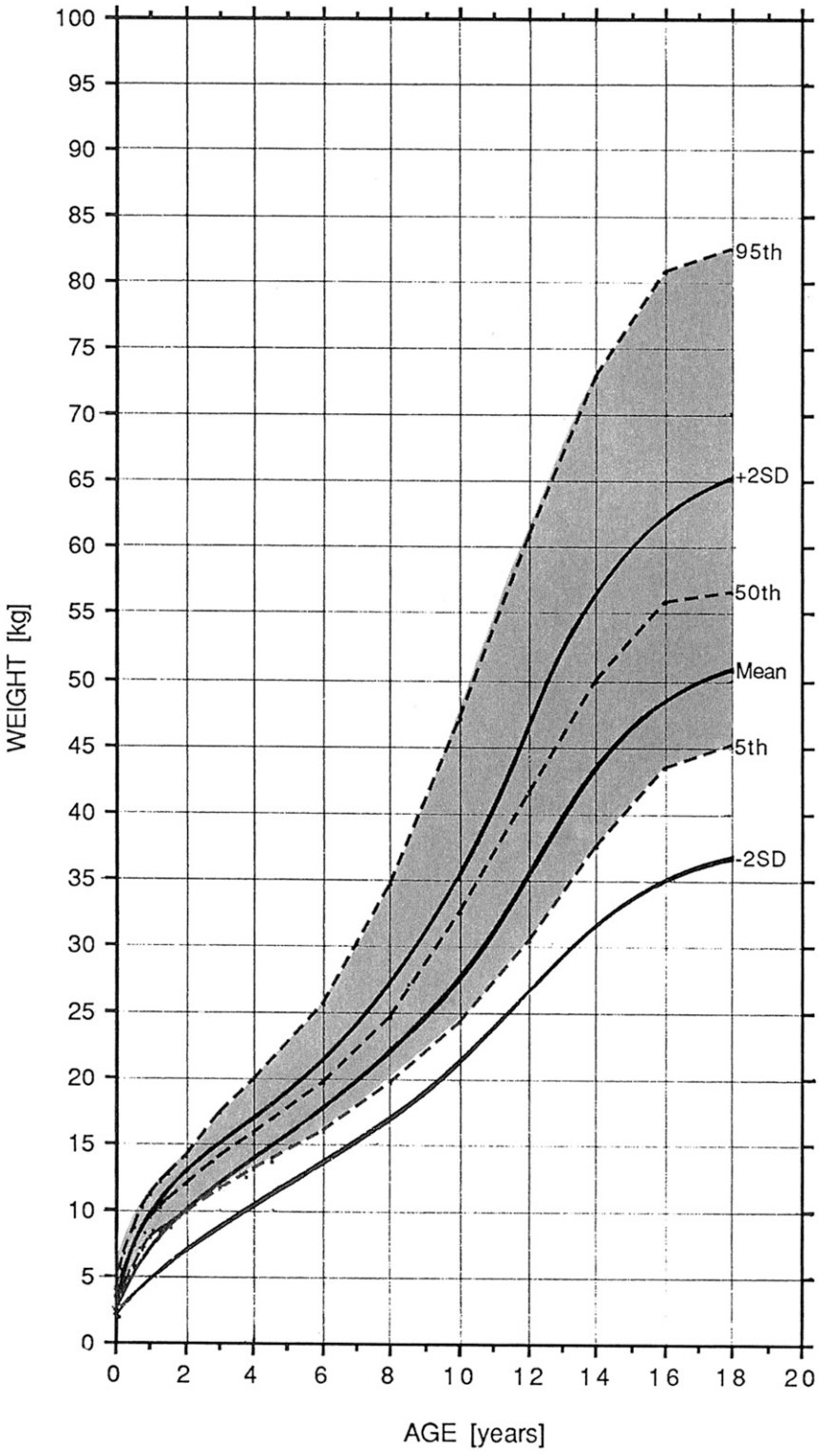

FIGURE 2C
Weight for females with Williams syndrome. Normal curves = dashed lines; affected patients = solid lines. Reprinted with permission from: Saul RA, Geer JS, Seaver LH, Phelan MC, Sweet KM, Mills MS. *Growth References: Third Trimester to Adulthood.* Greenwood, SC: Greenwood Genetic Center; 1998.

suspected clinically. Parents should be educated regarding the signs and symptoms of hypercalcemia. Children with WS and normocalcemia should have the reference daily intake of calcium,[34] and parents should be cautioned not to restrict calcium without medical supervision.[31] Infants with hypercalcemia are usually successfully treated with a low-calcium diet and increased water intake under medical and nutritional supervision, and they require more frequent surveillance of calcium concentrations. Serum blood urea nitrogen, creatinine, vitamin D concentrations (25-hydroxyvitamin D and 1,25-dihydroxyvitamin D), and intact parathyroid hormone should be checked if hypercalcemia is present.[35] The urine calcium/creatinine ratio in a random spot urine should be obtained at the time of diagnosis and if hypercalcemia is present (Table 2). If hypercalciuria is found, hydration status should be assessed, serum calcium concentration should be measured, dietary calcium intake should be assessed, and renal ultrasonography should be performed to evaluate for nephrocalcinosis. Referral to a pediatric nephrologist and/or pediatric endocrinologist should be considered for management of persistent hypercalcemia, hypercalciuria, or nephrocalcinosis.[32] Multivitamin preparations containing vitamin D should be avoided in early childhood, and vitamin D supplementation should be used with caution in older children and adults.[4] Approximately 50% of individuals with WS have impaired bone mineral status osteopenia or osteoporosis; the etiology is unknown.[1,14]

GASTROINTESTINAL

Infants and toddlers with WS often have difficulty feeding (eg, disordered suck and swallow and textural aversion) and may be brought for medical care because there are symptoms of gastroesophageal reflux,

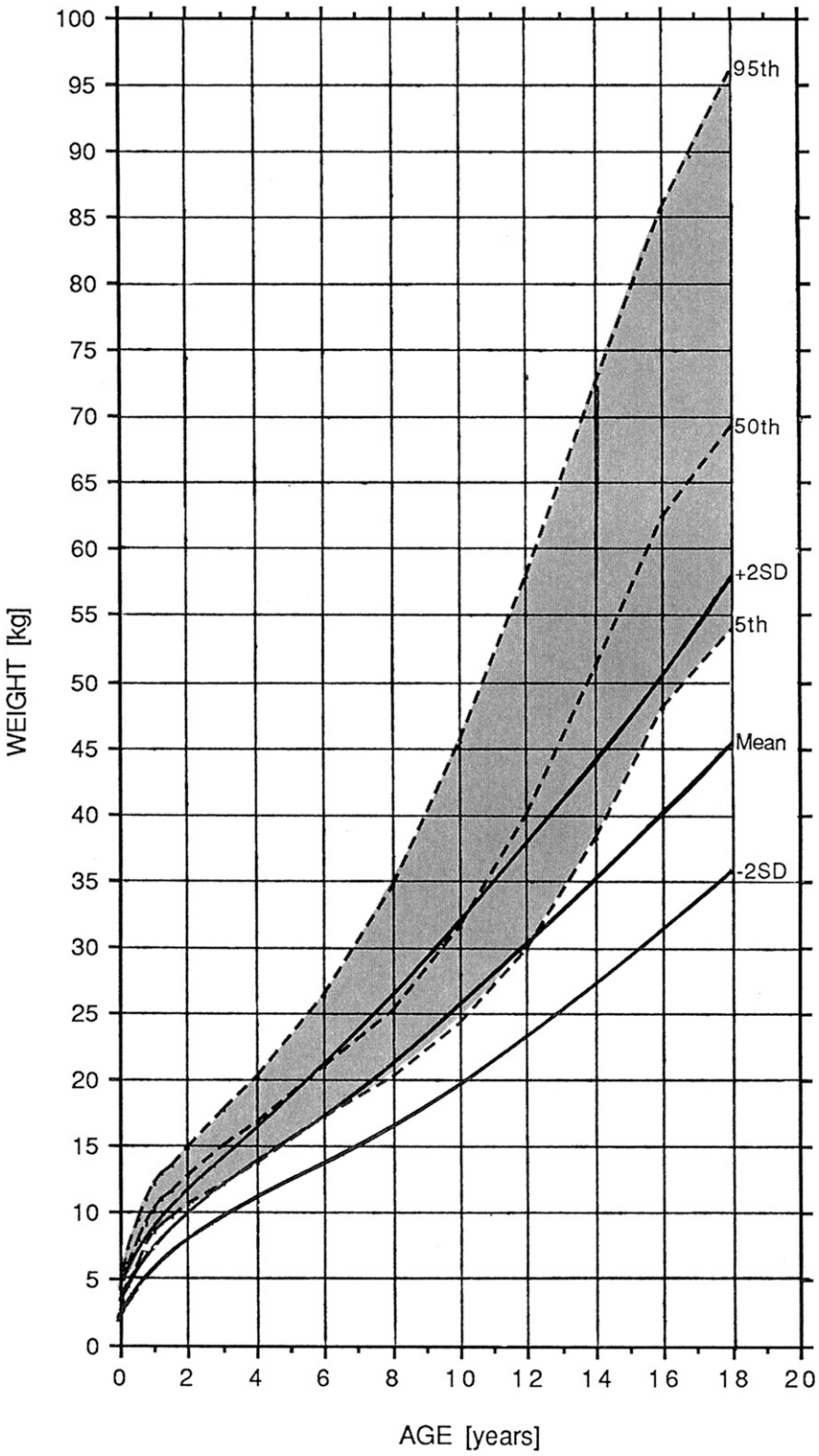

FIGURE 2D

Weight for males with Williams syndrome. Normal curves = dashed lines; affected patients = solid lines. Reprinted with permission from: Saul RA, Geer JS, Seaver LH, Phelan MC, Sweet KM, Mills MS. *Growth References: Third Trimester to Adulthood*. Greenwood, SC: Greenwood Genetic Center; 1998.

colic, or failure to achieve anticipated weight gain.[6] Feeding evaluation and therapy may be of benefit for infants having difficulty transitioning to solid foods, for assessment of aspiration risk and dysphagia, and for intervention for failure to gain weight appropriately according to WS growth curves. Feeding gastrostomy tubes are rarely necessary in WS. Obesity may become a problem for older children and adults.[13]

Chronic constipation is a common lifelong problem and must be aggressively treated. Typical interventions include increasing water and fiber in the diet followed by the addition of osmotic laxative treatment. Complications of constipation include rectal prolapse, hemorrhoids, and intestinal perforation. There is an increased incidence of diverticulitis occurring at a young age in adolescents and adults.[36] Abdominal pain is a frequent complaint in both children and adults; potential causes include gastroesophageal reflux, hiatal hernia, constipation, cholecystitis, diverticular disease, and discrete arterial stenosis causing ischemia.[37]

GENITOURINARY

Urinary tract malformations are present in 10% of children with WS,[38] bladder diverticula are present in 50%,[38,39] and a history of urinary tract infection is present in 25%.[40] Bladder capacity is reduced and detrusor overactivity is found in 60% of patients,[36] leading to urinary frequency in 69% and enuresis.[40] Daytime urinary continence is typically achieved by 4 years of age, and nocturnal continence is present in 50% at 10 years of age.[6] Children 4 to 12 years of age have a daytime urinary incontinence rate of 18% and nocturnal enuresis rate of 45%, whereas 2.7% of teenagers have daytime incontinence and 13.5% have nocturnal enuresis.[41] Ultrasonography of the kidneys and

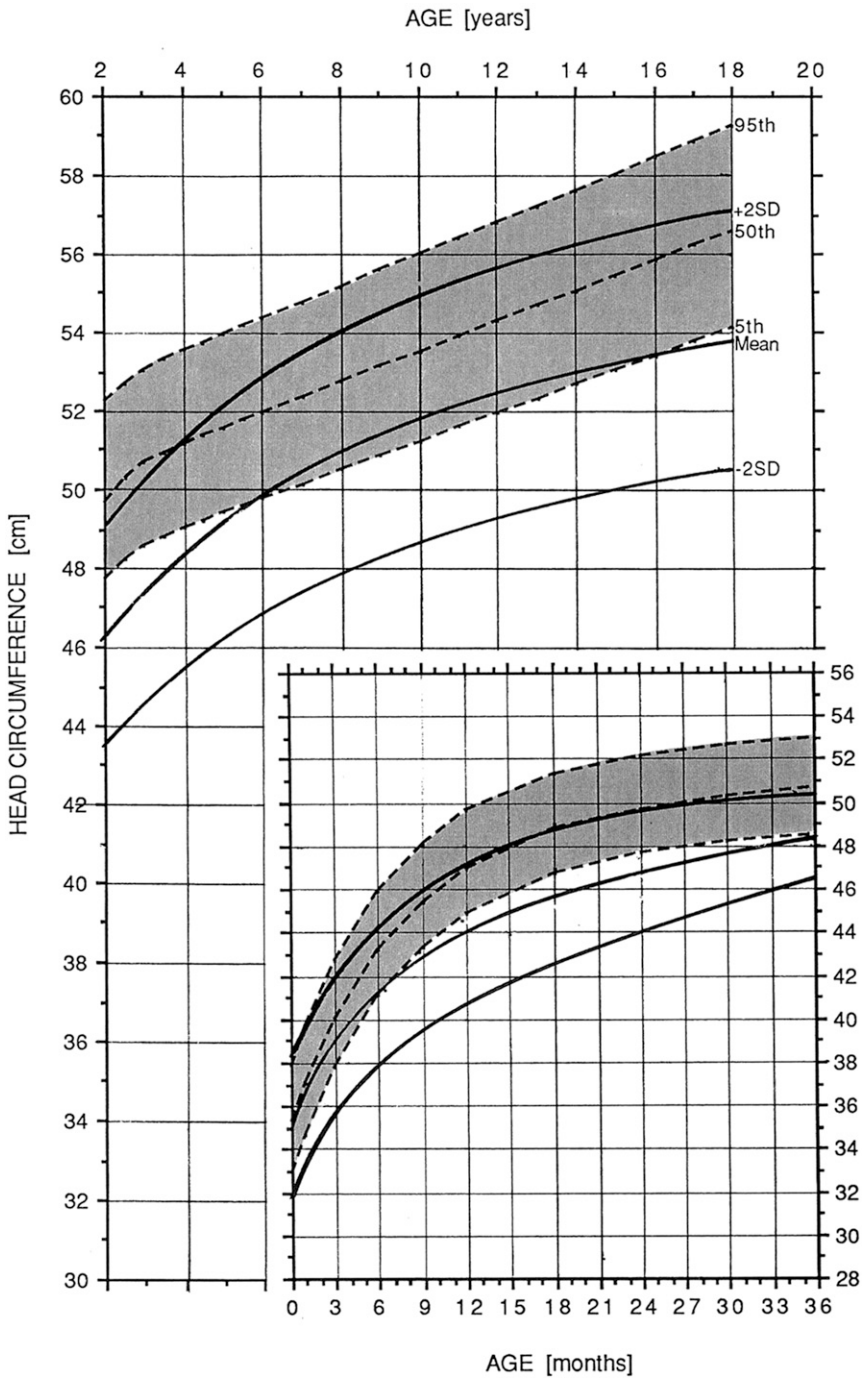

FIGURE 2E

Head circumference for females with Williams syndrome. Normal curves = dashed lines; affected patients = solid lines. Reprinted with permission from: Saul RA, Geer JS, Seaver LH, Phelan MC, Sweet KM, Mills MS. *Growth References: Third Trimester to Adulthood.* Greenwood, SC: Greenwood Genetic Center; 1998.

bladder should be completed at the time of diagnosis. Individuals with recurrent urinary tract infections may require additional urologic evaluation. The practitioner should maintain a low threshold for lower urinary tract imaging (voiding cystourethrography) for the evaluation of voiding dysfunction and/or urinary tract infection. Diverticula may lead to both of these symptoms and can be recurrent after surgical repair. Kidney function should be assessed at the time of diagnosis (serum urea nitrogen and creatinine concentrations and urinalysis).

NEUROLOGY, DEVELOPMENT, COGNITION, AND BEHAVIOR

Neurologic problems include axial hypotonia and peripheral hypertonia with increased deep tendon reflexes in the lower extremities. Signs of cerebellar dysfunction, such as ataxia and tremor, may increase with age.[42] Posterior fossa size is reduced in WS, although cerebellar volume is preserved and may contribute to Chiari I malformation in some individuals with WS.[43] Symptoms of headache, dizziness, and dysphagia should prompt the clinician to consider a pediatric neurology referral for evaluation for Chiari malformation. Developmental milestones are delayed,[6] and children should be referred to an early intervention program for physical, occupational, and speech therapy evaluation and treatment. Hippotherapy referral may be considered; hippotherapy uses equine movement during physical, occupational, and/or speech therapy and addresses problems of balance.[44] Although joint laxity is present in young children, joint contractures occur in older children and adults and lead to an awkward gait.[45] Nightly stretching range-of-motion exercises are often recommended. Radioulnar synostosis, found in 10% of affected children, does not respond to physiotherapy or surgical intervention.[46] Lordosis and kyphosis are common at all ages; 18% have scoliosis.[6,47]

Children with WS have a unique cognitive and behavioral profile.[7,48,49] Cognitive, motor, and language delay are universal, and in 75% of children, intellectual disability is ultimately diagnosed. Children demonstrate

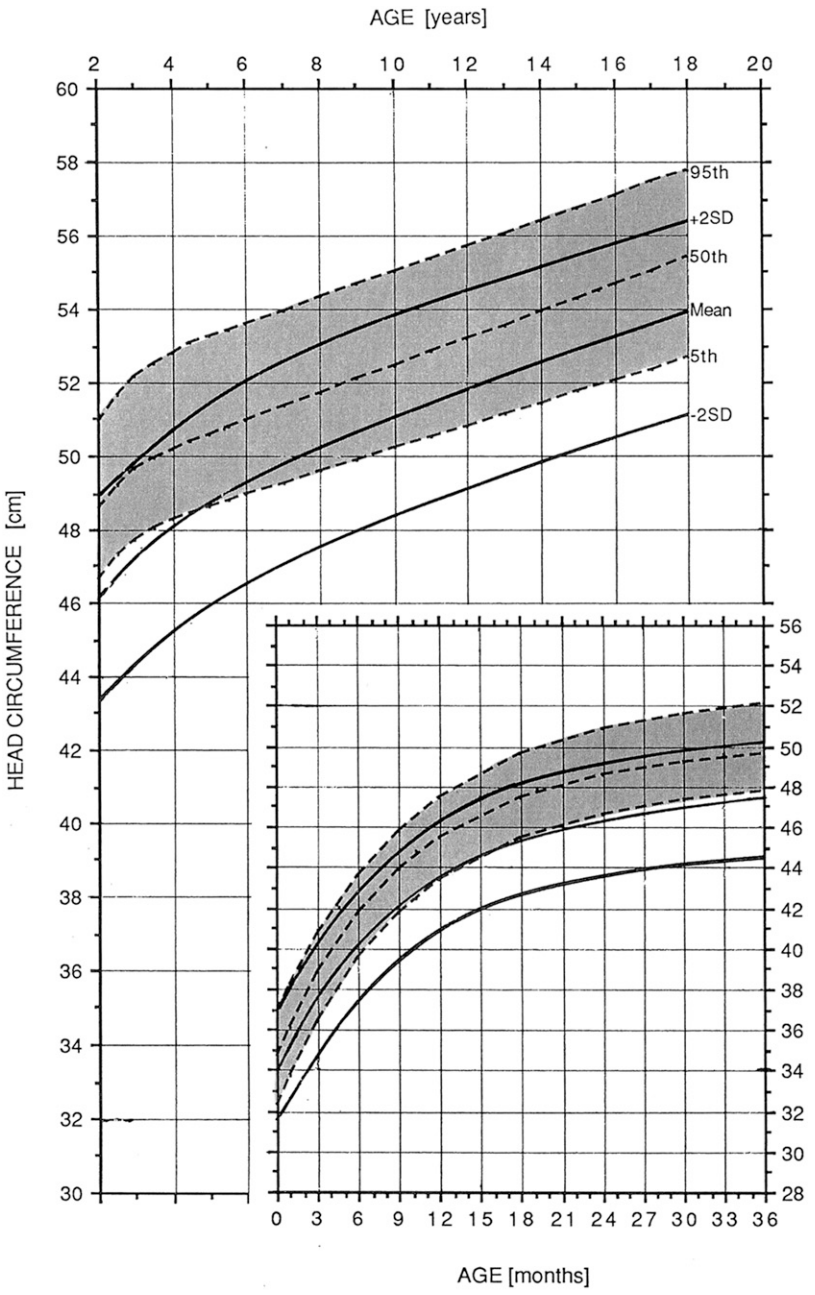

FIGURE 2F
Head circumference for males with Williams syndrome. Normal curves = dashed lines; affected patients = solid lines. Reprinted with permission from: Saul RA, Geer JS, Seaver LH, Phelan MC, Sweet KM, Mills MS. *Growth References: Third Trimester to Adulthood.* Greenwood, SC: Greenwood Genetic Center; 1998.

TABLE 2 Normal Values for Random Urinary Calcium/Creatinine Ratios

Age	Calcium/Creatinine Ratio (mg/mg; 95th Percentile for Age)
<7 mo	0.86
7–18 mo	0.6
19 mo–6 y	0.42
Adults	0.22

Adapted from Sargent JD, Stukel TA, Kresel J, Klein RZ. Normal values for random urinary calcium to creatinine ratios in infancy. *J Pediatr.* 1993;123(3):393–397

a relative strength in language and verbal short-term memory, with a significant weakness in visuospatial construction.[7] A detailed psychoeducational evaluation with information provided by the primary care pediatrician to the school regarding the unique cognitive and behavioral profile is important for school-aged children to develop an appropriate educational plan. A referral to a neuropsychologist may be of benefit. Speech and language, physical, and occupational therapies are important for school-aged children.

Behavioral problems may include hypersensitivity to sound, attention-deficit/hyperactivity disorder (ADHD), and nonsocial anxiety.[50] Approximately 50% of children with WS will require pharmacologic treatment of ADHD and/or anxiety. Although overfriendliness and an empathetic nature are commonly observed, many individuals have difficulty with emotional regulation.[51] In young children who have limited language, there may be symptom overlap with autism spectrum disorder, such as restricted interests and repetitive behaviors.[52] A referral for assessment for autism may be considered in those children. Behavioral interventions based on applied behavior analysis may be helpful, and older children benefit from social skills training and training to master daily living skills.[48] Adaptive behavior skills in both children and adults are often more impaired than would be expected for IQ.[53,54] Adults require vocational training and instruction in community living skills. Mental health problems, most commonly anxiety, are reported in 25% to 75% of adults.[13,55]

Sleep disorders are common (50% to 65%), including sleep onset delay, frequent awakenings, decreased sleep efficiency, and increased respiratory-related arousals.[56,57] An abnormal or absent melatonin peak may explain disturbance of circadian rhythm in some children.[58,59] The clinician

TABLE 3 Anticipatory Guidance in WS

Option	At Diagnosis	0–12 mo Old	1–5 y Old	6–12 y Old	13–18 y Old	Adult
Health maintenance physical examination	Yes	Each visit	Each visit	Yearly	Yearly	Yearly
Establish medical home	Yes	Yes	Yes	Yes	Yes	Yes
Plot growth parameters on WS growth charts	Yes	Each visit	Each visit	Each visit	Each visit	Monitor wt
Check blood pressure (both arms), auscultate for murmurs and bruits, check pulses	Yes	Each visit	Each visit	Each visit	Each visit	Each visit
Check for inguinal hernia	Yes	Each visit	Yearly	Yearly	Yearly	Yearly
Evaluate for neurologic abnormalities (hypotonia, hyperreflexia, cerebellar signs)	Yes	Each visit	Yearly	Yearly	Yearly	Yearly
Screen for musculoskeletal problems (joint laxity, joint contractures, kyphosis, scoliosis, lordosis)	Yes	Yearly	Yearly	Yearly	Yearly	Yearly
Review diagnosis and potential complications	Yes	PRN	PRN	PRN	PRN	PRN
Discuss feeding issues, nutrition	Yes	Yes	PRN	PRN	PRN	PRN
Counsel regarding symptoms of hypercalcemia; avoid multivitamins with vitamin D and advise calcium RDI	Yes	Yes	Yes	PRN	PRN	Yes
Discuss constipation, treat aggressively	Yes	Yes	Yearly	Yearly	Yearly	Yearly
Advise daily range-of-motion exercises	Yes	—	Yearly	Yearly	Yearly	Yearly
Inquire about sleep problems	Yes	Yes	Yearly	Yearly	Yearly	Yearly
Pediatric anesthesia consultation before procedures	Yes	Yes	Yes	Yes	Yes	—
Provide support group information	Yes	PRN	PRN	PRN	PRN	PRN
Ocular						
Vision screening for strabismus, refractive errors, cataracts (adults)	Yes	Yearly	Yearly	Yearly	Yearly	Yearly
Ophthalmologic evaluation	Yes	PRN	PRN	PRN	PRN	Yearly
Auditory						
Audiological evaluation	Yes	Yearly	Yearly	Yearly	Yearly	Yearly
Counsel regarding sensitivity to sound	Yes	PRN	PRN	PRN	PRN	PRN
Dental						
Dental cleaning	Yes	—	Every 6 mo	Every 6 mo	Every 4 mo	Every 4 mo
Refer to orthodontics for malocclusion	—	—	—	Yes	Yes	Yes
Calcium						
Serum concentration of calcium	Yes	Every 4 mo	Every 4–6 mo until age 2 y then every 2 y	Every 2 y	Every 2 y	Every 2 y
Spot random urine for urine calcium/creatinine ratio	Yes	PRN	PRN	PRN	PRN	PRN
Cardiovascular						
Pediatric cardiology evaluation to include 3 limb blood pressures and echocardiography, including Doppler flow studies; additional imaging studies (CT, MRA, catheterization) to be considered in the setting of severe SVAS, diminished femoral pulses, bruits, or suspicion of long segment aortic stenosis	Yes	Every 3 mo	Yearly	Every 2 y	Every 2 y	Every 2 y
Electrocardiogram	Yes	Yearly	Yearly	Yearly	Yearly	Yearly
Genitourinary						
Renal ultrasonography with Doppler and bladder ultrasonography evaluation for malformation, nephrocalcinosis, diverticulitis	Yes	—	—	Every 10 y	Every 10 y	Every 10 y
Serum BUN, creatinine	Yes	PRN	PRN	PRN	PRN	PRN
Urinalysis	Yes	Yearly	Yearly	Yearly	Yearly	Yearly
Refer to pediatric nephrologist and/or endocrinologist for persistent hypercalcemia, hypercalciuria, or nephrocalcinosis	Yes	Yes	PRN	PRN	PRN	PRN
Endocrine						
Thyroid function tests	Yes	Yearly	Yearly until age 3 y	Every 2 y	Every 2 y	Every 2 y
Consider treating early puberty	—	—	—	PRN	—	—
Fasting glucose level followed by oral glucose tolerance test if abnormal result	—	—	—	—	Yearly	Yearly
Development and cognition						
Multidisciplinary developmental evaluation	Yes	Yearly	Yearly	—	—	—
Neuropsychological evaluation	—	—	Yes at age 3 y	Every 3 y	Every 3 y	PRN
	Yes	Yes	Yes	Yes	Yes	Yes

TABLE 3 Continued

Option	At Diagnosis	0–12 mo Old	1–5 y Old	6–12 y Old	13–18 y Old	Adult
Refer for therapy (speech and language, physical and occupational), consider hippotherapy						
Feeding therapy if needed	Yes	PRN	PRN	—	—	—
Refer to early intervention program	Yes	Yes	—	—	—	—
Refer for special education	Yes	—	Yes	Yes	Yes	—
Behavior						
Assessment of behavior (attention, anxiety, adaptive skills)	Yes	—	Yearly	Yearly	Yearly	Yearly
Consider behavioral interventions based on applied behavior analysis	Yes	—	PRN	PRN	—	—
Treatment of mental health problems (ADHD, anxiety, depression)	Yes	—	PRN	PRN	PRN	PRN
Social skills training	Yes	—	Yes	Yes	Yes	Yes
Genetic counseling						
Medical genetics evaluation	Yes	PRN	PRN	PRN	PRN	PRN
Genetic counseling for family	Yes	—	—	—	—	—
Genetic counseling for individual	—	—	—	—	Yes	Yes
Transition						
Vocational training	—	—	—	—	Yes	Yes

BUN, blood urea nitrogen; CT, computed tomography; MRA, magnetic resonance angiography; PRN, as needed; RDI, Reference Daily Intake; —, not applicable.

should discuss appropriate sleep hygiene and consider a sleep study if obstructive sleep apnea is suspected.

OCULAR AND AUDITORY

Hyperopia, nasolacrimal duct obstruction, and strabismus are common in WS.[60] An ophthalmologic evaluation should be performed at the time of diagnosis with follow-up as necessary. Mild to moderate sensorineural hearing loss is present in 60% of children and 90% of adults.[61] Audiologic assessment should be performed between 6 and 12 months of age and repeated annually.[61] Recurrent otitis media is common. The use of noise-canceling headphones is helpful to children who have increased sensitivity to sound or specific phobia for loud noises. Earwax buildup is a common problem and may be treated with cerumen-softening drops.[13]

DENTAL

Dental problems include microdontia, missing teeth, and localized enamel hypoplasia.[62] Poor fine motor skills cause difficulty with maintenance of dental hygiene and increase the risk of dental caries. A dental home should be established by 1 year of age or within 6 months of the eruption of the first tooth. The dental recall interval should be based on caries risk; dental cleaning every 4 months has been recommended.[4] Caregivers should be instructed to assist with brushing and flossing. If dental procedures require anesthesia, WS-specific sedation and anesthesia recommendations should be followed.[29,30] Dental malocclusion is present in 85% of individuals with WS and responds to orthodontic treatment. An orthodontic assessment should be part of the evaluation in the dental home.

ENDOCRINE

Hypothyroidism is present in 5% to 10% of children[33] At a minimum, thyroid function should be assessed at the time of diagnosis, annually for the first 3 years, and every 2 years thereafter. Subclinical hypothyroidism (mild thyroid-stimulating hormone elevation with normal thyroxine [T4]) is present in 30%.[63] Puberty often occurs early (18% of girls), but true precocious puberty is rare.[64] A gonadotropin-releasing hormone agonist may be used to treat early puberty; treatment in girls successfully delays menarche and results in taller height compared with controls.[65] Abnormal glucose tolerance test results have been documented in 60% to 75% of adults with WS with an increased prevalence of type 2 diabetes mellitus.[66,67] An oral glucose tolerance test is recommended at 30 years of age and should be repeated every 5 years if results are normal.[13]

MEDICAL HOME AND TRANSITION

Establish a medical home with a clear emphasis on continuity of care and the role of the family members as partners in the ongoing management and care of the child. A summary of anticipatory guidance is provided in Table 3. Counsel the family regarding networks of support, such as extended family, friends, clergy, support groups, and community agencies that serve children and adults with disabilities. The diagnosis should be reviewed and discussed with the affected individual in adolescence with referral to support groups for the adolescent (see American Academy of Pediatrics policy statement "Transition of Care Provided for Adolescents With Special Needs").[68]

Assist in transition to adult care (especially for cardiology care). Many pediatricians feel comfortable continuing to provide primary care

well into young adulthood. Pediatricians can educate the adult and family regarding medical management for adults with WS.[37] Counseling should be provided regarding sexuality and reproductive issues, and genetic counseling should be provided. Vocational training and social skills training are essential for successful transition to independent functioning within the community for adults.

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REFERENCES

1. Williams JC, Barratt-Boyes BG, Lowe JB. Supravalvular aortic stenosis. *Circulation*. 1961;24:1311–1318
2. Strømme P, Bjørnstad PG, Ramstad K. Prevalence estimation of Williams syndrome. *J Child Neurol*. 2002;17(4):269–271
3. Morris CA. Williams Syndrome. In: Pagon RA, Adam MP, Ardinger HH, eds., et al *GeneReviews*. Seattle, WA: University of Washington, Seattle; 1999:1993–2014
4. Pober BR. Williams-Beuren syndrome. *N Engl J Med*. 2010;362(3):239–252
5. Beuren AJ. Supravalvular aortic stenosis: a complex syndrome with and without mental retardation. *Natl Found March Dimes Birth Defects Orig Art Ser*. 1972;8:45–56
6. Morris CA, Demsey SA, Leonard CO, Dilts C, Blackburn BL. Natural history of Williams syndrome: physical characteristics. *J Pediatr*. 1988;113(2):318–326
7. Mervis CB, Robinson BF, Bertrand J, Morris CA, Klein-Tasman BP, Armstrong SC. The Williams syndrome cognitive profile. *Brain Cogn*. 2000;44(3):604–628
8. Ewart AK, Morris CA, Atkinson D, et al. Hemizygosity at the elastin locus in a developmental disorder, Williams syndrome. *Nat Genet*. 1993;5(1):11–16
9. Hobart HH, Morris CA, Mervis CB, et al. Inversion of the Williams syndrome region is a common polymorphism found more frequently in parents of children with Williams syndrome. *Am J Med Genet C Semin Med Genet*. 2010;154C(2):220–228
10. Pankau R, Partsch CJ, Neblung A, Gosch A, Wessel A. Head circumference of children with Williams-Beuren syndrome. *Am J Med Genet*. 1994;52(3):285–290
11. Saul RA, Stevenson RE, Rogers RC, Skinner SA, Prouty LA, Flannery DB. Williams syndrome. In: Proceedings of the Greenwood Genetic Center. Greenwood, SC: Greenwood Genetic Center; 1988:204–209
12. Nogueira RJ, Zimmerman LF, Moreno YM, et al. Anthropometric and body-mass composition suggests an intrinsic feature in Williams-Beuren syndrome. *Rev Assoc Med Bras (1992)*. 2011;57(6):681–685
13. Cherniske EM, Carpenter TO, Klaiman C, et al. Multisystem study of 20 older

adults with Williams syndrome. *Am J Med Genet A*. 2004;131(3):255–264

14. Stagi S, Manoni C, Scalini P, et al. Bone mineral status and metabolism in patients with Williams-Beuren syndrome. *Hormones (Athens)*. 2016; 15(3):404–412
15. Committee on Genetics. American Academy of Pediatrics: health care supervision for children with Williams syndrome. [published correction appears in *Pediatrics*. 2002;109(2):329]. *Pediatrics*. 2001;107(5):1192–1204
16. Collins RT II, Kaplan P, Somes GW, Rome JJ. Long-term outcomes of patients with cardiovascular abnormalities and Williams syndrome. *Am J Cardiol*. 2010; 105(6):874–878
17. Collins RT II. Cardiovascular disease in Williams syndrome. *Circulation*. 2013; 127(21):2125–2134
18. Kececioglu D, Kotthoff S, Vogt J. Williams-Beuren syndrome: a 30-year follow-up of natural and postoperative course. *Eur Heart J*. 1993;14(11):1458–1464
19. Pham PP, Moller JH, Hills C, Larson V, Pyles L. Cardiac catheterization and operative outcomes from a multicenter consortium for children with Williams syndrome. *Pediatr Cardiol*. 2009;30(1): 9–14
20. Collins RT II, Aziz PF, Gleason MM, Kaplan PB, Shah MJ. Abnormalities of cardiac repolarization in Williams syndrome. *Am J Cardiol*. 2010;106(7):1029–1033
21. Bouchireb K, Boyer O, Bonnet D, et al. Clinical features and management of arterial hypertension in children with Williams-Beuren syndrome. *Nephrol Dial Transplant*. 2010;25(2):434–438
22. Del Campo M, Antonell A, Magano LF, et al. Hemizygosity at the NCF1 gene in patients with Williams-Beuren syndrome decreases their risk of hypertension. *Am J Hum Genet*. 2006;78(4):533–542
23. Kozel BA, Danback JR, Waxler JL, et al. Williams syndrome predisposes to vascular stiffness modified by antihypertensive use and copy number changes in NCF1. *Hypertension*. 2014; 63(1):74–79
24. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004;114(2 ,suppl 4th report): 555–576
25. Bird LM, Billman GF, Lacro RV, et al. Sudden death in Williams syndrome: report of ten cases. *J Pediatr*. 1996; 129(6):926–931
26. Latham GJ, Ross FJ, Eisses MJ, Richards MJ, Geiduschek JM, Joffe DC. Perioperative morbidity in children with elastin arteriopathy. *Paediatr Anaesth*. 2016;26(9):926–935
27. Wessel A, Gravenhorst V, Buchhorn R, Gosch A, Partsch CJ, Pankau R. Risk of sudden death in the Williams-Beuren syndrome. *Am J Med Genet A*. 2004; 127A(3):234–237
28. Ergul Y, Nisli K, Kayserili H, et al. Evaluation of coronary artery abnormalities in Williams syndrome patients using myocardial perfusion scintigraphy and CT angiography. *Cardiol J*. 2012;19(3):301–308
29. Burch TM, McGowan FX Jr., Kussman BD, Powell AJ, DiNardo JA. Congenital supravalvular aortic stenosis and sudden death associated with anesthesia: what's the mystery? *Anesth Analg*. 2008;107(6):1848–1854
30. Matisoff AJ, Olivieri L, Schwartz JM, Deutsch N. Risk assessment and anesthetic management of patients with Williams syndrome: a comprehensive review. *Paediatr Anaesth*. 2015;25(12): 1207–1215
31. Martin ND, Snodgrass GJ, Cohen RD. Idiopathic infantile hypercalcaemia–a continuing enigma. *Arch Dis Child*. 1984; 59(7):605–613
32. Sindhar S, Lugo M, Levin MD, et al. Hypercalcemia in patients with Williams-Beuren syndrome. *J Pediatr*. 2016;178: 254–260.e4
33. Kim YM, Cho JH, Kang E, et al. Endocrine dysfunctions in children with Williams-Beuren syndrome. *Ann Pediatr Endocrinol Metab*. 2016;21(1):15–20
34. Ross AC, Taylor CL, Yaktine AL, Del Valle HB, eds. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington, DC: National Academies Press; 2011
35. Lameris AL, Geesing CL, Hoenderop JG, Schreuder MF. Importance of dietary calcium and vitamin D in the treatment of hypercalcaemia in Williams-Beuren syndrome. *J Pediatr Endocrinol Metab*. 2014;27(7–8):757–761
36. Stagi S, Lapi E, Chiarelli F, de Martino M. Incidence of diverticular disease and complicated diverticular disease in young patients with Williams syndrome. *Pediatr Surg Int*. 2010;26(9):943–944
37. Pober BR, Morris CA. Diagnosis and management of medical problems in adults with Williams-Beuren syndrome. *Am J Med Genet C Semin Med Genet*. 2007;145C(3):280–290
38. Pankau R, Partsch CJ, Winter M, Gosch A, Wessel A. Incidence and spectrum of renal abnormalities in Williams-Beuren syndrome. *Am J Med Genet*. 1996;63(1): 301–304
39. Sammour ZM, de Bessa J Jr., Hisano M, et al. Lower urinary tract symptoms in children and adolescents with Williams-Beuren syndrome. *J Pediatr Urol*. 2017; 13(2):203.e1-203.e6
40. Sammour ZM, Gomes CM, Duarte RJ, Trigo-Rocha FE, Srougi M. Voiding dysfunction and the Williams-Beuren syndrome: a clinical and urodynamic investigation. *J Urol*. 2006;175(4): 1472–1476
41. von Gontard A, Niemczyk J, Borggrefe-Moussavian S, Wagner C, Curfs L, Equit M. Incontinence in children, adolescents and adults with Williams syndrome. *Neurourol Urodyn*. 2016;35(8):1000–1005
42. Chapman CA, du Plessis A, Pober BR. Neurologic findings in children and adults with Williams syndrome. *J Child Neurol*. 1996;11(1):63–65
43. Pober BR, Filiano JJ. Association of Chiari I malformation and Williams syndrome. *Pediatr Neurol*. 1995;12(1): 84–88
44. Giagazoglou P, Arabatzi F, Dipla K, Liga M, Kellis E. Effect of a hippotherapy intervention program on static balance and strength in adolescents with intellectual disabilities. *Res Dev Disabil*. 2012;33(6):2265–2270
45. Kaplan P, Kirschner M, Watters G, Costa MT. Contractures in patients with Williams syndrome. *Pediatrics*. 1989; 84(5):895–899
46. Morris CA, Carey JC. Three diagnostic signs in Williams syndrome. *Am J Med Genet Suppl*. 1990;6:100–101
47. Morris CA, Pani AM, Mervis CB, Rios CM, Kistler DJ, Gregg RG. Alpha 1 antitrypsin

deficiency alleles are associated with joint dislocation and scoliosis in Williams syndrome. *Am J Med Genet C Semin Med Genet*. 2010;154C(2):299–306

48. Mervis CB, John AE. Cognitive and behavioral characteristics of children with Williams syndrome: implications for intervention approaches. *Am J Med Genet C Semin Med Genet*. 2010;154C(2): 229–248
49. Leyfer OT, Woodruff-Borden J, Klein-Tasman BP, Fricke JS, Mervis CB. Prevalence of psychiatric disorders in 4 to 16-year-olds with Williams syndrome. *Am J Med Genet B Neuropsychiatr Genet*. 2006;141B(6):615–622
50. Woodruff-Borden J, Kistler DJ, Henderson DR, Crawford NA, Mervis CB. Longitudinal course of anxiety in children and adolescents with Williams syndrome. *Am J Med Genet C Semin Med Genet*. 2010;154C(2):277–290
51. Pitts CH, Klein-Tasman BP, Osborne JW, Mervis CB. Predictors of specific phobia in children with Williams syndrome. *J Intellect Disabil Res*. 2016;60(10): 1031–1042
52. Klein-Tasman BP, Phillips KD, Lord C, Mervis CB, Gallo FJ. Overlap with the autism spectrum in young children with Williams syndrome. *J Dev Behav Pediatr*. 2009;30(4):289–299
53. Mervis CB, Pitts CH. Children with Williams syndrome: developmental trajectories for intellectual abilities, vocabulary abilities, and adaptive behavior. *Am J Med Genet C Semin Med Genet*. 2015;169(2):158–171
54. Howlin P, Udwin O. Outcome in adult life for people with Williams syndrome–results from a survey of 239 families. *J Intellect Disabil Res*. 2006;50(pt 2): 151–160
55. Stinton C, Elison S, Howlin P. Mental health problems in adults with Williams syndrome. *Am J Intellect Dev Disabil*. 2010;115(1):3–18
56. Annaz D, Hill CM, Ashworth A, Holley S, Karmiloff-Smith A. Characterisation of sleep problems in children with Williams syndrome. *Res Dev Disabil*. 2011;32(1):164–169
57. Mason TB, Arens R, Sharman J, et al. Sleep in children with Williams syndrome. *Sleep Med*. 2011;12(9): 892–897
58. Santoro SD, Giacheti CM, Rossi NF, Campos LM, Pinato L. Correlations between behavior, memory, sleep-wake and melatonin in Williams-Beuren syndrome. *Physiol Behav*. 2016;159: 14–19
59. Sniecinska-Cooper AM, Iles RK, Butler SA, Jones H, Bayford R, Dimitriou D. Abnormal secretion of melatonin and cortisol in relation to sleep disturbances in children with Williams syndrome. *Sleep Med*. 2015;16(1):94–100
60. Winter M, Pankau R, Amm M, Gosch A, Wessel A. The spectrum of ocular features in the Williams-Beuren syndrome. *Clin Genet*. 1996;49(1):28–31
61. Marler JA, Sitcovsky JL, Mervis CB, Kistler DJ, Wightman FL. Auditory function and hearing loss in children and adults with Williams syndrome: cochlear impairment in individuals with otherwise normal hearing. *Am J Med Genet C Semin Med Genet*. 2010;154C(2): 249–265
62. Hertzberg J, Nakisbendi L, Needleman HL, Pober B. Williams syndrome–oral presentation of 45 cases. *Pediatr Dent*. 1994;16(4):262–267
63. Palacios-Verdú MG, Segura-Puimedon M, Borralleras C, et al. Metabolic abnormalities in Williams-Beuren syndrome. *J Med Genet*. 2015;52(4): 248–255
64. Partsch CJ, Japing I, Siebert R, et al. Central precocious puberty in girls with Williams syndrome. *J Pediatr*. 2002; 141(3):441–444
65. Spielmann S, Partsch CJ, Gosch A, Pankau R. Treatment of central precocious puberty and early puberty with GnRH analog in girls with Williams-Beuren syndrome. *J Pediatr Endocrinol Metab*. 2015;28(11–12):1363–1367
66. Pober BR, Wang E, Caprio S, et al. High prevalence of diabetes and pre-diabetes in adults with Williams syndrome. *Am J Med Genet C Semin Med Genet*. 2010; 154C(2):291–298
67. Masserini B, Bedeschi MF, Bianchi V, et al. Prevalence of diabetes and pre-diabetes in a cohort of Italian young adults with Williams syndrome. *Am J Med Genet A*. 2013;161A(4):817–821
68. American Academy of Pediatrics Committee on Children with Disabilities and Committee on Adolescence. Transition of care provided for adolescents with special health care needs. *Pediatrics*. 1996;98(6, pt 1): 1203–1206

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