



# Health Care Supervision for Children With Williams Syndrome

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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.<sup>1</sup> It is present at birth with a prevalence of 1 in 7500<sup>2</sup> 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%).<sup>1,3-7</sup>

The deleted portion of chromosome 7q11.23 seen in WS is 1.5 to 1.8 Mb and contains 26 to 28 genes.<sup>3,4,8</sup> 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.

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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 |
| <b>Ocular and visual</b>                           |                      |         |           |       |
| Esotropia  | 50                   | x       | —         | —     |
| Hyperopia  | 50                   | —       | x         | x     |
| <b>Auditory</b>                                    |                      |         |           |       |
| Recurrent otitis media                             | 50                   | x       | x         | —     |
| Hypersensitivity to sound                          | 90                   | x       | x         | x     |
| Progressive sensorineural hearing loss             | 65                   | —       | x         | x     |
| <b>Dental</b>                                      |                      |         |           |       |
| Malocclusion                                       | 85                   | —       | x         | x     |
| Microdontia  | 95                   | —       | x         | x     |
| <b>Cardiovascular</b>                              |                      |         |           |       |
| 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     |
| <b>Genitourinary</b>                               |                      |         |           |       |
| Structural anomaly                                 | 5                    | x       | x         | x     |
| Enuresis   | 50                   | —       | x         | —     |
| Nephrocalcinosis                                   | <5                   | x       | —         | x     |
| Bladder diverticula                                | 50                   | —       | x         | x     |
| <b>Gastrointestinal</b>                            |                      |         |           |       |
| Feeding difficulties                               | 70                   | x       | x         | —     |
| Constipation                                       | 50                   | x       | x         | x     |
| Colon diverticula                                  | 30                   | —       | x         | x     |
| Rectal prolapse                                    | 15                   | x       | x         | —     |
| <b>Integument</b>                                  |                      |         |           |       |
| Soft, lax skin                                     | 90                   | x       | x         | x     |
| Inguinal hernia                                    | 40                   | x       | —         | —     |
| Umbilical hernia                                   | 50                   | x       | —         | —     |
| Prematurely gray hair                              | 90                   | —       | —         | x     |
| <b>Musculoskeletal</b>                             |                      |         |           |       |
| 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     |
| <b>Calcium</b>                                     |                      |         |           |       |
| Hypercalcemia                                      | 15–40 <sup>a</sup>   | x       | —         | x     |
| Hypercalciuria                                     | 30                   | x       | x         | x     |
| <b>Endocrine</b>                                   |                      |         |           |       |
| Hypothyroidism                                     | 5–10                 | x       | x         | x     |
| Early puberty (but rarely true precocious puberty) | 20                   | —       | x         | —     |
| Diabetes mellitus                                  | 15                   | —       | —         | x     |
| Obesity  | 30                   | —       | x         | x     |
| <b>Neurologic</b>                                  |                      |         |           |       |
| Hyperactive deep tendon reflexes                   | 75                   | —       | x         | x     |
| Chiari I malformation                              | 10                   | x       | x         | x     |
| Hypotonia (central)                                | 80                   | x       | x         | —     |
| Hypertonia (peripheral)                            | 50                   | —       | x         | x     |
| <b>Cognitive</b>                                   |                      |         |           |       |
| Developmental delay                                | 95                   | x       | x         | —     |
| Intellectual disability                            | 75                   | —       | x         | x     |
| Normal intelligence                                | 5                    | —       | x         | x     |
| Impaired visuospatial constructive cognition       | 95                   | —       | x         | x     |
| <b>Behavioral</b>                                  |                      |         |           |       |
| 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, supraaortic pulmonic stenosis, VSD, ventricular septal defect; —, not applicable.

<sup>a</sup> 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.<sup>9</sup> 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.<sup>10</sup> Growth parameters should be plotted on WS growth charts<sup>11</sup> (Fig 2A–2F). Children with WS typically have decreased fat

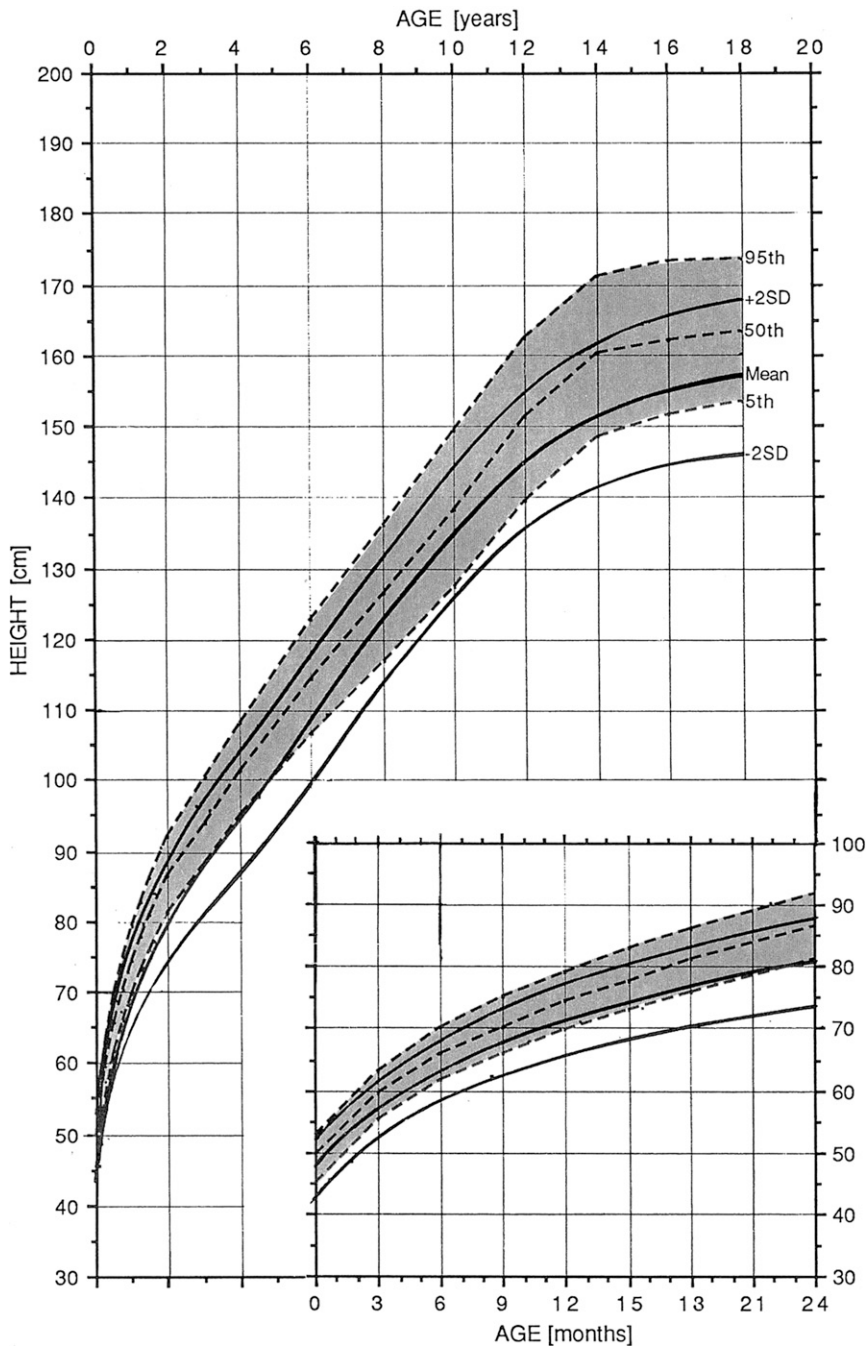


**FIGURE 1**  
 A, Infants and young children with WS. Top row (left to right) is as follows: newborn boy, 6-month-old boy, 9-month-old boy, and 1-year-old girl. Bottom row (left to right) is as follows: 2-year-old girl, 4-year-old boy, and 4-year-old girl (front view and profile). B, Children and adults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

stores,<sup>12</sup> but obesity may become a problem in teenagers and adults.<sup>13,14</sup> The recommendations in this report reflect review of the current literature, including

previously peer-reviewed and published management suggestions for WS,<sup>3,4,13,15</sup> as well as the consensus of physicians and





**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

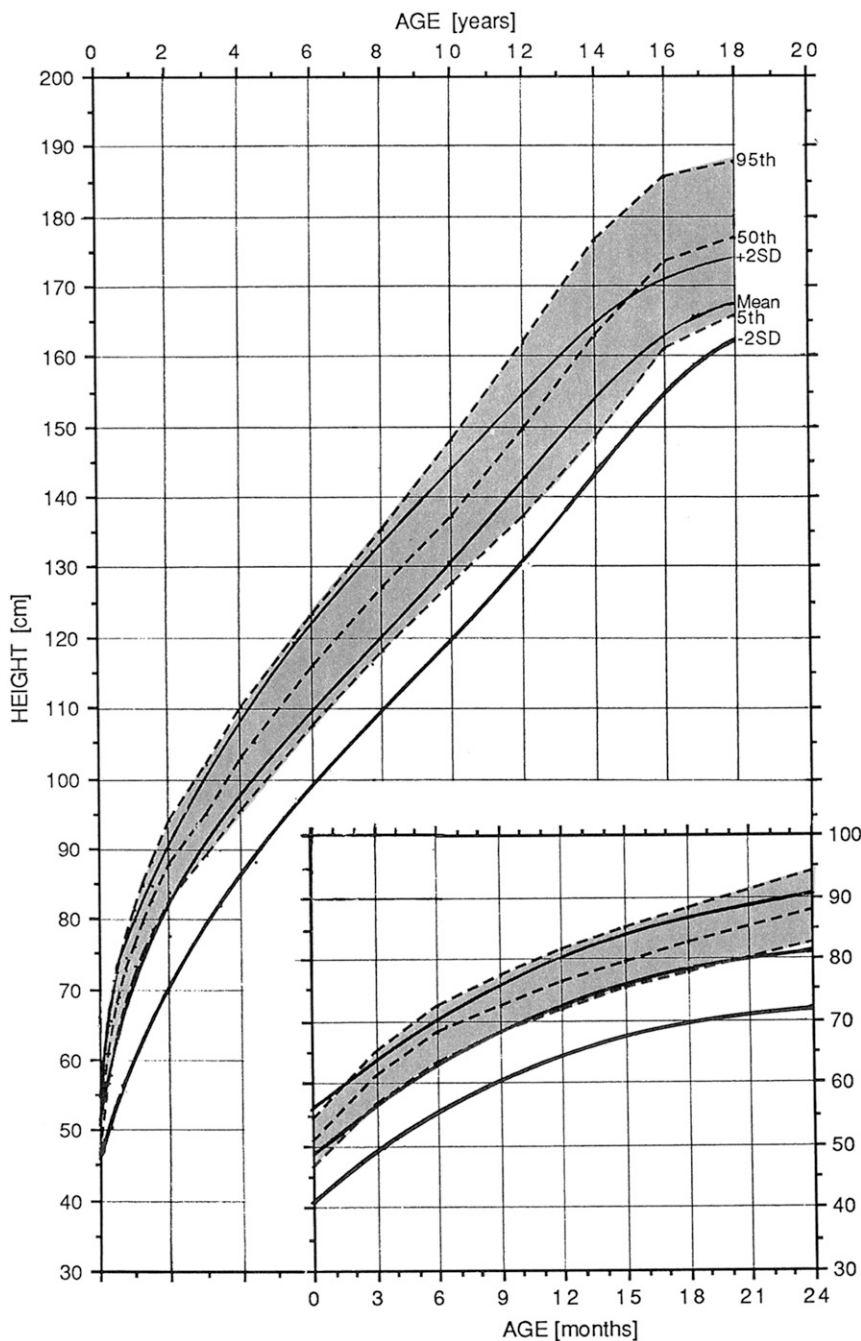
The majority of children with WS have cardiovascular anomalies secondary to elastin arteriopathy, the

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.<sup>16</sup> SVAS is most commonly a discrete hourglass stenosis or may be a long segment stenosis (~15%).<sup>17</sup> Approximately 30% of children with SVAS will require surgical correction.<sup>18</sup> The mortality rate is 6% for cardiac surgery or catheterization.<sup>19</sup> 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.<sup>20</sup>

Hypertension is present in 50% of people with WS, may occur at any age, and is occasionally associated with renal artery stenosis.<sup>21-23</sup> 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.<sup>23</sup> 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.<sup>21,23</sup> Consider cardiology or nephrology referral for hypertension (blood pressure >90th percentile for age and height).<sup>24</sup>

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.<sup>25</sup> Individuals with biventricular outflow tract obstruction are at the greatest risk.<sup>19,26</sup> Sudden death in WS (1 per 1000 patient-years)<sup>27</sup> may be related to abnormalities of the coronary arteries (ostial or diffuse stenosis or dilatation)<sup>28</sup> or biventricular outflow tract obstruction. Because there is an increased risk of adverse events with



**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.

sedation and anesthesia, recommendations have been developed for management of sedation and anesthesia in individuals with WS.<sup>26,29,30</sup>

Children with WS should be evaluated by a pediatric cardiologist

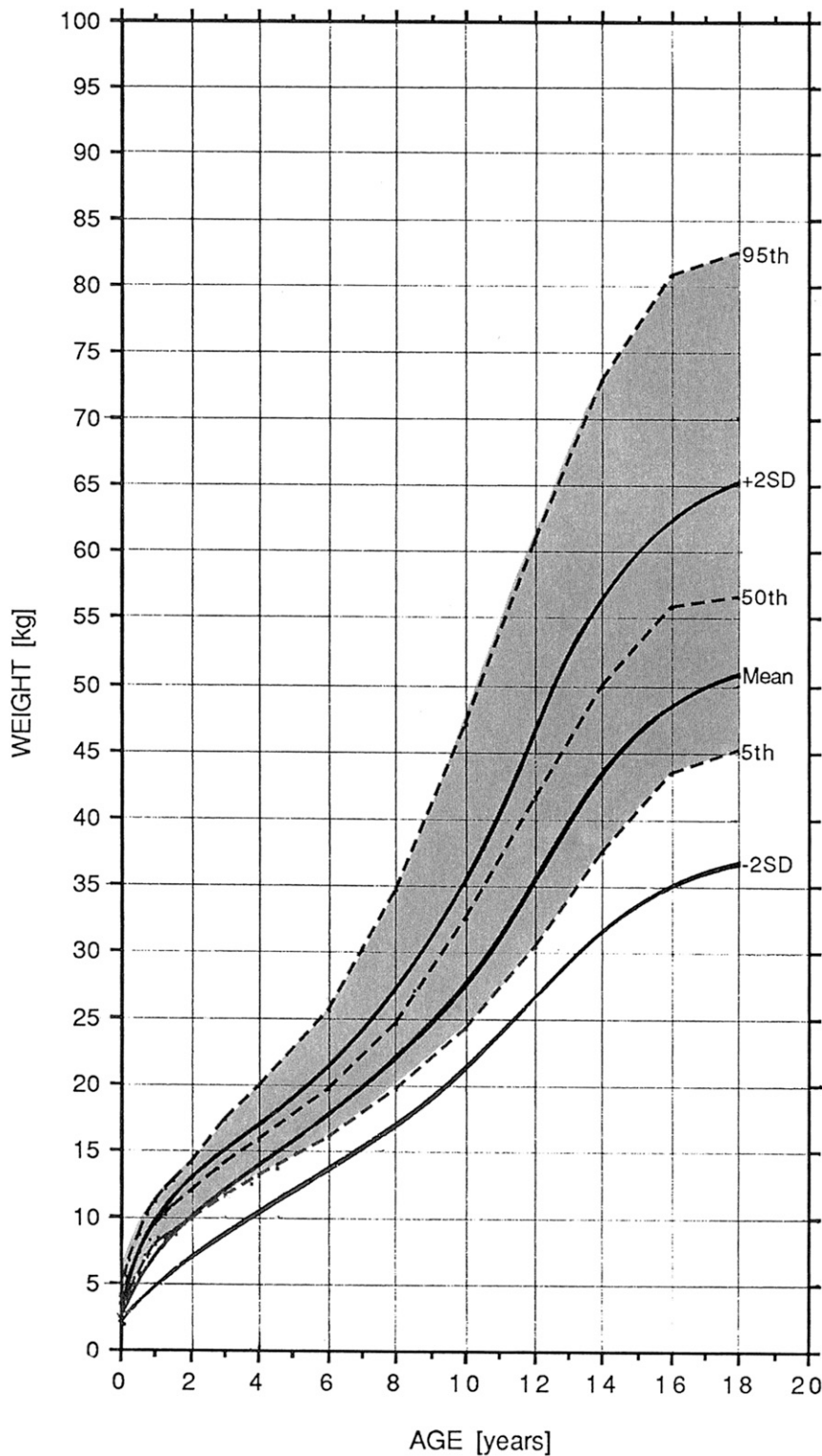
with experience in treating WS when feasible. The initial evaluation should include 3 limb blood pressures (2 arms and 1 leg); echocardiogram, including Doppler flow studies; and electrocardiogram. Cardiology follow-up should occur frequently (every 3

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.<sup>26,29,30</sup>

## HYPERCALCEMIA

Idiopathic infantile hypercalcemia may contribute to the presence of extreme irritability, vomiting, constipation, and muscle cramps associated with this condition.<sup>6,31</sup> Problems associated with hypercalcemia include dehydration, hypercalciuria, and nephrocalcinosis.<sup>32</sup> Symptomatic hypercalcemia is most common in the first 2 years and usually resolves during childhood,<sup>3,33</sup> 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.<sup>32</sup> There is increased calcium absorption from the gut; the cause of the abnormality in calcium metabolism is unknown.<sup>14</sup>

Serum calcium determination should be obtained every 4 to 6 months until 2 years of age, every 2 years thereafter, and when hypercalcemia is suspected clinically. Parents should be educated regarding the signs and



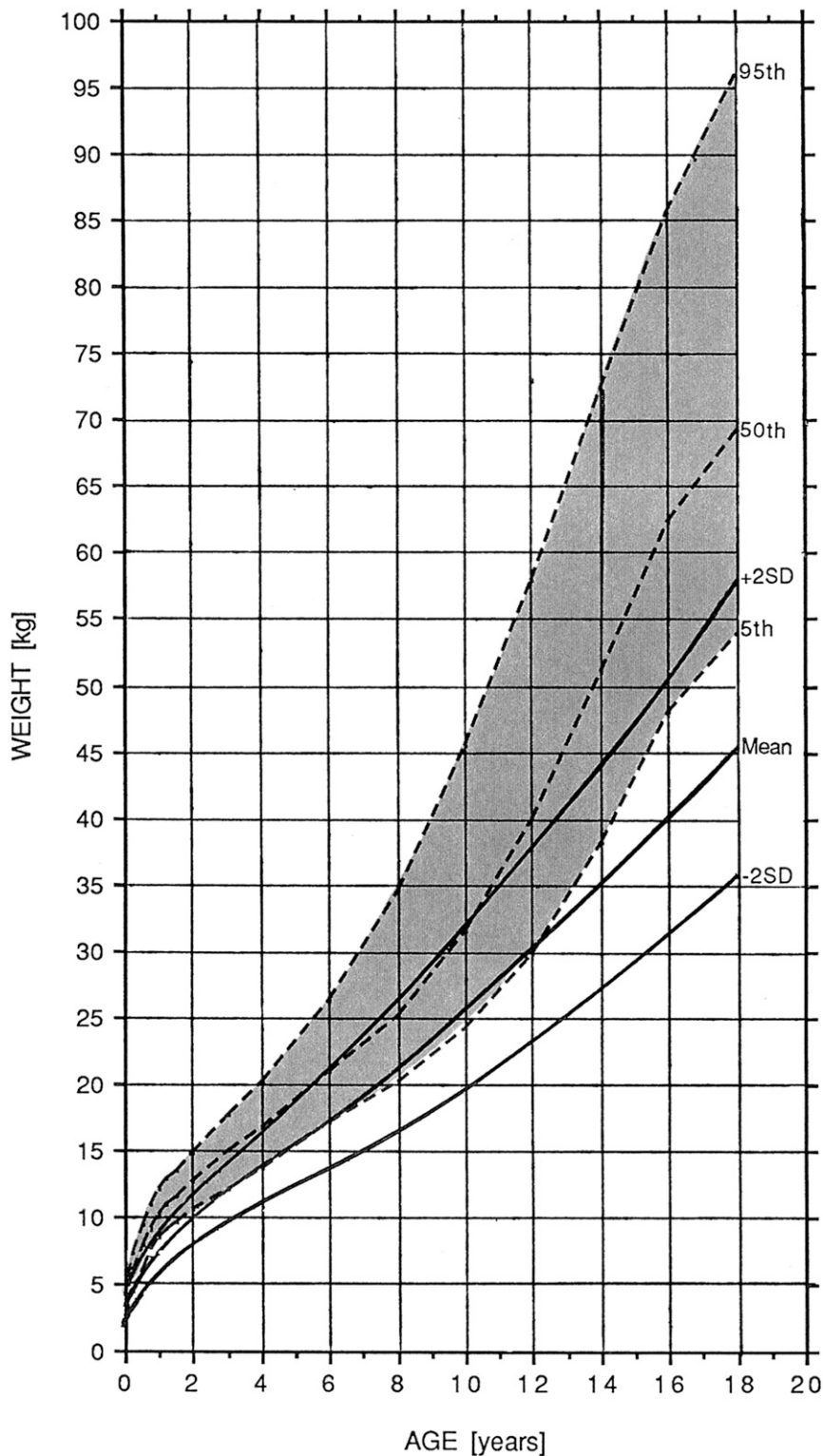
**FIGURE 2C**  
 Weight for females with Williams syndrome. Normal curves = dashed lines; affected patients = solid lines. Reprinted with permission from: Saul RA, Geer JS, Seaver LH, Phelan MC, Sweet KM, Mills MS. *Growth References: Third Trimester to Adulthood*. Greenwood, SC: Greenwood Genetic Center;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

symptoms of hypercalcemia. Children with WS and normocalcemia should have the reference daily intake of calcium,<sup>34</sup> and parents should be cautioned not to restrict calcium without medical supervision.<sup>31</sup> 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.<sup>35</sup> 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.<sup>32</sup> 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.<sup>4</sup> Approximately 50% of individuals with WS have impaired bone mineral status osteopenia or osteoporosis; the etiology is unknown.<sup>1,14</sup>

## 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, colic, or failure to achieve anticipated weight gain.<sup>6</sup> Feeding evaluation and





**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.

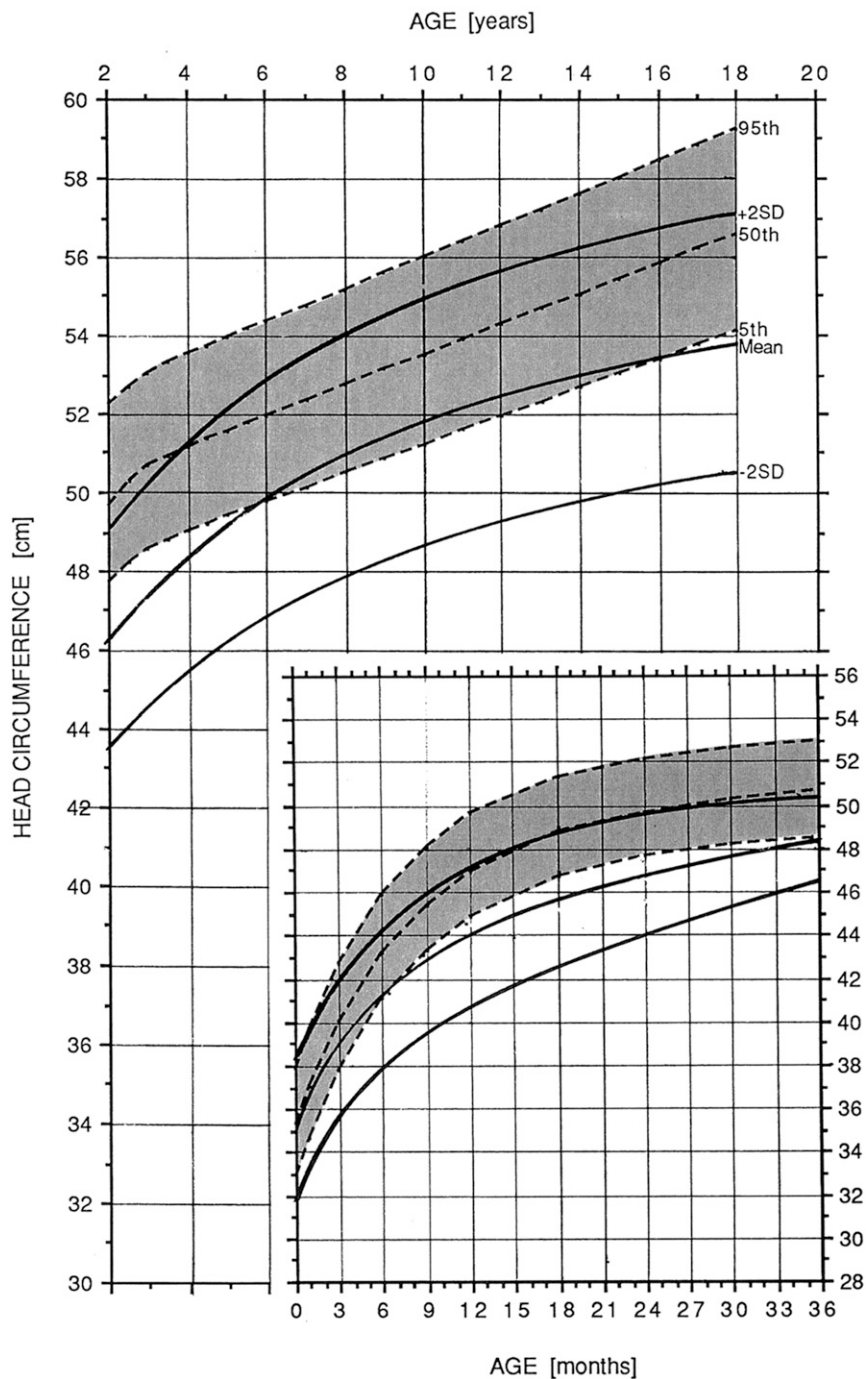
therapy may be of benefit for infants having difficulty transitioning to solid foods, for assessment of aspiration risk and dysphagia, and for intervention for failure to gain weight appropriately according to WS growth curves. Feeding gastrostomy tubes are rarely necessary in WS. Obesity may become a problem for older children and adults.<sup>13</sup>

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.<sup>36</sup> 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.<sup>37</sup>

### GENITOURINARY

Urinary tract malformations are present in 10% of children with WS,<sup>38</sup> bladder diverticula are present in 50%,<sup>38,39</sup> and a history of urinary tract infection is present in 25%.<sup>40</sup> Bladder capacity is reduced and detrusor overactivity is found in 60% of patients,<sup>36</sup> leading to urinary frequency in 69% and enuresis.<sup>40</sup> Daytime urinary continence is typically achieved by 4 years of age, and nocturnal continence is present in 50% at 10 years of age.<sup>6</sup> 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.<sup>41</sup>

Ultrasonography of the kidneys and bladder should be completed at the time of diagnosis. Individuals with



**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.

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

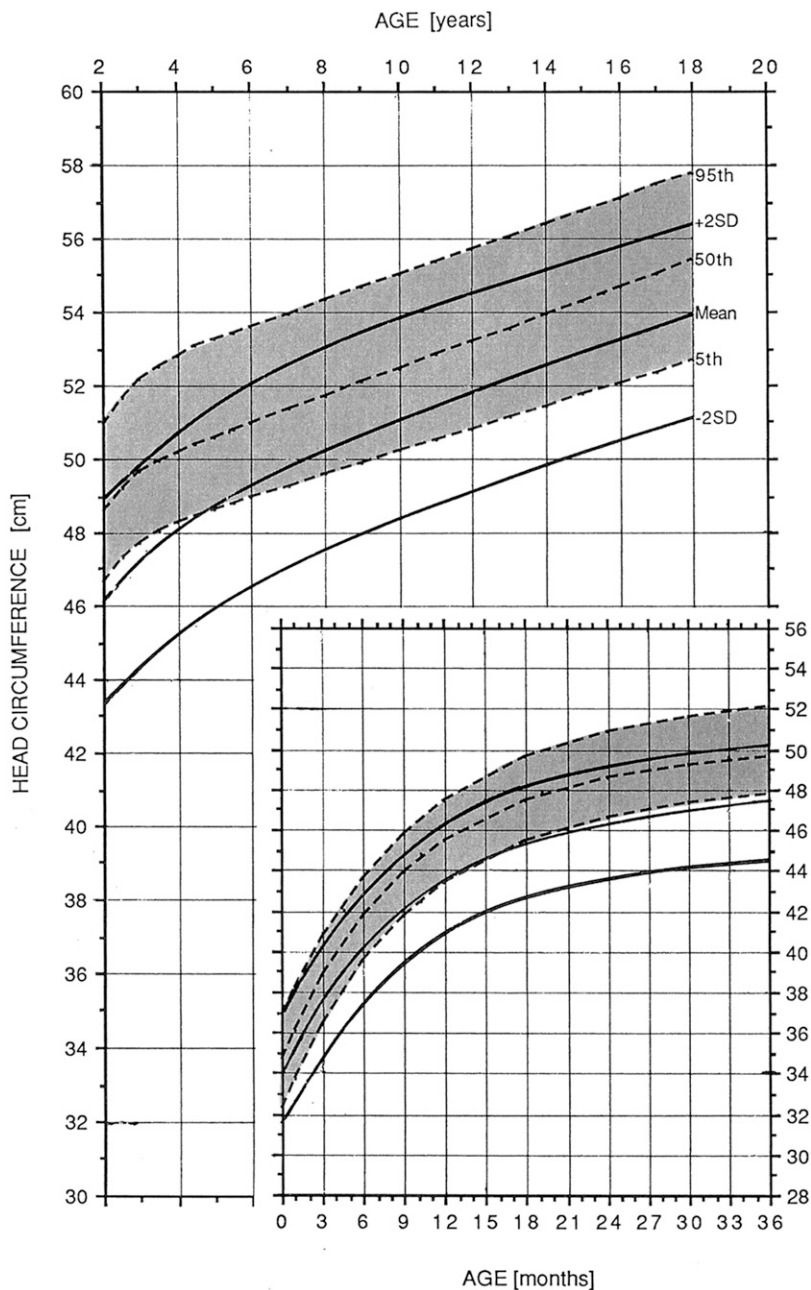
surgical repair. Kidney function should be assessed at the time of diagnosis (serum urea nitrogen and creatinine concentrations and urinalysis).

## 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.<sup>42</sup> Posterior fossa size is reduced in WS, although cerebellar volume is preserved and may contribute to Chiari I malformation in some individuals with WS.<sup>43</sup> 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,<sup>6</sup> 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.<sup>44</sup> Although joint laxity is present in young children, joint contractures occur in older children and adults and lead to an awkward gait.<sup>45</sup> 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.<sup>46</sup> Lordosis and kyphosis are common at all ages; 18% have scoliosis.<sup>6,47</sup>

Children with WS have a unique cognitive and behavioral profile.<sup>7,48,49</sup> Cognitive, motor, and language delay are universal, and in 75% of children, intellectual disability is ultimately diagnosed. Children demonstrate a relative strength in language and verbal short-term memory, with





**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 significant weakness in visuospatial construction.<sup>7</sup> 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.<sup>50</sup> 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.<sup>51</sup> In young children who have limited language, there may be symptom overlap with autism spectrum disorder, such as restricted interests and repetitive behaviors.<sup>52</sup> 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.<sup>48</sup> Adaptive behavior skills in both children and adults are often more impaired than would be expected for IQ.<sup>53,54</sup> Adults require vocational training and instruction in community living skills. Mental health problems, most commonly anxiety, are reported in 25% to 75% of adults.<sup>13,55</sup>

Sleep disorders are common (50% to 65%), including sleep onset delay, frequent awakenings, decreased sleep efficiency, and increased respiratory-related arousals.<sup>56,57</sup> An abnormal or absent melatonin peak may explain disturbance of circadian rhythm in some children.<sup>58,59</sup> 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        |
| <b>Ocular</b>   |              |             |   |            |             |            |
| Vision screening for strabismus, refractive errors, cataracts (adults)  | Yes          | Yearly      | Yearly                                    | Yearly     | Yearly      | Yearly     |
| Ophthalmologic evaluation   | Yes          | PRN         | PRN                                       | PRN        | PRN         | Yearly     |
| <b>Auditory</b>   |              |             |   |            |             |            |
| Audiological evaluation   | Yes          | Yearly      | Yearly                                    | Yearly     | Yearly      | Yearly     |
| Counsel regarding sensitivity to sound  | Yes          | PRN         | PRN                                       | PRN        | PRN         | PRN        |
| <b>Dental</b>   |              |             |   |            |             |            |
| Dental cleaning   | Yes          | —           | Every 6 mo                                | Every 6 mo | Every 4 mo  | Every 4 mo |
| Refer to orthodontics for malocclusion  | —            | —           | —   | Yes        | Yes         | Yes        |
| <b>Calcium</b>  |              |             |   |            |             |            |
| 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        |
| <b>Cardiovascular</b>   |              |             |   |            |             |            |
| 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     |
| <b>Genitourinary</b>  |              |             |   |            |             |            |
| 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        |
| <b>Endocrine</b>  |              |             |   |            |             |            |
| 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     |
| <b>Development and cognition</b>  |              |             |   |            |             |            |
| 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<br>Diagnosis | 0–12 mo<br>Old | 1–5 y Old | 6–12 y<br>Old | 13–18 y<br>Old | Adult  |
|--|-----------------|----------------|-----------|---------------|----------------|--------|
| Refer for therapy (speech and language, physical and occupational),<br>consider hippotherapy |                 |                |           |               |                |        |
| Feeding therapy if needed  | Yes             | PRN            | PRN       | —             | —              | —      |
| Refer to early intervention program  | Yes             | Yes            | —         | —             | —              | —      |
| Refer for special education  | Yes             | —              | Yes       | Yes           | Yes            | —      |
| <b>Behavior</b>  |                 |                |           |               |                |        |
| 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    |
| <b>Genetic counseling</b>  |                 |                |           |               |                |        |
| Medical genetics evaluation  | Yes             | PRN            | PRN       | PRN           | PRN            | PRN    |
| Genetic counseling for family  | Yes             | —              | —         | —             | —              | —      |
| Genetic counseling for individual  | —               | —              | —         | —             | Yes            | Yes    |
| <b>Transition</b>  |                 |                |           |               |                |        |
| 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.<sup>60</sup> 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.<sup>61</sup> Audiologic assessment should be performed between 6 and 12 months of age and repeated annually.<sup>61</sup> 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.<sup>13</sup>

**DENTAL**

Dental problems include microdontia, missing teeth, and localized enamel hypoplasia.<sup>62</sup> 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.<sup>4</sup> Caregivers should be instructed to assist with brushing and flossing. If dental procedures require anesthesia, WS-specific sedation and anesthesia recommendations should be followed.<sup>29,30</sup> 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.<sup>33</sup> 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%.<sup>63</sup> Puberty often occurs early (18% of girls), but true precocious puberty is rare.<sup>64</sup> 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.<sup>65</sup> 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.<sup>66,67</sup> An oral glucose tolerance test is recommended at 30 years of age and should be repeated every 5 years if results are normal.<sup>13</sup>

**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”).<sup>68</sup>

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.<sup>37</sup> 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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