

Management of Williams Syndrome

A Clinical Guideline

Williams Syndrome Guideline Development Group

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(<https://williams-syndrome.org.uk/clinical-guidelines/>)



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Introduction...

... to Williams Syndrome (WS)

Williams Syndrome is a rare condition, that occurs in at least 1 in 20,000 births. The current definition of WS was agreed by the Williams Syndrome Guideline Development Committee at the Williams Syndrome Management Consensus Meeting held in Manchester in May 2009.

It remains pertinent in 2017 when the guidelines were updated.

“Williams Syndrome is a sporadic genetic disorder due to deletion of a small part of chromosome 7. Features may include a distinctive facial appearance, congenital heart defects and high levels of calcium in infancy. Early feeding problems are common and development is delayed. People with WS have sociable personalities, characteristic behavioural traits and variable degrees of learning disability.”

... to the Williams Syndrome Guideline Development Project

The guidelines have been developed using a robust methodology based on the one utilised by the Scottish Intercollegiate Guidelines Network (SIGN). The method has been adapted to suit rare conditions where the evidence base is limited and expert consensus plays a greater role.

The papers selected for review and consideration in formulating management recommendations for Williams Syndrome, are listed by clinical sign in the bibliography from page 37. Evidence from these papers was considered, and complemented by consensus on good practice, by the members of the guideline development group, who are listed on page 51. The guidelines were updated and substantially added to in January 2017. In particular sections were added relating to surgical care, behaviour, psychology, mental health and education.

... to the Williams Syndrome Clinical Management Guidelines

What are the aims of the guidelines?

Guidelines for the medical supervision of people with WS have been published amongst others in 2001 by the American Academy of Pediatrics Committee on Genetics and in France (CLAD-Ouest) in 2014. Whilst valuable, they are not entirely transferable to the UK. Therefore, in order to optimise the medical and psychological care of people with WS, the aim of the guidelines is to provide clear evidence-based management recommendations applicable to U.K. individuals.

Who are they aimed at?

As WS is so rare, it is probable that the primary care clinicians usually responsible for coordinating the care of someone with the condition will have had little prior experience of the syndrome. Because WS is a multisystem disorder, people with WS require various tests, screens, assessments, referrals and multidisciplinary interventions at different stages of their lives. These guidelines lay out these requirements in a format that is accessible to anybody who is involved in the care of an individual with WS, including their parents.

How are they constructed?

The guidelines are divided into recommendations for four age groups: infancy; childhood; adolescence; and adults.

On pages 4-5, recommended baseline investigations are listed. These should be considered alongside the age group-specific recommendations which are pertinent when the diagnosis is made. For each age group, the recommended tests are listed, and follow-up options are indicated.

On pages 48-49, a Summary of Investigations for Children with Williams Syndrome summarises when, and how often, specific tests and screens should take place for children with Williams Syndrome.

Clinical features and recommended baseline investigations in WS

Clinical Features of Williams Syndrome	Baseline investigations
Confirm diagnosis of Williams Syndrome by testing for microdeletion on chromosome 7 using specialist molecular techniques and refer to a geneticist. (Historically a FISH test was used but this has now been superseded by the Array Comparative Genomic Hybridisation test or more simply the "microarray" test.	
• Distinctive facial features (subtle in infancy) • Congenital heart defects (especially supraaortic stenosis (SVAS) and peripheral pulmonary artery stenosis) • Raised blood/urine calcium levels and nephrocalcinosis • Genitourinary problems (undescended testes, hypospadias) • Hypertension • Inguinal hernias • Gastrointestinal problems and feeding problems- gastro-oesophageal reflux; rectal prolapse; colonic diverticular • Failure to thrive/slow growth rate • Endocrine abnormalities / short stature • Scoliosis and other musculoskeletal problems	(where investigation not initially indicated for a specific clinical feature, please refer to the relevant age group- specific page for management recommendations) • Cardiovascular assessment including BP (blood pressure) measurement in both upper limbs (4 - limb in infants), oxygen saturation pre and post ductally, ECG and Echocardiography. (Chest x-ray may also be indicated.) • Blood calcium and urine calcium : creatinine ratio • Blood creatinine, electrolytes and urinary tract ultrasound • Plasma renin activity and renal artery doppler studies • Coeliac screen and plot weight on appropriate WS growth chart • Thyroid Function Tests and plot length and occipito frontal head circumference (OFC) on WS growth chart • Radiology tests as appropriate

Clinical features and recommended baseline investigations in WScontinued....

Clinical Features of Williams Syndrome	Baseline investigations
Confirm diagnosis of Williams Syndrome by testing for microdeletion on chromosome 7 using specialist molecular techniques and refer to a geneticist. (Historically a FISH test was used but this has now been superseded by the Array Comparative Genomic Hybridisation test or more simply the "microarray" test.	
• Dental anomalies • Developmental delay : Across all domains including language (particularly comprehension), visual, spatial and social cognition. • Distinctive behavioural characteristics (including irritability, hyperactivity, perseverative behaviour, anxiety and overfriendliness). • Visual problems: Strabismus, poor acuity, visual crowding, poor depth perception and refractive errors (usually hypertonia and astigmatism) • Auditory problems and hypersensitivity to noise • Sleep issues	(where investigation not initially indicated for a specific clinical feature, please refer to the relevant age group- specific page for management recommendations) • Developmental assessment (Age appropriate) • Consider additional specific investigations as appropriate. • First step, parents should keep a sleep diary using http://kidsleepdr.com to discuss with GP. Consider referral to sleep clinic for assessment and sleep management. Further information on sleep issues can be found on the WSF website http://williams-syndrome.org.uk.

Recommendations for the management of Williams Syndrome

~ in infancy(1)~

AGE 0—1

Recommended Testing/Screening

- Cardiac screening
- Blood Calcium and Urine Calcium: creatinine ratio

Clinical Management Recommendations

If the diagnosis is made in the neonatal period, a cardiac assessment should be carried out and referral made to a paediatric cardiologist for echocardiography. Where the diagnosis is made later in infancy, referral to a paediatric cardiologist should be made within 3 months. At least annual cardiac examination by a paediatric cardiologist should be carried out until 4 years of age.

NB The presence of SVAS or PPAS may be diagnosed in infancy when developmental delay or the typical facial appearance is not recognised. In all such cases the paediatric cardiologist should request a genetic opinion or arrange appropriate genetic testing.

Measure at diagnosis. Age appropriate normal ranges should be used. 5 - 10% of WS infants may require therapy for hypercalcaemia. If initial tests are normal, further testing need only be performed if symptoms develop. Renal ultrasound to exclude nephrocalcinosis (See below)

Management of Hypercalcaemia

Hypercalcaemia should be treated in a stepwise fashion

- Intravenous fluids to correct dehydration and to meet increased urinary losses caused by hypercalcaemia and therapy (See below)
 - Loop diuretics such as Frusemide enhance calcium excretion
 - Low calcium diet. Achieved by substituting Locasol [SHS International (Nutricia Advanced Medical Nutrition) Liverpool, UK] for all milk feeds. This contains calcium <7mg/100ml and no added vitamin D. Total daily dietary calcium intake should be restricted to 50% of recommended nutrient intake (RNI)
 - Calcium rich hard water or mineral water should not be used to prepare formula feeds. Boiling tap water may help to reduce its calcium content.
 - Sun-block creams should be used to limit cutaneous vitamin D synthesis
 - Vitamin D supplement should be avoided
 - In infants with normal renal function, and resistant hypercalcaemia, treatment with intravenous bisphosphonates (usually Pamidronate) is effective in reducing serum calcium levels. In infants with impaired renal function lower doses of bisphosphonates should be used after discussion with a nephrologist.
 - Blood calcium, alkaline phosphatase and parathyroid hormone levels should be measured at intervals until values become normal.
 - The calcium diet should be 'relaxed' if the alkaline phosphatase and parathyroid hormone levels start to rise. Prolonged calcium and vitamin D restriction may result in rickets.
- Refer to nephrologist if nephrocalcinosis is detected with evidence of renal impairment. If renal function is normal, repeat scan at appropriate interval. If structural abnormalities detected investigate as appropriate.

Recommendations for the management of Williams Syndrome ~ in neonates & infancy(2)~

AGE 0—1

Recommended Testing/Screening

- Genitourinary screening
- Hypertension screening
- Inguinal hernia screening
- Gastrointestinal and feeding problems
- Thyroid function tests(TFTs)
- Musculoskeletal problems
- Dental screening to prevent dental disease

Clinical Management Recommendations

Examine male infants for hypospadias and undescended testes (10% and 30% respectively in published series) and refer to a paediatric surgeon according to local guidelines. A urinary tract ultrasound should be performed and structural abnormalities managed accordingly. The incidence of urinary tract infections is increased and should be routinely investigated

Monitoring blood pressure annually in 4 limbs. Hypertension is defined as the average systolic BP and/or diastolic BP greater than or equal to the 95th centile for gender, age and height on > 3 occasions. If associated with renovascular disease (RVD), refer to nephrologist. Intervention for the management of hypertension secondary to RVD with either percutaneous transluminal angioplasty and/or surgical vascular reconstruction is not recommended for the initial management of hypertension. Medical management of hypertension under the supervision of a nephrologist is recommended.

Examine for inguinal hernias. Their incidence is significantly increased in both sexes, especially in girls. Refer to a paediatric surgeon according to local guidelines.

Take feeding history. Enquire about bowel habit, vomiting and symptoms of gastro oesophageal reflux (GOR). If failing to thrive, measure plasma calcium, thyroid function tests and coeliac screen. Refer for appropriate dietetic support. Manage GOR with standard therapies and investigate for potential hiatus hernias or strictures where symptoms persist or infant fails to thrive. Manage rectal prolapse conservatively, treating constipation. Faltering growth is common in WS. Use the syndrome specific growth charts and consider nasogastric or percutaneous gastrostomy feeding.

Ensure baseline test are undertaken. Repeat thyroid function test if patient symptomatic. Measure TSH levels and if elevated, consider thyroid scanning and replacement therapy. Plot growth and OFC 3monthly.

Examine for scoliosis and radio-ulnar synostosis. Refer to paediatric orthopaedic surgeon as appropriate.

Enrol patient in an individualised preventative oral healthcare programme from an early age. Routine follow up and regular dental examinations by a family dentist or local community dental services are essential. Follow guidance in 'Delivering Better Oral Health: an evidenced-base tool kit for prevention'. (www.gov.uk).

Recommendations for the management of Williams Syndrome ~ in neonates & infancy(3)~

AGE 0—1

Recommended Testing/Screening

- Multidisciplinary development assessment
- Hearing screening
- Vision screening

Clinical Management Recommendations

Coordinate an assessment by the local multidisciplinary team within 6 months of diagnosis. Adaptive behaviours especially feeding and sleeping should be reviewed. The assessment should include involvement of a physiotherapist, occupational therapist, speech therapist and if available clinical psychologist. Referral to Early Intervention services and provision of a Key worker should be arranged as soon as possible.

Newborn hearing screening programme (NHSP) .

Visual screening should take place once the diagnosis has been made, carried out by the community orthoptist/optometrist where services exist. Referral to the local paediatric ophthalmology services if any abnormality is detected (or community services do not exist). Encourage parents to report any concerns to the orthoptist.

NB. Anaesthesia

A paediatric anaesthetist should be involved in the perioperative care, for any surgical procedure, in all children with WS. Unless there are existing cardiac problems, cardiac assessment within 12 months prior to a general anaesthetic is sufficient. Pre-op assessment should take place 1-2 weeks prior to planned surgery, to assess cardiac, airway, joints, renal and emotional status. This should include an ECG to exclude prolonged QT interval.

Recommendations for the management of Williams Syndrome

~ in childhood(1) ~

AGE 2-11

Recommended Testing/Screening

- Cardiac screening
- Blood calcium and urine calcium: creatinine ratio

Clinical Management Recommendations

Annual cardiac examination until 4 years of age. Thereafter complete cardiac assessment, including echocardiography, at least every 5 years.

Measure at diagnosis. Age appropriate normal ranges should be used. 5 - 10% of WS children may require therapy for hypercalcaemia. If initial tests are normal, further testing should only be performed if symptoms develop.

Management of Hypercalcaemia

Hypercalcaemia should be treated in a stepwise fashion

- Intravenous fluids to correct dehydration and to meet increased urinary losses caused by hypercalcaemia and therapy (See below)
- Loop diuretics such as Frusemide enhance calcium excretion
- Low calcium diet. Achieved by substituting Locasol [SHS International (Nutricia Advanced Medical Nutrition) Liverpool, UK] for all milk feeds. This contains calcium <7mg/100ml and no added vitamin D. Total daily dietary calcium intake should be restricted to 50% of recommended nutrient intake (RNI)
- Calcium rich hard water or mineral water should not be used to prepare formula feeds. Boiling tap water may help to reduce its calcium content.
- Sun-block creams should be used to limit cutaneous vitamin D synthesis
- Vitamin D supplement should be avoided
- In infants with normal renal function, and resistant hypercalcaemia, treatment with intravenous bisphosphonates (usually Pamidronate) is effective in reducing serum calcium levels. In infants with impaired renal function lower doses of bisphosphonates should be used after discussion with a nephrologist.

- Genitourinary tract screening

Assess for urinary tract infections and bladder dyssynergy. Day and night-time urinary incontinence is common and may persist into adulthood. Bladder dyssynergy increases the risk of bladder diverticula and calculi developing. Examine boys for undescended testes and hypospadias. Renal tract ultrasound should be performed to include kidneys and bladder. If recurrent urinary infections occur, consider excluding bladder diverticula, ureteric reflux or stones. If urinary incontinence is prominent consider excluding and treating bladder dysynergy. If nephrocalcinosis exists, with evidence of renal impairment, refer to a paediatric nephrologist. Test serum creatinine every 2–4 years. Undertake detailed renal function tests and/or refer to a nephrologist if evidence of renal impairment.

Recommendations for the management of Williams Syndrome ~ in childhood (2)~

AGE 2–11

Recommended Testing/Screening

- Hypertension screening
- Inguinal hernia screening
- Gastrointestinal and feeding problems
- Thyroid function tests(TFTs)
- Growth & Puberty

Clinical Management Recommendations

Monitor blood pressure annually in both arms. Hypertension is defined as the average systolic BP and/or diastolic BP greater than or equal to the 95th centile for gender, age and height on > 3 occasions. If associated with renovascular disease (RVD), refer to nephrologist. Intervention for the management of hypertension secondary to RVD with either percutaneous transluminal angioplasty and/or surgical vascular reconstruction is not recommended for the initial management of hypertension. Medical management of hypertension under the supervision of a nephrologist is recommended.

Opportunist examination to exclude development of inguinal hernias.

Enquire about nutritional problems and bowel habit. Treat constipation. Symptomatic colonic diverticular disease has been reported in children as young as 9 years. Consider diverticulosis in a child with recurrent abdominal pain. Screen for coeliac disease around 3 years of age with low threshold to repeat if symptoms suggestive. Significant gastro-oesophageal reflux tends to reduce with age but may remain problematic. Risk of oesophageal strictures if untreated.

Test if patient is symptomatic. Measure TSH levels and if elevated, consider thyroid scanning, Consider treatment with L-Thyroxin if patient has overt hypothyroidism, or progressive deterioration of thyroid function.

Chart height, weight and OFC measurements annually (use WS growth charts). Mid parental height centile should be estimated. Routine investigations for abnormal growth velocity and precocious puberty (< 8 years). Where necessary, consider gonadotropin releasing hormone (GnRH) therapy.

Recommendations for the management of Williams Syndrome ~ in childhood(3)~

AGE 2–11

Recommended Testing/Screening

- Musculoskeletal problems
- Screening for dental anomalies
- Multidisciplinary developmental assessment
- Hearing screening
- Visual screening

Clinical Management Recommendations

Enquire about skeletal problems. Check spine for kyphoscoliosis and range of other joint movements. X-ray/refer to paediatric orthopaedic team as indicated.

Enrol patient in an individualised preventative oral healthcare programme from an early age. Routine follow up and regular dental examinations by a family dentist or local community dental services are essential. Follow guidance in 'Delivering Better Oral Health: an evidenced-base tool kit for prevention' (www.gov.uk). Missing teeth/ malocclusion/prolonged retention of primary teeth and other dental anomalies: refer to a consultant or specialist in paediatric dentistry for multidisciplinary assessment and management. If cardiac anomalies exist, antibiotic prophylaxis may be advised for dental procedures - check with cardiologist.

Refer to local Child Development Team. Learning/cognitive disability may include delays of development with difficulties in all domains. Particular difficulties of attention, visual-motor actions, and spatial memory are often noted. From 5 years to adulthood, speech and language development is usually relatively good compared to visual, motor and spatial abilities. Assessment based on expressive language skills may overestimate general ability. Monitor feeding and sleeping. Support learning and development with assessment of the child's special educational needs and request an Educational Health Care Plan (EHCP) at 2 years of age. (See below) <https://www.gov.uk/children-with-special-educational-needs/overview>.

Carry out at 2 years if speech is delayed (This is likely to be due to developmental delay) If hyperacusis is present, consider implementing a programme of desensitisation with maskers (if services are available).

Visual screening should be carried out at primary school entry and at transition to secondary education by the community orthoptist/optometrist unless an abnormality is detected. Where these services do not exist the child should be seen in the hospital ophthalmic service. Parents should be encouraged to report any concerns to their orthoptist/optometrist. Screening tests suitable for children with learning disabilities should be used e.g. crowded card/single optotype symbols.

Recommendations for the management of Williams Syndrome

~ in childhood(4)~

AGE 2–11

Recommended Testing/Screening

- Behavioural & Mental Health issues
- Educational issues
- Sleep issues

Clinical Management Recommendations

Provide behavioural management advice with support to family as required. Refer for psychological intervention for anxiety or major life events. Consider screening with a behavioural assessment tool. Consider referral to a sleep disorders clinic if problems merit intervention. Involve primary mental health services if available. Be aware of issues related to social vulnerability and put in place appropriate social support structures/environments. Additional advice on this aspect of care can be obtained from the Williams Syndrome Foundation www.williams-syndrome.org.uk.

Children with WS have difficulties in language and communication; cognition and learning (attention, reading, writing and number development); social, emotional, mental health, sensory and physical needs. Therefore they often need specialist advice from speech and language therapy, occupational therapy, physiotherapy, dietetics, clinical psychology, educational psychology, audiology and other specialists and hence will qualify for an EHCP. WS children and adults have great difficulty in writing with a pen or pencil and should be encouraged using a computer for writing and preferably a large keyboard. Development is atypical, which has implications for intervention (e.g. counting is helped by using verbal rather than visual strategies; reading is heavily reliant on phonology in WS; both numeracy and literacy deficits can be related to attention impairments). Further information about the specific requirements of an EHCP and educational advice relating to WS can be obtained through the Williams Syndrome Foundation www.williams-syndrome.org.uk.

First step, parents should keep a sleep diary using <http://kidssleepdr.com> to discuss with GP. Consider referral to sleep clinic for assessment and sleep management. Further information on sleep issues can be found on the WSF website <http://williams-syndrome.org.uk>

†NB. Anaesthesia

A paediatric anaesthetist should be involved in the perioperative care, for any surgical procedure, in all children with WS. Unless there are existing cardiac problems, cardiac assessment within 12 months prior to a general anaesthetic is sufficient. Pre-op assessment should take place 1-2 weeks prior to planned surgery, to assess cardiac, airway, joints, renal and emotional status. This should include an ECG to exclude prolonged QT interval.

Recommendations for the management of Williams Syndrome

~ in adolescence(1)~

AGE 11-18

Recommended Testing/Screening

- Cardiac screening
- Blood calcium and urine calcium: creatinine ratio
- Genitourinary tract screening
- Hypertension screening
- Inguinal hernias
- Gastrointestinal problems
- Thyroid function tests(TFTs)
- Growth & sexual health

Clinical Management Recommendations

Cardiac assessment including scans at least every 5 years. Appropriate follow up if symptomatic.

Test if symptoms suggest hypercalcaemia. If present, hypercalcaemia is likely to be due to an alternative diagnosis. Investigate and manage as appropriate.

Take history for urinary tract infections or symptoms of bladder dyssynergia. Check for position of testes. Renal ultrasound at puberty and 5 yearly thereafter or if symptomatic. Test blood creatinine every 2–4 years. Investigate/refer as appropriate for urinary tract infection; exclude obstructive lesion(s); undertake detailed renal function tests and/or refer to a nephrologist if evidence of renal impairment. If nephrocalcinosis persists refer to nephrologist.

Monitoring blood pressure annually in both arms. Hypertension is defined as the average systolic BP and/or diastolic BP greater than or equal to the 95th centile for gender, age and height on > 3 occasions. If associated with renovascular disease (RVD), refer to nephrologist. Intervention for the management of hypertension secondary to RVD with either percutaneous transluminal angioplasty and/or surgical vascular reconstruction is not recommended for the initial management of hypertension. Medical management of hypertension under the supervision of a nephrologist is recommended.

Examine for inguinal hernias which remain common into adulthood.

Enquire annually about bowel habit. Treat constipation and consider investigating for diverticular disease if relevant and unexplained symptoms. Screen for coeliac disease if symptomatic. The incidence of significant GOR decreases with age but may remain problematic. Treat for response or refer for assessment. Risk of oesophageal strictures causing dysphagia if untreated.

Test if patient is symptomatic. Measure TSH levels and if elevated, consider thyroid scanning. Consider treatment with L-Thyroxin if patient has overt hypothyroidism, or progressive deterioration of thyroid function.

Chart growth annually, and avoid excessive weight gain. Offer contraceptive advice/contact details of organisations who can advise on contraception for people with learning disabilities.

Recommendations for the management of Williams Syndrome

~ in adolescence(2)~

AGE 11-18

Recommended Testing/Screening

- Musculoskeletal problems
- Screening for dental anomalies
- Multidisciplinary developmental assessment
- Hearing screening
- Visual screening

Clinical Management Recommendations

Check spine clinically for kyphoscoliosis at puberty and x-ray/refer to orthopaedic team as indicated.

Enrol patient in an individualised preventative oral healthcare programme from an early age. Routine follow up and regular dental examinations by a family dentist or local community dental services are essential. Follow guidance in 'Delivering Better Oral Health: an evidenced-base tool kit for prevention'. (www.gov.uk) Missing teeth/malocclusion/prolonged retention of primary teeth and other dental anomalies: refer to a consultant or specialist in paediatric dentistry for multidisciplinary assessment and management. If cardiac anomalies exist, antibiotic prophylaxis may be advised for dental procedures - check with cardiologist

Involve local Child Development or Learning Difficulties (LD) Teams. Advice and support may be required in areas of disability including visual-motor skills (e.g. stair descent, crossing road), spatial memory, navigation skills (e.g. using public transport, learning a walked route, strategies when lost), planning ahead / problem solving and attention deficits. Additional assessments for the EHCP will need to be required in most cases <https://www.gov.uk/children-with-special-educational-needs/overview> Refer for psychological intervention for anxiety, and when major life events occur. Be aware of issues related to social vulnerability and put in place appropriate social support structures/environments. Additional advice on this aspect of care can be obtained from the Williams Syndrome Foundation www.williams-syndrome.org.uk.

Arrange routine audiology check at 11 and 18 years for hyperacusis & high frequency hearing loss. If hyperacusis is present consider implementing a programme of desensitisation with maskers.

Screens for strabismus and refractive error can be carried out if indicated by the local optometrist who may refer to local ophthalmology services.

Recommendations for the management of Williams Syndrome ~ in adolescence(3)~

AGE 11-18

Recommended Testing/Screening

- Mental health issues

Clinical Management Recommendations

Phobias, anxiety and sleep problems are significantly more common among young people with WS. Social and behavioural problems may also be indications of poor mental health. Underlying causes include impairments in attention, social understanding, emotion recognition, sensory processing (in particular hyperacusis), adaptive behaviours and disrupted sleeping patterns. Assessment and intervention must also take account of potential situational factors (e.g. major life events, inadequate support systems, inappropriate environment).

NB. Apparent friendliness and sociability can mask depression and anxiety.

The evidence base for treatments for mental health problems in WS is limited. Potentially useful interventions include: programmes to enhance adaptive and self-help skills and social functioning and understanding; cognitive-behavioural therapies including mindfulness; education and occupational interventions. The provision of a suitable supportive and structured environment is important and advice to improve sleeping patterns may also be required.

The evidence base for pharmacological treatments is weak. There are some positive reports for SSRI's and non-SSRIs in the treatment of depression and anxiety and for methylphenidate to improve attention and hyperactivity. However unwanted side effects are also very common. National guidance recommends annual review of mental health issues in young persons with learning disability

<https://www.nice.org.uk/guidance/qs142>.

- Educational issues

Additional assessments for the EHCP will be needed on transition from primary to secondary and secondary to 16+ education <https://www.gov.uk/children-with-special-educational-needs/overview>. Access to social skills training, and programmes to teach basic self-help and daily living skills will be useful.

Further information about the specific requirements of an EHCP relating to WS can be obtained through the Williams Syndrome Foundation www.williams-syndrome.org.uk.

Be aware of issues related to social vulnerability and put in place appropriate social support structures/environments. Additional advice on this aspect of care can be obtained from the Williams Syndrome Foundation www.williams-syndrome.org.uk.

Recommendations for the management of Williams Syndrome ~ in adolescence(4)~

AGE 11–18

†NB. Anaesthesia

†A paediatric anaesthetist should be involved in the perioperative care, for any surgical procedure, in all children with WS.

†Unless there are existing cardiac problems, cardiac assessment within 12 months prior to a general anaesthetic is sufficient.

†Pre-op assessment should take place 1-2 weeks prior to planned surgery, to assess cardiac, airway, joints, renal and emotional status.

†This should include an ECG to exclude prolonged QT interval.

Recommendations for the management of Williams Syndrome

~ in adulthood(1)~

AGE 18+

Recommended Testing/Screening

- Cardiac screening
- Blood calcium and urine calcium: creatinine ratio
- Genitourinary tract screening
- Hypertension screening
- Inguinal hernias
- Gastrointestinal issues
- Thyroid function tests (TFTs)
- Growth & sexual Health
- Screening for diabetes

Clinical Management Recommendations

- Assessment including scans, every 5 years throughout life. Adults with Williams Syndrome should be referred to their regional Adult Congenital Cardiology Service for routine follow up.
- Test if symptoms suggest hypercalcaemia. If present, hypercalcaemia is likely to be due to an alternative diagnosis. Investigate and manage as appropriate.
- Check for urinary tract infection and symptoms of bladder dyssynergy: day or night time incontinence. Bladder & kidney ultrasonography every 5 year. Investigate evidence of renal scarring, bladder diverticulae or calculi. If nephrocalcinosis persists refer to nephrologist. Test serum creatinine every 2–4 years.
- Monitor blood pressure annually in both arms. In adults with WS, hypertension is defined as the average systolic BP and/or diastolic BP greater than or equal to 140/90mmHg. If associated with renovascular disease (RVD), refer to nephrologist. Intervention for the management of hypertension secondary to RVD with either percutaneous transluminal angioplasty and/or surgical vascular reconstruction is not recommended for the initial management of hypertension. Medical management of hypertension under the supervision of a physician is recommended.
- Examine for inguinal hernias which remain common into adulthood.
- Enquire about bowel habit. Treat constipation and consider investigating for diverticular disease. Screen for coeliac disease if symptomatic. Treat symptoms of gastro oesophageal reflux for response or refer for treatment.
- Repeat if patient is symptomatic (check for anti-thyroid antibodies). Consider thyroid scanning and thyroid hormone replacement therapy.
- Weigh annually, and avoid excessive weight gain—encourage an ‘active’ lifestyle. Offer contraceptive advice/contact details of organisations who can advise on contraception for people with learning disabilities.
- At 30 years old: Oral Glucose Tolerance Test (OGTT), or fasting insulin if considered more appropriate. Control impaired glucose tolerance with exercise & diet. Avoid large glucose loads. Avoid diabetogenic drugs. Manage clinical diabetes in WS by current national guidelines.

Recommendations for the management of Williams Syndrome

~ in adulthood(2)~

AGE 18+

Recommended Testing/Screening

- Musculoskeletal problems
- Screening for dental anomalies

- Hearing screening
- Vision screening
- Mental health issues

Clinical Management Recommendations

Investigate or refer if symptomatic

Enrol patient in an individualised preventative oral healthcare programme from an early age. Routine follow up and regular dental examinations by a family dentist or local community dental services are essential. Follow guidance in 'Delivering Better Oral Health: an evidenced-base tool kit for prevention'. (www.gov.uk) Missing teeth/ malocclusion/prolonged retention of primary teeth and other dental anomalies: refer to a consultant or specialist in paediatric dentistry for multidisciplinary assessment and management. If cardiac anomalies exist, antibiotic prophylaxis may be advised for dental procedures - check with cardiologist.

Screen every 5 -10 years (for hearing loss).

As required by the local optician.

Phobias and anxieties are significantly more common among young people with WS than in the general population. Social and behavioural problems may also be indications of poor mental health. Underlying causes include impairments in executive functioning; social understanding; emotion recognition; sensory processing (in particular hyperacusis); adaptive behaviours and disrupted sleeping patterns.

Assessment and intervention must take account of these potential situational factors (e.g. major life events, inadequate support systems, inappropriate environment).

NB. Apparent friendliness and sociability can mask depression and anxiety. The evidence base for treatments for mental health problems in WS is limited.

Particularly useful interventions include: programmes to enhance adaptive and self- help skills and social functioning and understanding; cognitive-behaviour therapies including mindfulness; education and occupational interventions. The provision of a suitable supportive and structured environment is also important.

The evidence base for pharmacological treatments is weak. There are some positive reports for SSRI's and non-SSRIs in the treatment of depression and anxiety. Also for methylphenidate to improve attention and hyperactivity. However unwanted side effects are also very common.

Access to support for employment, self-help and independent living is important and social skills intervention may be required.

Recommendations for the management of Williams Syndrome

~ in adulthood(3)~

AGE 18+

Recommended Testing/Screening

- Educational issues

Clinical Management Recommendations

An EHCP will normally have been requested at an earlier age. This can be extended to age 25 and can be requested by the young person themselves from 16 years of age. <https://www.gov.uk/children-with-special-educational-needs/overview>

Farther information about the specific requirements of an EHCP relating to WS can be obtained through the Williams Syndrome Foundation www.williams-syndrome.org.uk.

Support for employment, self-help, independent living and sexual health/education is vital. Support should include areas of intellectual disability which can negatively impact independence, such as navigation; using public transport; learning a walked route to get to place of employment; strategies when lost and how to ask for help; safe road crossing; planning ahead; problem solving (e.g. packing a bag for the day, keeping effects in order).

Be aware of issues related to social vulnerability and put in place appropriate social support structures/environments. Additional advice on this aspect of care can be obtained from the Williams Syndrome Foundation www.williams-syndrome.org.uk.

!General anaesthesia for any surgical procedure remains a significant risk and the anaesthetist should be fully aware of the particular issues relating to WS. Unless there are existing cardiac problems, cardiac assessment within 12 months prior to a general anaesthetic is sufficient. Pre-operative assessment should take place 1-2 weeks prior to planned surgery, to assess cardiac, airway, joints, renal and emotional status. This should include an ECG to exclude prolonged QT interval.

Williams Syndrome Growth Charts

For Girls 21

... WEIGHT:0–1 year old 21

... WEIGHT:1–5 years old 22

... WEIGHT:5–18 years old 23

... LENGTH: 0–1 year old 24

... HEIGHT:1–5years old 25

... HEIGHT:5–18years old 26

... OFC: 0–1 year old 27

... OFC: 1–5 years old 28

For Boys 29

... WEIGHT:0–1year old 29

... WEIGHT:1–5 years old 30

... WEIGHT:5–18 years old 31

... LENGTH: 0–1year old 32

... HEIGHT:1–5years old 33

... HEIGHT:5–18years old 34

... OFC: 0–1 year old 35

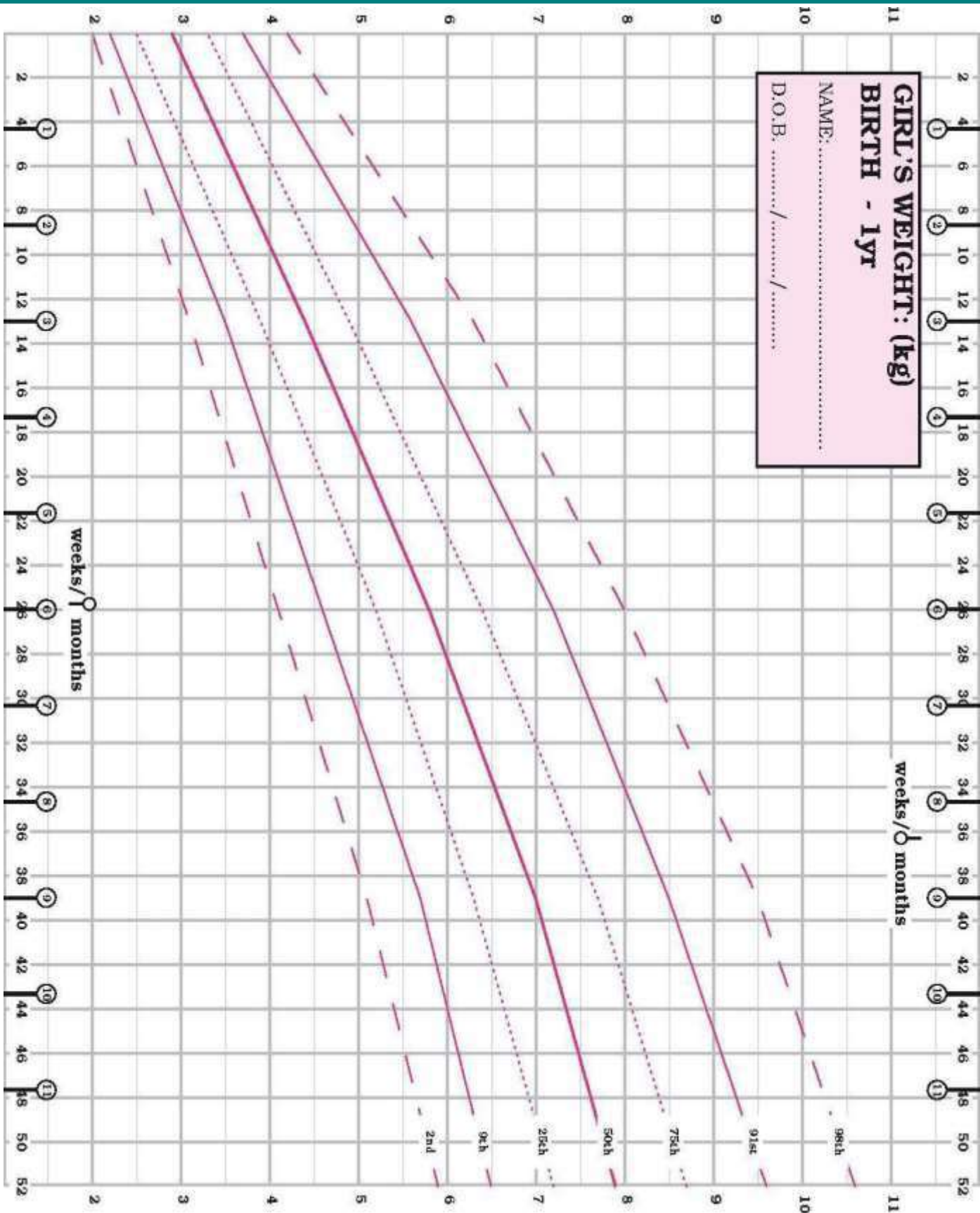
... OFC: 1–5years old 36

All growth charts are reproduced with the kind permissions of Harlow Printing Limited and Dr Neil Martin.

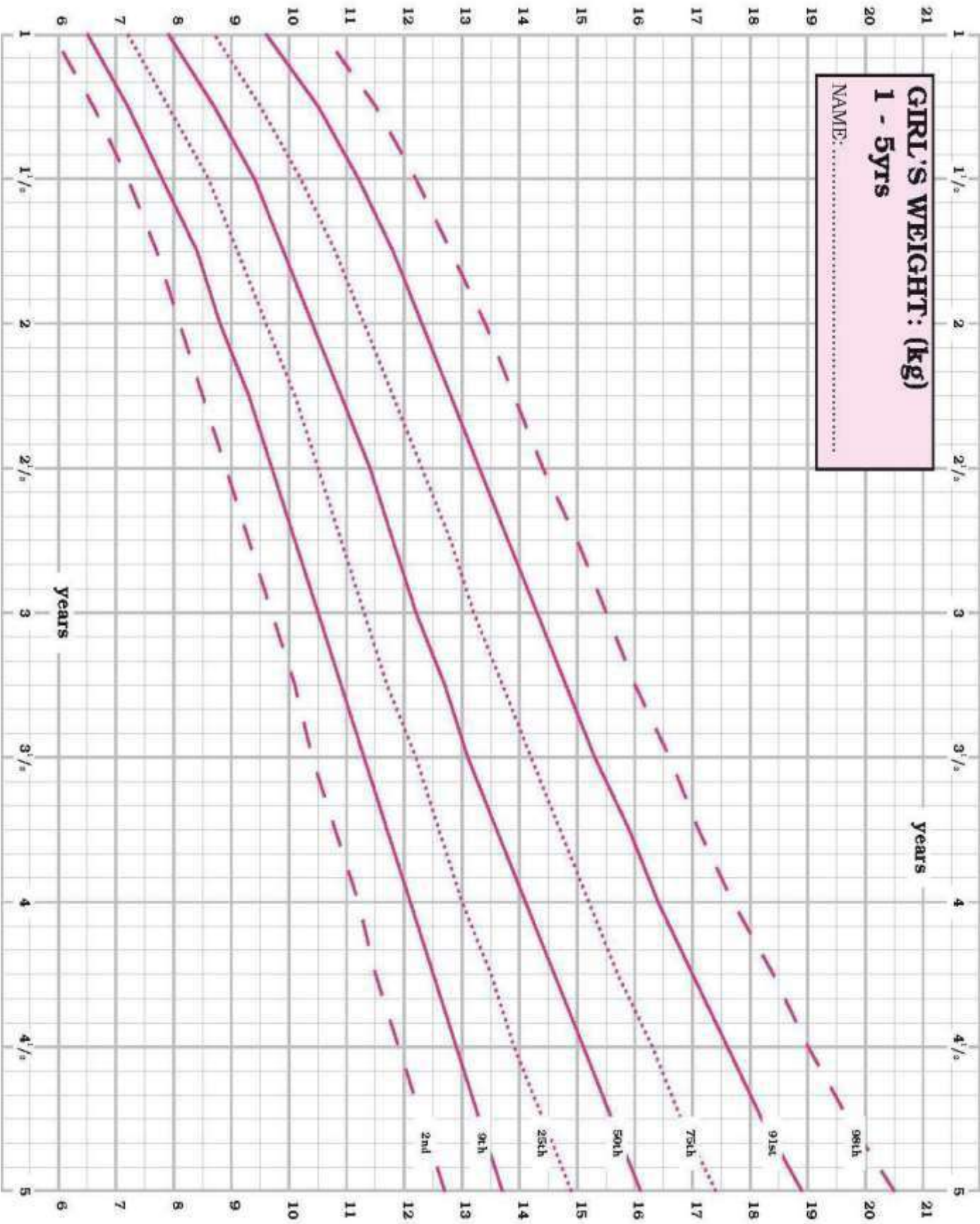
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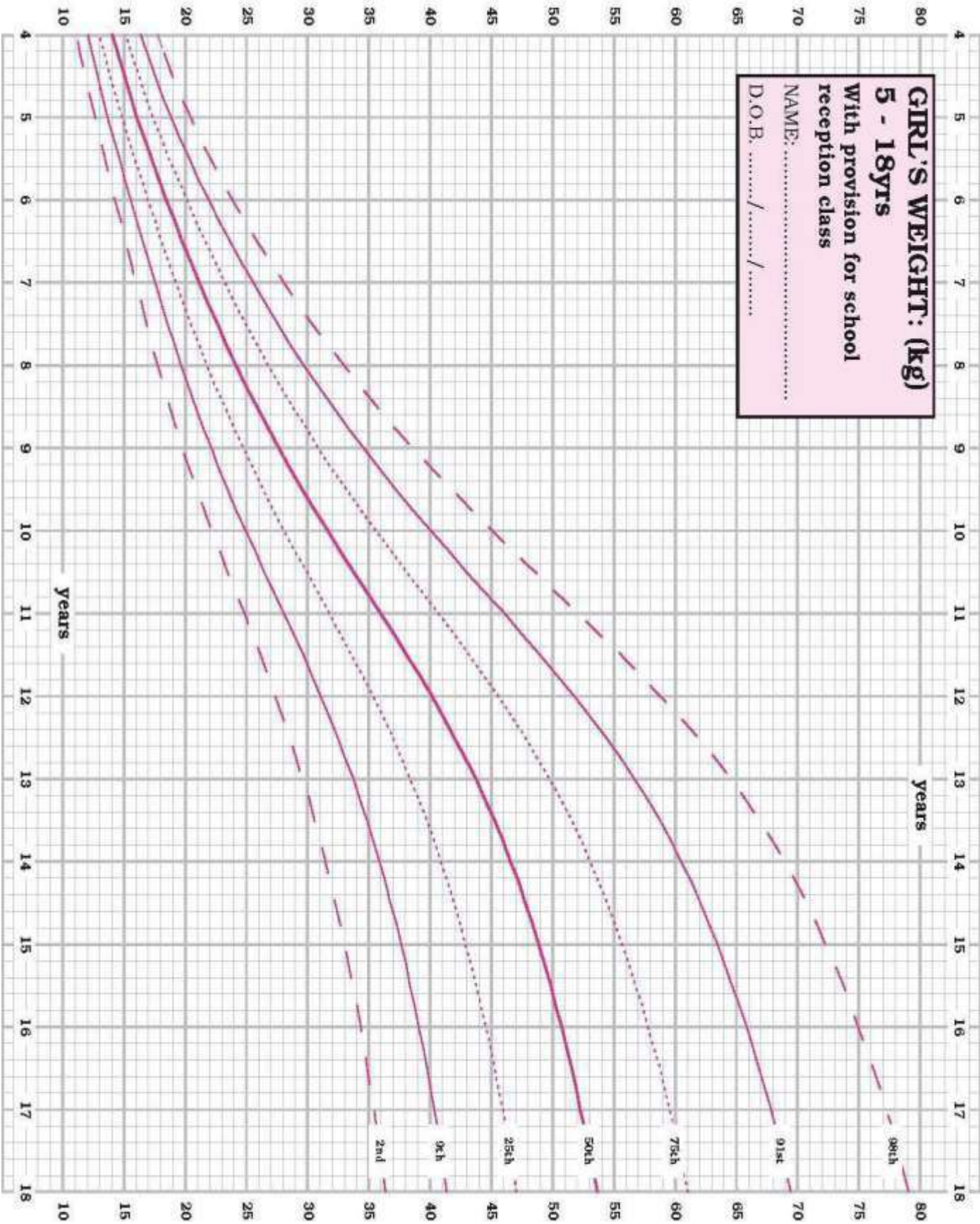
Williams Syndrome Clinical Management Guidelines



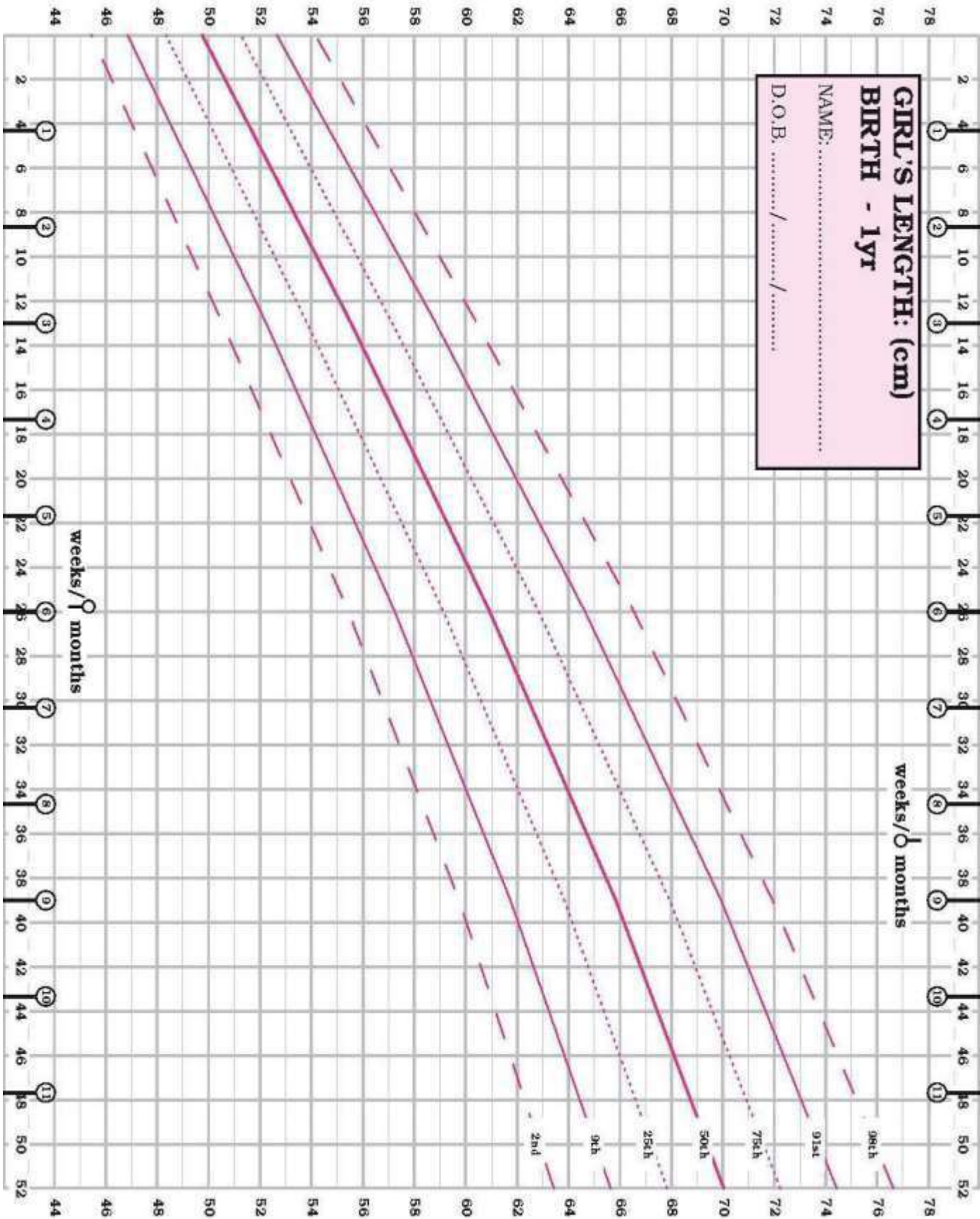
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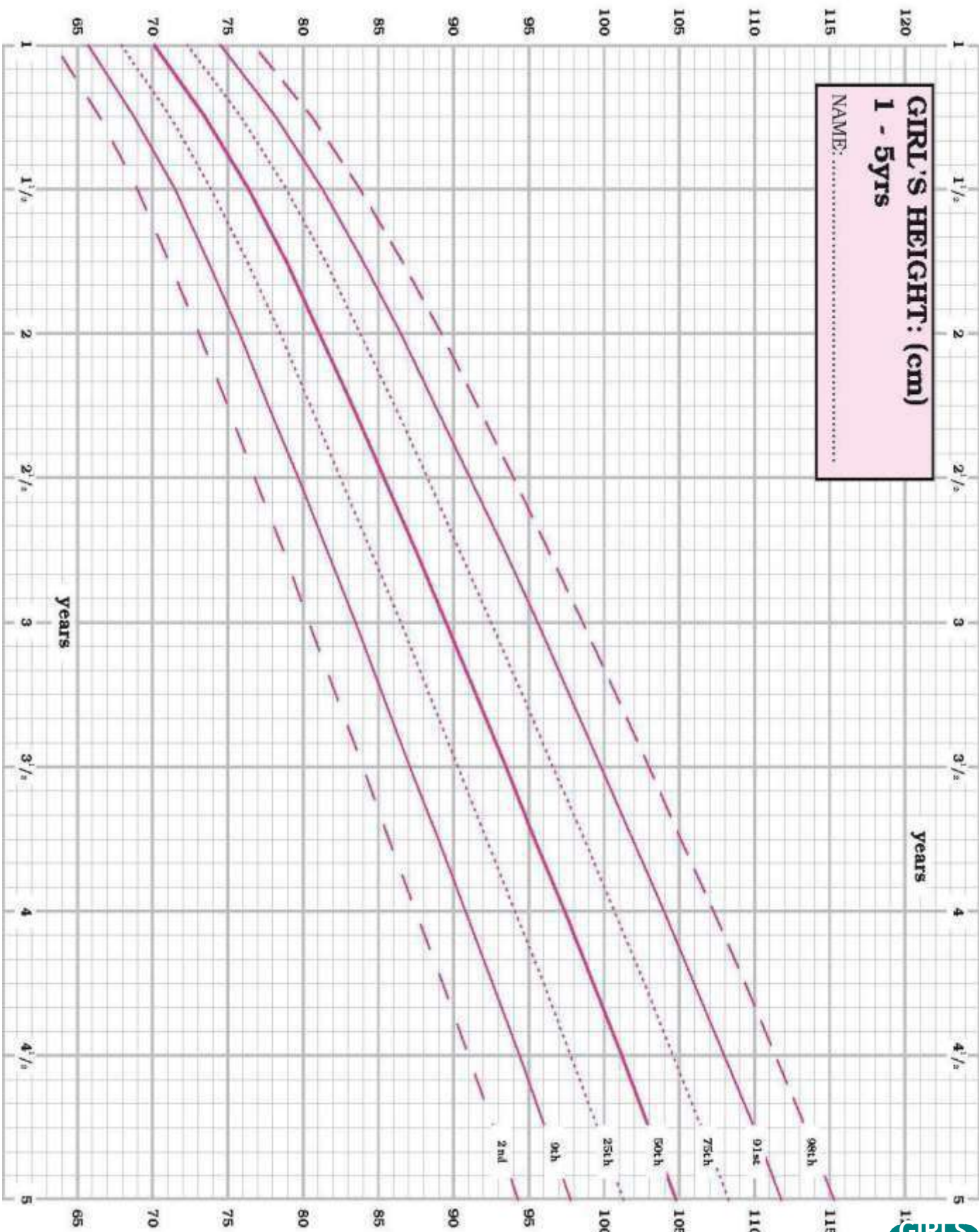


Williams Syndrome Clinical Management Guidelines

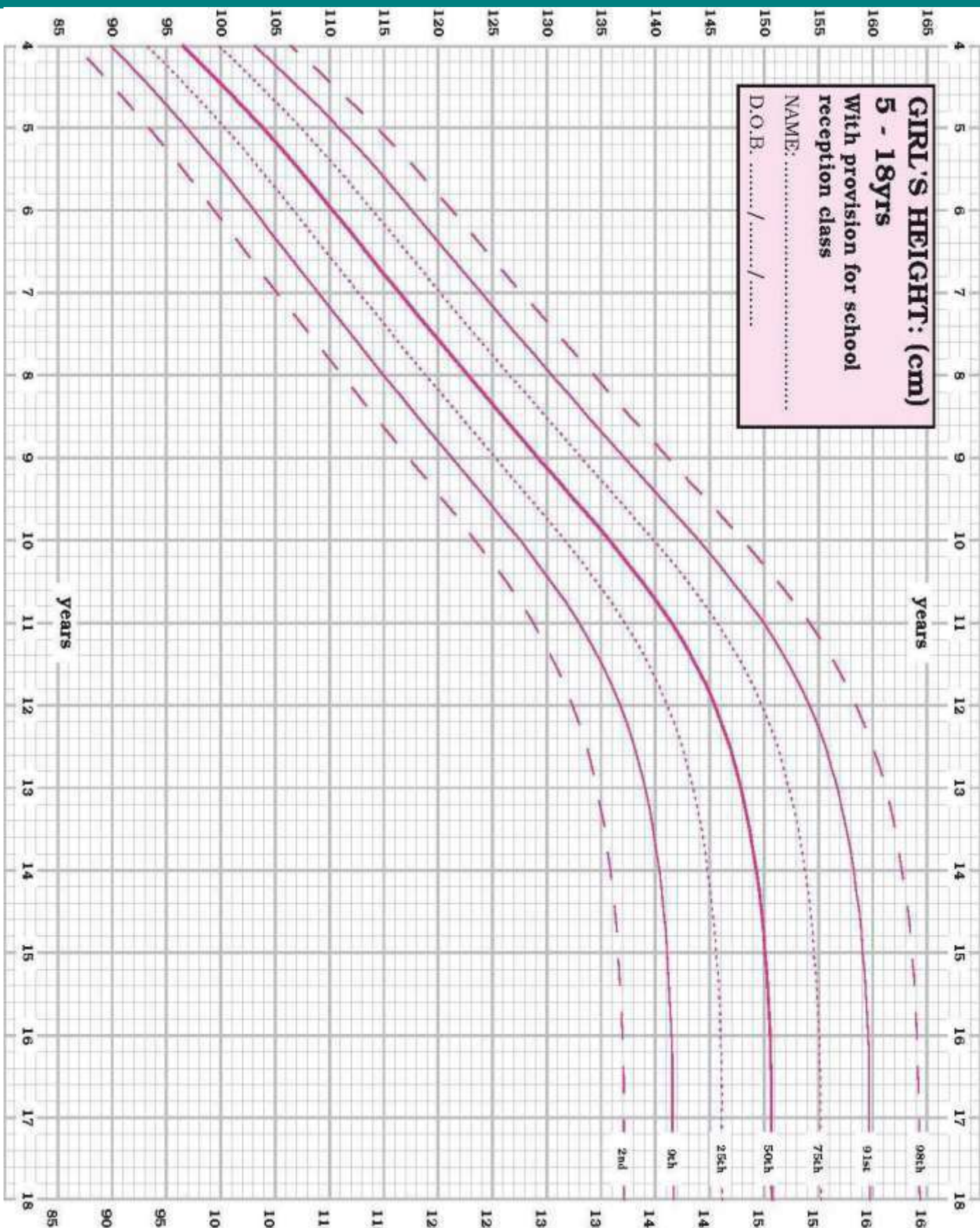


GIRLS
0-1
LENGTH

Williams Syndrome Clinical Management Guidelines

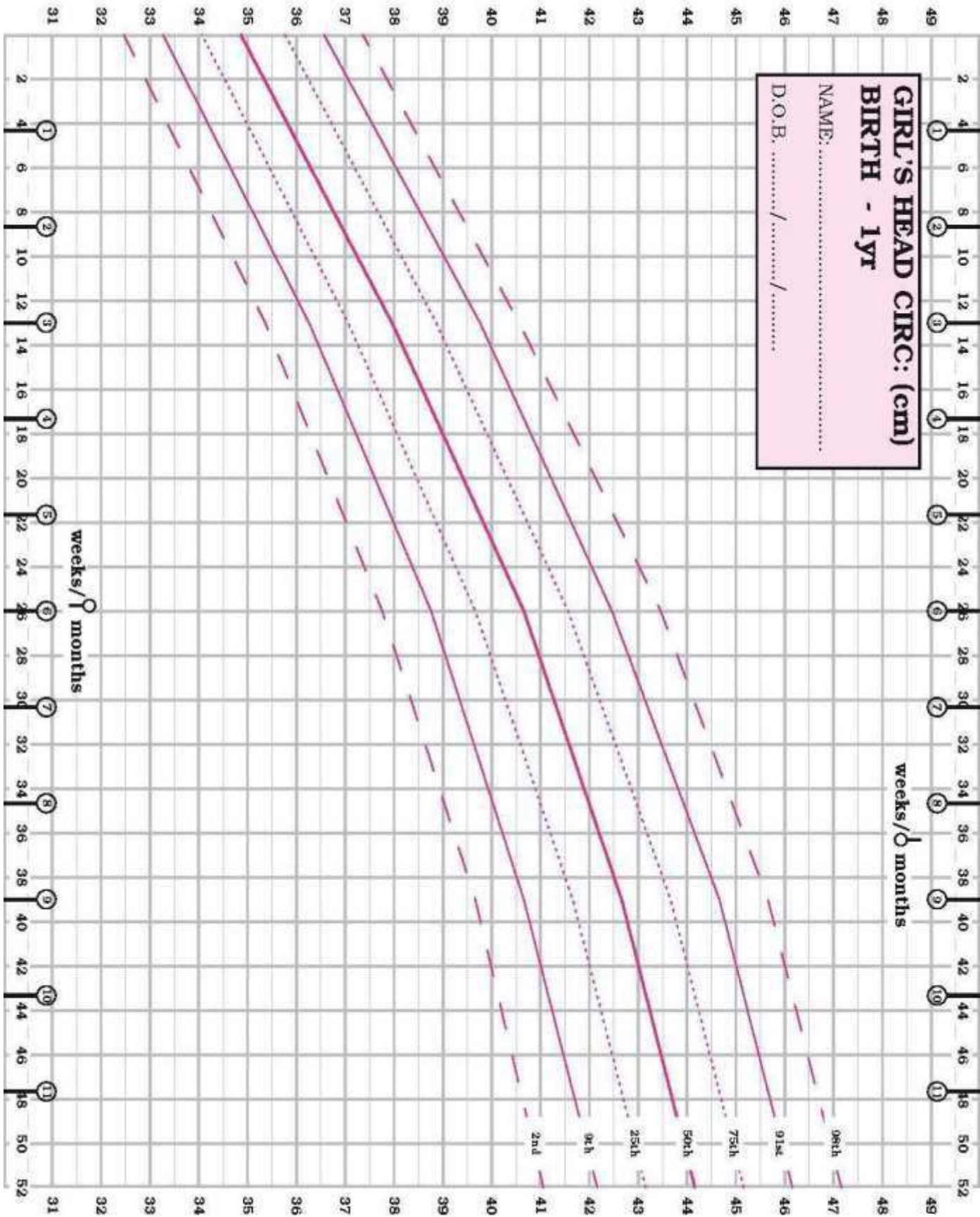


Williams Syndrome Clinical Management Guidelines

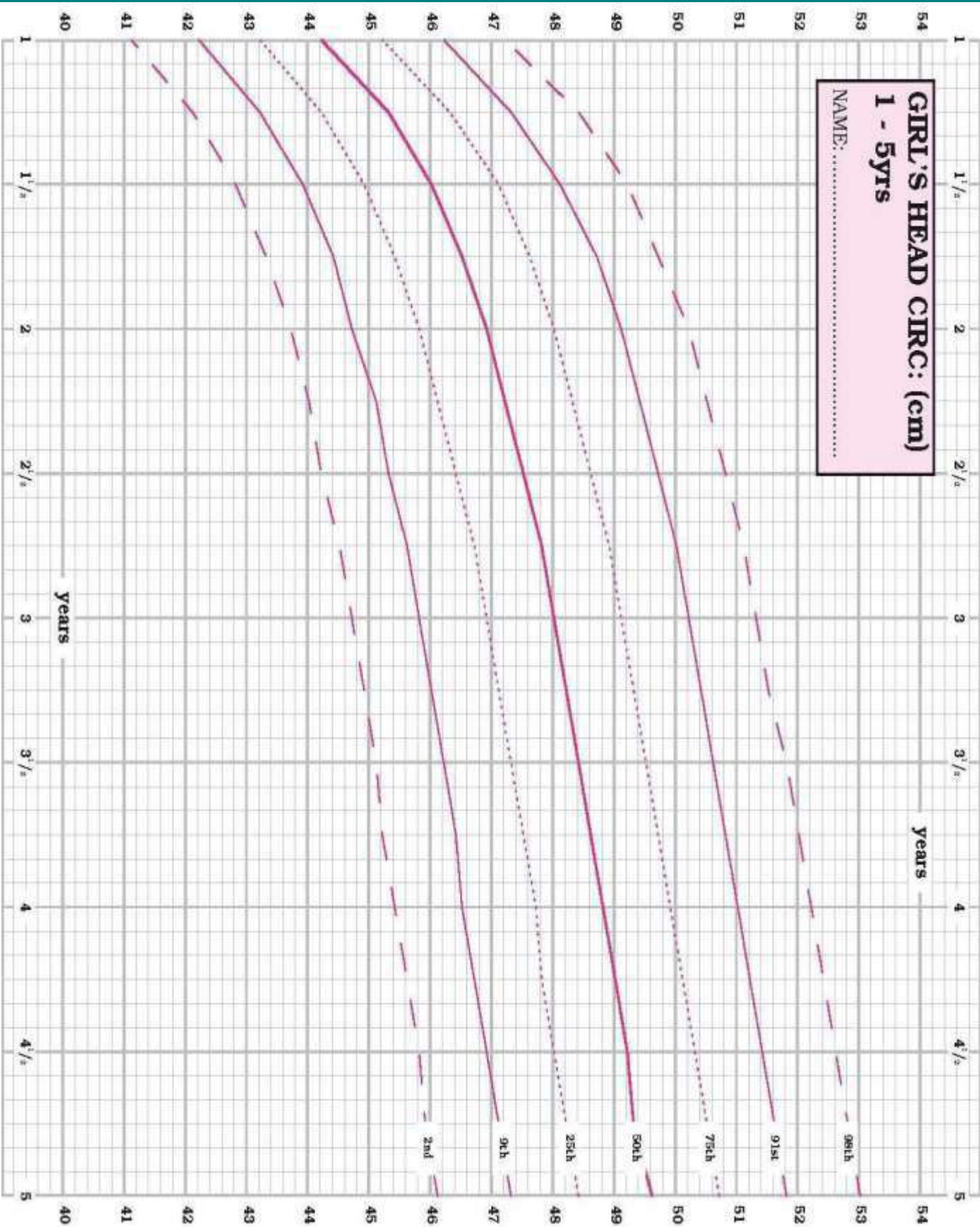


GIRLS
5-18
HEIGHT

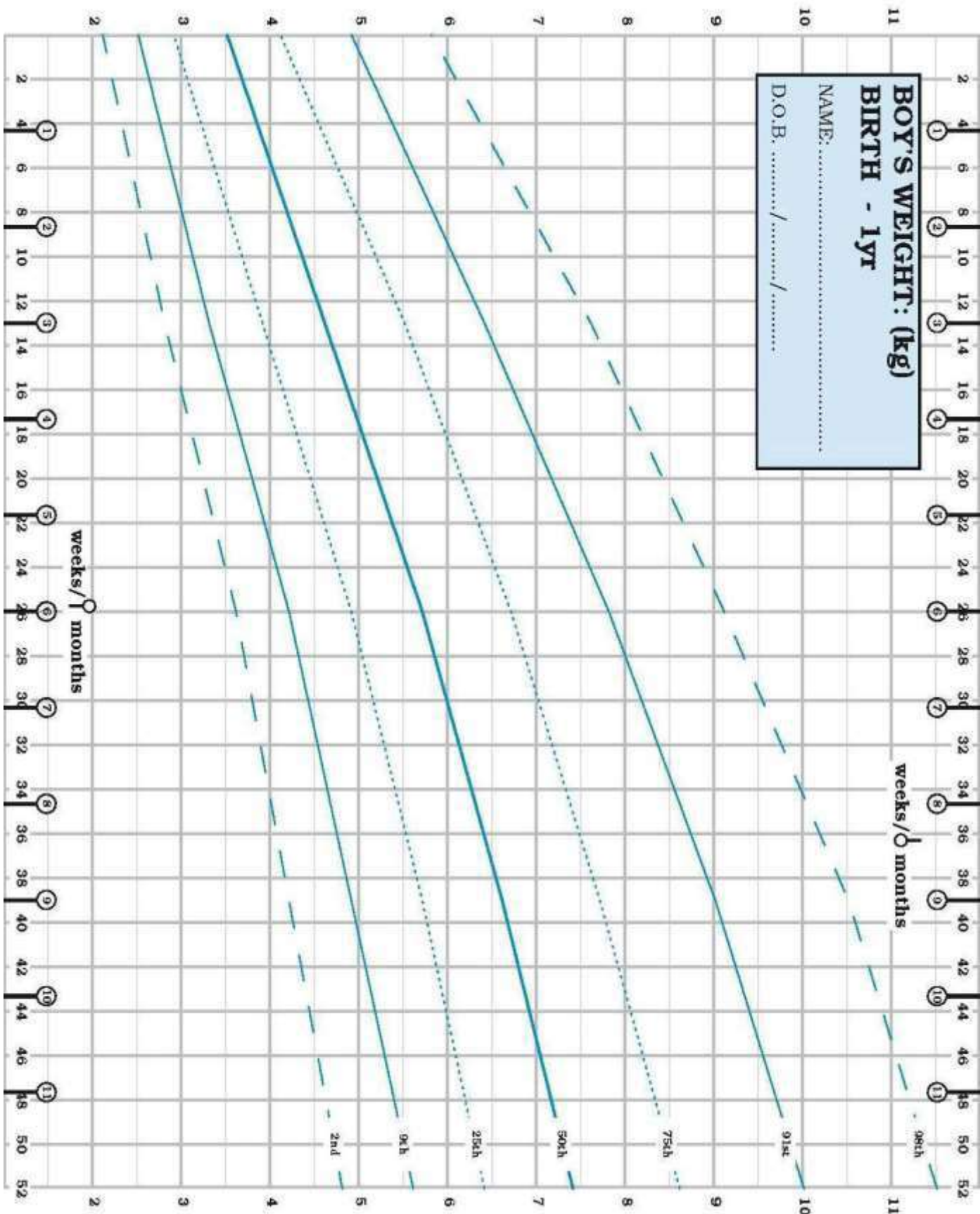
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Williams Syndrome Clinical Management Guidelines

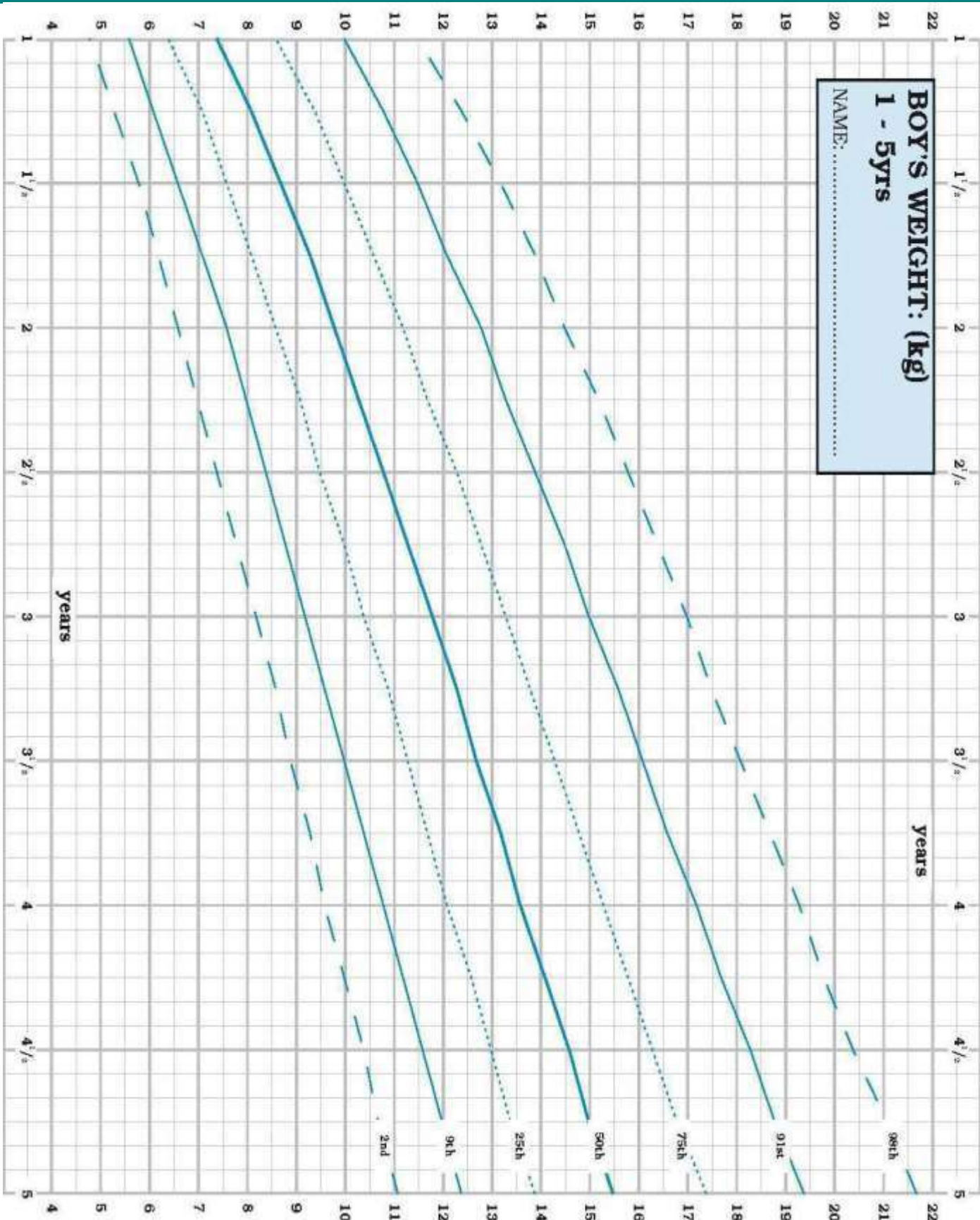


Williams Syndrome Clinical Management Guidelines

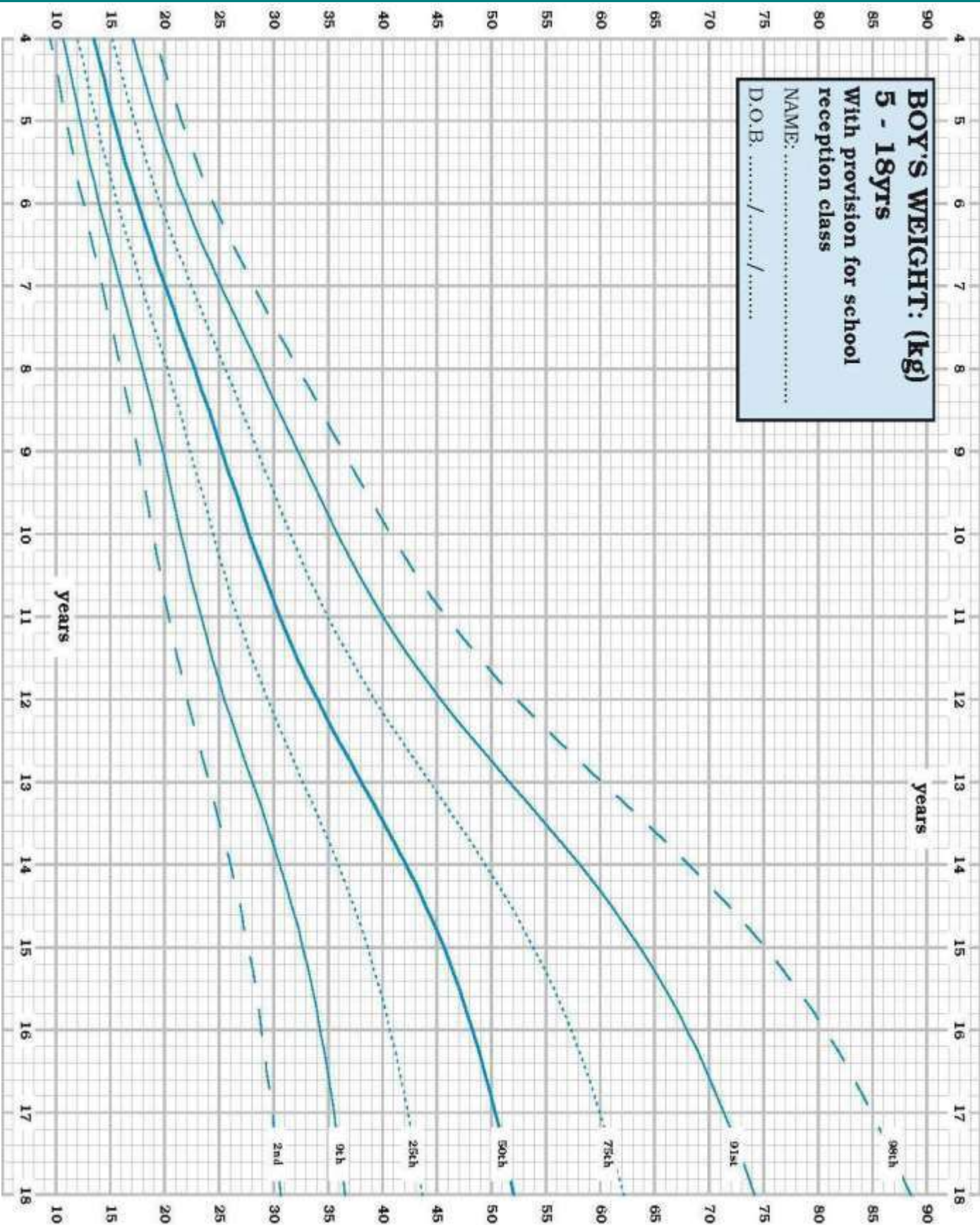


BOYS
0-1
WEIGHT

Williams Syndrome Clinical Management Guidelines

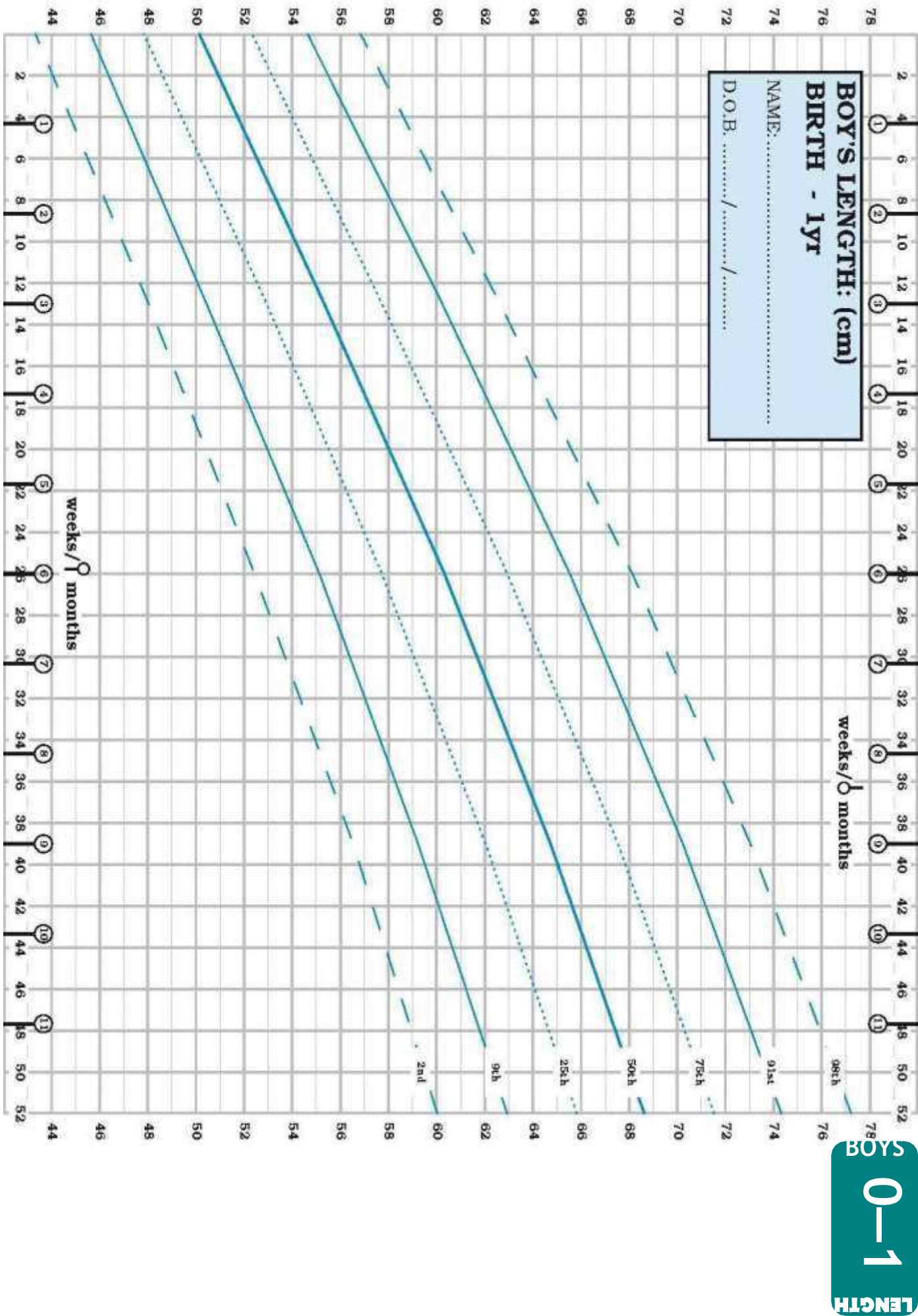


Williams Syndrome Clinical Management Guidelines

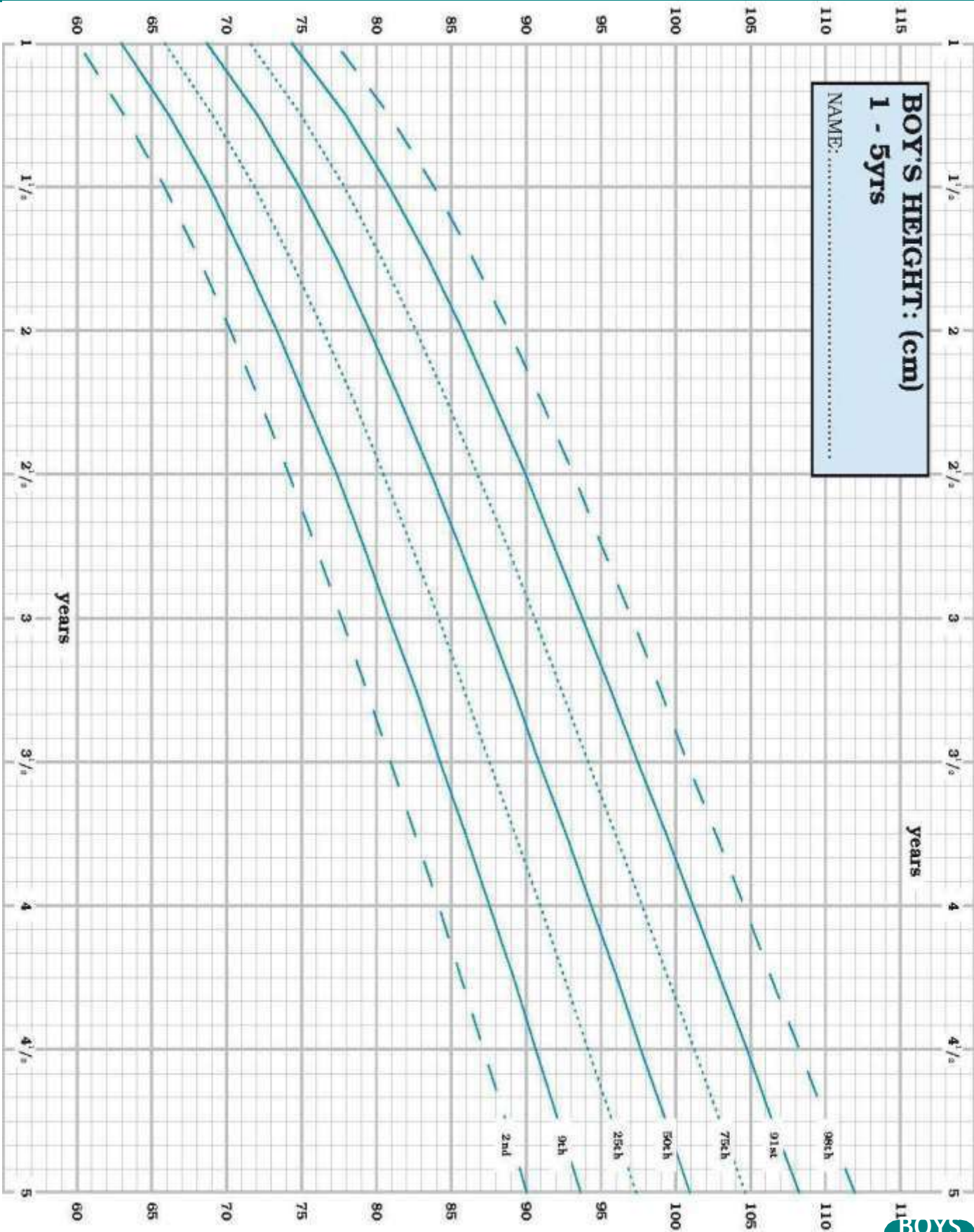


BOYS
5-18
WEIGHT

Williams Syndrome Clinical Management Guidelines

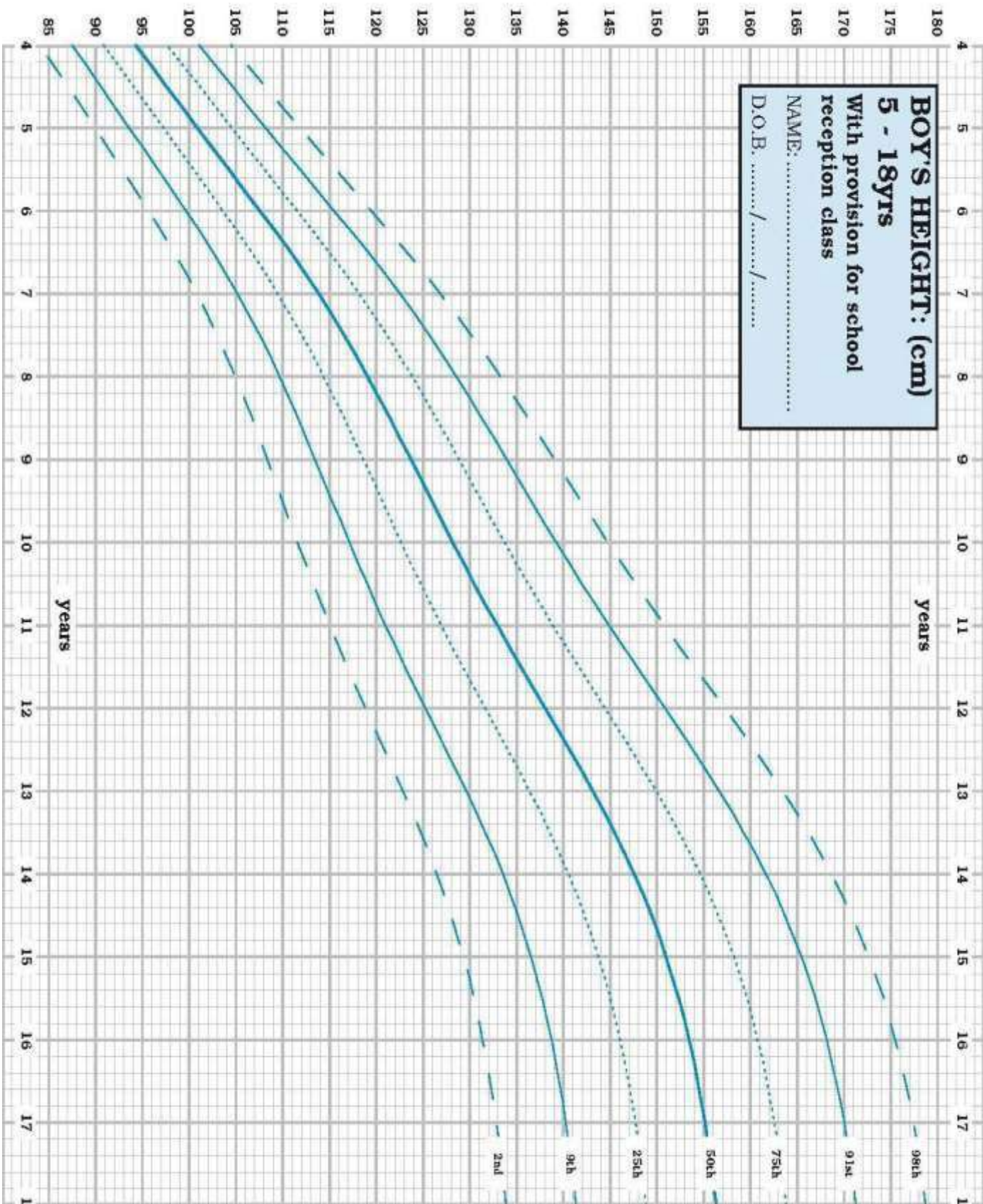


Williams Syndrome Clinical Management Guidelines



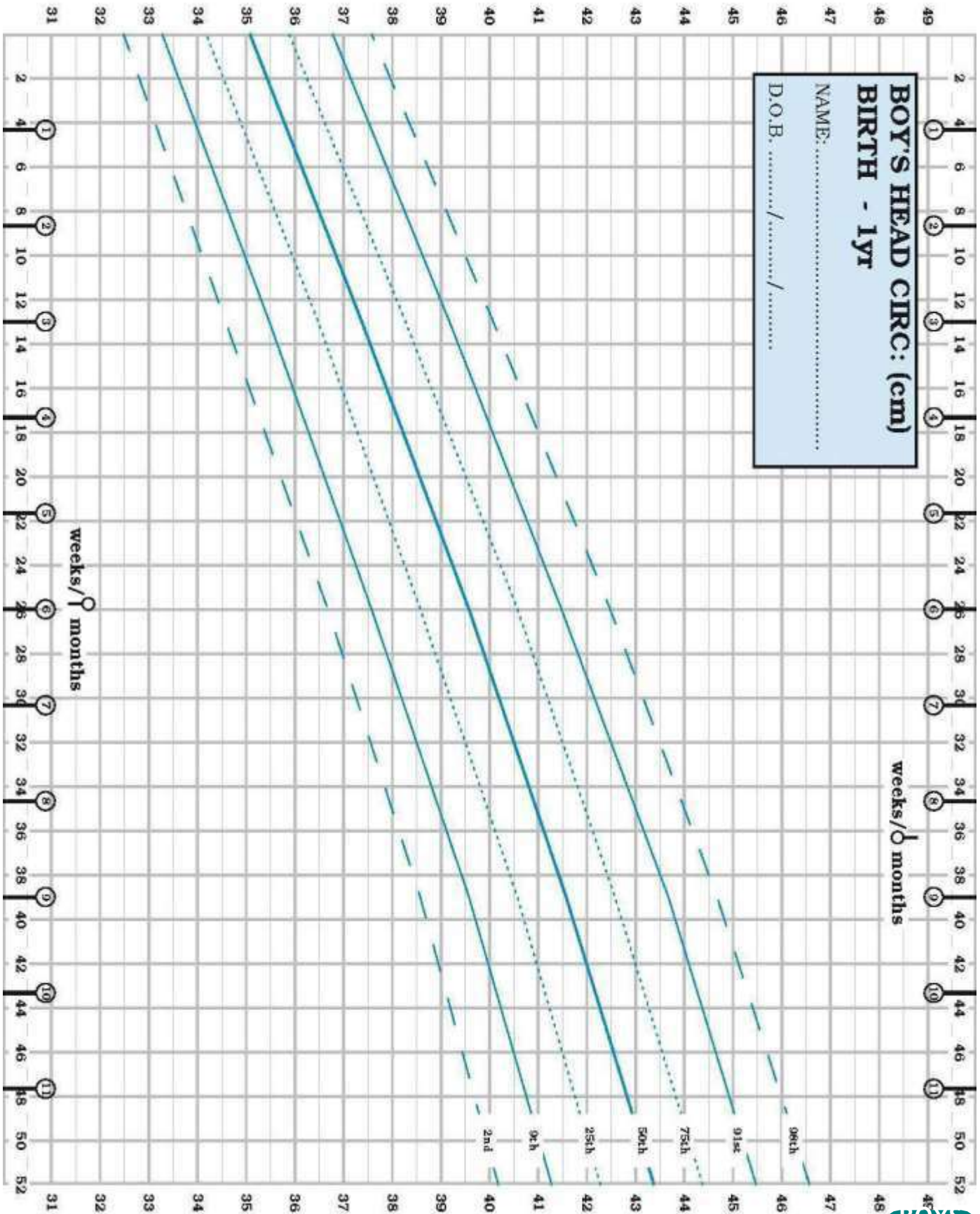
BOYS
1-5
HEIGHT

Williams Syndrome Clinical Management Guidelines



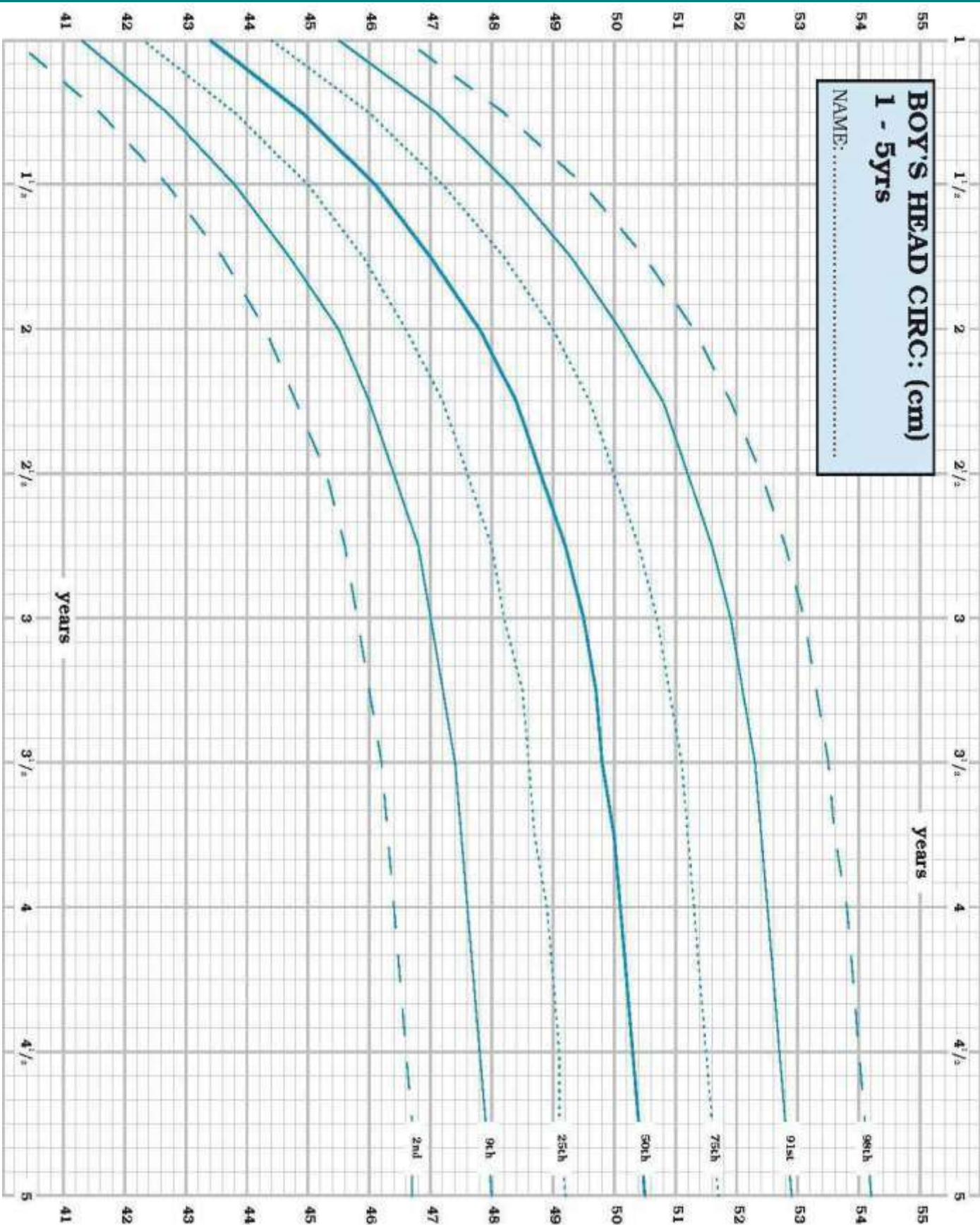
BOYS
5-18
HEIGHT

Williams Syndrome Clinical Management Guidelines



BOYS
0-1
OF

Williams Syndrome Clinical Management Guidelines



Bibliography

(papers selected for review by the Williams Syndrome Guideline Development Group, and considered in the formulation of management recommendations)

General papers & Guidelines

- American Academy of Pediatrics, Committee on Genetics (2001). "Health Care Supervision for Children With Williams Syndrome." *Pediatrics* 107 (5): 1192-1204.
- Cherniske, E. M., T. O. Carpenter, et al. (2004). "Multisystem study of 20 older adults with Williams syndrome." *Am J Med Genet A* 131(3): 255-64.
- Ferrero, G. B., E. Biamino, et al. (2007). "Presenting phenotype and clinical evaluation in a cohort of 22 Williams-Beuren syndrome patients." *Eur J Med Genet* 50(5):327-37.
- Greenberg, F. (1990). "Williams syndrome professional symposium." *American Journal of Medical Genetics* 37(S1): 85-88.
- Metcalfe k. (1999) Williams Syndrome: an update on clinical and molecular aspects. *Arch Dis Child* 81 (3): 198-200
- Pober, B. R. and C. A. Morris (2007). "Diagnosis and management of medical problems in adults with Williams-Beuren syndrome." *Am J Med Genet C Semin Med Genet* 145C(3):280-90.
- Pober, B. R. "Williams-Beuren Syndrome." *N Engl J Med* 362(3): 239-252.
- Protocol National de Diagnostic et de Soins (PNDS) Syndrome de Williams-Beuren; Centre de Reference Labellise pour les Anomalies du Developpement et les syndromes malformatifs de l'ouest (CLAD-Ouest) -Fevrier 2014
- Scottish Intercollegiate Guidelines Network (2008). "SIGN 50: A Guideline Developer's Handbook." <http://www.sign.ac.uk/pdf/sign50.pdf>
- Udwin, O. et al, (2007). "Williams Syndrome - Guidelines for Parents." UNPUBLISHED - from Williams Syndrome Foundation web-site: www.williams-syndrome.org.uk
- Udwin, O. et al (2007). "Williams Syndrome - Guidelines for Teachers." UNPUBLISHED - from Williams Syndrome Foundation web-site: www.williams-syndrome.org.uk
- Udwin, O. et al (2007). "Adults with Williams Syndrome Guidelines for Families and Professionals." UNPUBLISHED -from Williams Syndrome Foundation website: www.williams-syndrome.org.uk
- Udwin, O. et al. (2007). "Adults with Williams Syndrome Guidelines for Employers and Supervisors." UNPUBLISHED -from Williams Syndrome Foundation website: www.williams-syndrome.org.uk

Anaesthesia

- Burch, T. M., F. X. McGowan, Jr., et al. (2008). "Congenital Supravalvular Aortic Stenosis and Sudden Death Associated with Anesthesia: What's the Mystery?" *Anesth Analg* 107(6):1848-1854.
- Horowitz, P. E., S. Akhtar, et al. (2002). "Coronary artery disease and anesthesia-related death in children with Williams syndrome." *J Cardiothorac VascAnesth* 16(6):739-41.
- Kohase, H., R. Wakita, et al. (2007). "General anesthesia for dental treatment in a Williams syndrome patient with severe aortic and pulmonary valve stenosis: suspected episode of postoperative malignant hyperthermia." *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 104(4): e17-20.
- Matthews, A. J. and J. M. Vernon (1991). "Masseter spasm in Williams syndrome." *Anaesthesia* 46(8):706.
- Medley, J., P. Russo, et al. (2005). "Perioperative care of the patient with Williams syndrome." *Paediatr Anaesth* 15(3): 243-7.
- Patel, J. and M. J. Harrison (1991). "Williams syndrome: masseter spasm during anaesthesia." *Anaesthesia* 46(2):115-6.

Calcium metabolism

- Brooke, B. S., A. Bayes-Genis, et al. (2003). "New insights into elastin and vascular disease." *Trends Cardiovasc Med* 13(5):176-81.
- Cagle, A. P., S. G. Waguespack, et al. (2004). "Severe Infantile Hypercalcemia Associated With Williams Syndrome Successfully Treated With Intravenously Administered Pamidronate." *Pediatrics* 114(4):1091-1095.
- Mathias, R. S. (2000). "Rickets in an infant with Williams syndrome." *Pediatr Nephrol* 14(6):489-92.
- Metz, M.P. (2006). "Determining urinary calcium/creatinine cut-offs for the paediatric population using published data". *Ann Clin Biochem* 43:398-401.

Bibliography continued...

(papers selected for review by the Williams Syndrome Guideline Development Group, and considered in the formulation of management recommendations)

Calcium metabolism continued...

- Oliveri, B. et al. (2004). "Long-term control of hypercalcaemia in an infant with Williams-Beuren syndrome after a single infusion of biphosphonate (Pamidronate)." *Acta Paediatr* 93(7): 1002-3.
- Rodd, C. and Goodyer, P. (1999). "Hypercalcemia of the newborn: etiology, evaluation, and management." *Pediatr Nephrol* 13(6): 542-7.
- Sindhar S. et al (2016) Hypercalcaemia in patients with Williams Beuren Syndrome. *J Paediatrics* 178: 254 -60.
- Sforzini, C., D. Milani, et al. (2002). "Renal tract ultrasonography and calcium homeostasis in Williams-Beuren syndrome." *Pediatr Nephrol* 17(11): 899-902.
- Weber, K. T., R. U. Simpson, et al. (2008). "Vitamin D and calcium dyshomeostasis-associated heart failure." *Heart* 94(5): 540-541.

Cardiovascular

- Bajracharya P et al (2011) Mitral valve disease in Williams syndrome - Case report and review of the literature. *Echocardiography*28(8):156-9
- Bird, L. M., G. F. Billman, et al. (1996). "Sudden death in Williams syndrome: report of ten cases." *J Pediatr* 129(6):926-31.
- Brown, J. W, M. Ruzmetov et al. (2002). "Surgical repair of congenital supravalvular aortic stenosis in children." *Eur J Cardiothor Surg* 21(1): 50-6.
- Bruno, E., N. Rossi, et al. (2003). "Cardiovascular findings, and clinical course, in patients with Williams syndrome." *Cardiol Young* 13(6): 532-6.
- Casanelles M et al. (2003). "Portal hypertension in Williams syndrome: report of two patients." *Am J Med Genet A* 118A(4): 372-6.
- Collins, R. T. et al. (2008). "Abstract 5717: Cardiovascular Abnormalities and Outcomes in a Large Williams Syndrome Cohort." *Circulation* 118 (18_MeetingAbstracts): S_990-c-991.
- De Rubens Figuero, J. et al. (2008). "Cardiovascular spectrum in Williams-Beuren syndrome: the mexican experience in 40 patients." *Tex Heart Inst J* 35(3): 279-85.
- Eronen, M. et al. (2002). "Cardiovascular manifestations in 75 patients with Williams syndrome." *J Med Genet* 39(8): 554-8.
- Harikrishnan, S. et al. (2003). "Supravalvar aortic stenosis: clinical and hemodynamic profile, and surgical outcome." *Indian Heart J* 55(1):49-54.
- Hickey, E. J. et al. (2008). "Congenital Supravalvular Aortic Stenosis: Defining Surgical and Nonsurgical Outcomes." *Ann Thorac Surg* 86(6): 1919-1927.
- Ishibashi, N. et al. (2007). "Modified Myers and coronary artery bypass grafting using free internal thoracic artery graft for complicated supravalvular aortic stenosis." *J Card Surg* 22(1):56-7.
- Kaplan, P. et al. (1995). "Cerebral artery stenoses in Williams syndrome cause strokes in childhood." *J Pediatr* 126(6):943-5.
- Kim, Y. M., S. J. Yoo, et al. (1999). "Natural course of supravalvar aortic stenosis and peripheral pulmonary arterial stenosis in Williams' syndrome." *Cardiol Young* 9(1):37-41.
- Nakamoto, S. et al. (2003). "Williams syndrome associated with complete atrioventricular septal defect." *Heart* 89(5):e15.
- Park, J. H. et al. (2008). Demonstration of peripheral pulmonary stenosis and supravalvular aortic stenosis by different cardiac imaging modalities in a patient with Williams syndrome--usefulness of noninvasive imaging studies. *Int J Cardiol* 128(3):e95-7.
- Pober B. R. et al. (2008). Mechanisms and treatment of cardiovascular disease in Williams-Beuren syndrome. *J Clin Invest* 118(5):1606-15.
- Sadler, L. S. et al. (1998). Carotid ultrasound examination in Williams syndrome. *J Pediatr* 132(2):354-6.
- Scheiber, D. et al. (2006). Echocardiographic findings in patients with Williams-Beuren syndrome. *Wiener Klinische Wochenschrift* 118(17): 538-542.
- Wang, C. C. et al. (2007). Outcome of pulmonary and aortic stenosis in Williams-Beuren syndrome in an Asian cohort. *Acta Paediatr* 96(6):906-9.
- Wessel, A. et al. (1994). Three decades of follow-up of aortic and pulmonary vascular lesions in the Williams-Beuren syndrome. *Am J Med Genet* 52(3): 297-301.
- Wessel, A. et al. (2004). Risk of sudden death in the Williams-Beuren syndrome. *Am J Med Genet A* 127A(3):234-7.
- Youn, H. J. et al. (2002). Demonstration of supravalvar aortic stenosis by different cardiac imaging modalities in Williams syndrome. *Heart* 88(4):438.

Bibliography continued...

(papers selected for review by the Williams Syndrome Guideline Development Group, and considered in the formulation of management recommendations)

Cognition- intelligence, attention and education skills:

- Ansari D. et al (2003). What makes counting count? Verbal and visuo-spatial contributions to typical and atypical number development . J Exp Child Psychol 85:, 50 - 62.
- Breckenridge K. et al. (2013) Attention in Williams syndrome and Down's syndrome: Performance on the new early childhood attention battery. British Journal of Developmental Psychology 31(2):257-269
- Camp J.S. et al (2016) Cross-syndrome comparison of real-world executive functioning and problem solving using a new problem-solving questionnaire. Research in Developmental Disabilities 59;80-92
- Costanzo et al. (2013) Executive functions in intellectual disabilities: A comparison between Williams Syndrome and Down Syndrome. Res in Dev Disabilities 34(5): 1770-80
- Davies, M. et al. (1997). Independence and adaptive behavior in adults with Williams syndrome. American Journal of Medical Genetics 70(2): 188-195.
- Greer j. et al (2013) Attentional lapse and inhibition control in adults with Williams Syndrome. Research in developmental disabilities 34(11) 4170-4177.
- Howlin P. et al (1998). Cognitive functioning in adults with Williams syndrome. Journal of Child Psychology and Psychiatry 39: 183 - 89.
- Karmiloff-Smith (2012) Perspectives on the dynamic development of cognitive capacities: Insights from Williams syndrome. Current Opinion in Neurology 25(2):106-111
- Levy Y. et al (2003). Word reading and reading-related skills in adolescents with Williams syndrome . Journal of Child Psychology and Psychiatry 44: 576 -87.
- Libertus M.E. et al. (2014) Understanding the mapping between numerical approximation and number words: evidence from Williams syndrome and typical development. Science 17 (6):905-919
- Mervis C.B., Pitts C.H (2015) Children with Williams Syndrome: Developmental trajectories for intellectual abilities, vocabulary abilities and adaptive behaviour. Am J of Med Genetics 169(2):158-171
- Pitts C.H., Mervis C.B. (2016) Performance on the Kaufman Brief Intelligence Test-2 by Children With Williams Syndrome. Am J. Intel Dev. Disabil 121 (1): 33-47.
- Rhodes S.M. et al. (2011) The extent of working memory deficits associated with Williams syndrome: Exploration of verbal and spatial domains and executively controlled processes. Brain and Cognition 77(2) 208-214.
- Steele, A., Karmiloff-Smith, A., Cornish, K.M., & Scerif, G. (2012). The multiple sub-functions of attention: Differential developmental gateways to literacy and numeracy. Child Development, 83, 2028-41.
- Steele, A., Scerif, G., Cornish, K., & Karmiloff-Smith, A. (2013). Learning to read in Williams syndrome and Down syndrome: Syndrome-specific precursors and developmental trajectories. Journal of Child Psychology and Psychiatry, 54, 754-762.
- Varuzza C., et al. (2015) Writing abilities in intellectual disabilities: a comparison between Down and Williams syndrome. Res in Dev Disabil 37: 135-142.
- Vicari, S. (2004). "Memory development and intellectual disabilities." Acta Paediatr Suppl 93(445): 60-3; discussion 63-4.

Cognition-Spatial

- Atkinson J. et al (2001). Visual and visuo-spatial development in young Williams Syndrome children. Developmental Medicine & Child Neurology 43: 330-337.
- Atkinson, J. et al (2003). Neurobiological models of visuospatial cognition in children with Williams Syndrome: Measures of dorsal-stream and frontal function. Developmental Neuropsychology 23(1/2): 139-172.
- Atkinson, J et al (1997). A specific deficit of dorsal stream function in Williams Syndrome. NeuroReport 8:1919-1922.
- Atkinson J., Braddick O. (2011) From genes to brain development to phenotypic behaviour. "Dorsal-stream vulnerability" in relation to spatial cognition, attention, and planning of actions in Williams syndrome (WS) and other developmental disorders Publisher Elsevier.

Bibliography continued...

(papers selected for review by the Williams Syndrome Guideline Development Group, and considered in the formulation of management recommendations)

Cognition - Spatial continued...

- Bernardino I. et al (2013) Egocentric and allocentric spatial representations in Williams syndrome. *Journal of the International Neuropsychological Society* 19(1):54-62
- Broadbent H.J. et al (2014) Egocentric and allocentric navigation strategies in Williams syndrome and typical development. *Developmental science* 17(6):920-934
- Broadbent H.J et al (2015) Sequential egocentric navigation and reliance on landmarks in Williams syndrome and typical development. *Frontiers in Psychology* 6:216
- Carretti B. et al (2015) Exploring spatial working memory performance in individuals with Williams syndrome: the effect of presentation format and configuration. *Research in developmental disabilities* 37: 37-44
- Farran E.K. et al (2012) How useful are landmarks when learning a route in a virtual environment? Evidence from typical development and Williams syndrome. *Journal of Experimental Child Psychology* 111(4): 571-586
- Farran E.K. et al (2015) Route knowledge and configural knowledge in typical and atypical development: A comparison of sparse and rich environments. *Journal of Neurodevelopmental Disorders* 7(1)
- Ferrara K., Landau B. (2015) Geometric and featural systems, separable and combined: Evidence from reorientation in people with Williams syndrome. *Cognition* 144:123-133
- Hudson K.D., Farran E.K (2013) Facilitating complex shape drawing in Williams syndrome and typical development. *Research in Developmental Disabilities* 34(7):2133-2142
- Hudson K.D., Farran E.K. (2014) Perceiving and acting in depth in Williams syndrome and typical development. *Research in Developmental Disabilities* 35(8):1850-1855
- Nardini M et al (2008). Developmental trajectories for spatial frames of reference in Williams syndrome. *Developmental Science* 11(4):583-595.

Cognition - Visuo-motor integration & co-ordination:

- Barozzi S. et al (2013) Balance function in patients with Williams syndrome. *Gait and Posture* 38(2) 221-5
- Cowie D. et al (2012) Visually guided step descent in children with Williams syndrome *Developmental Science* 15(1):74-86
- Fu T.J. et al (2015) The Association of Intelligence, Visual-Motor Functioning, and Personality Characteristics With Adaptive Behavior in Individuals With Williams Syndrome. *American Journal on Intellectual and Developmental Disabilities* 120(4):273-288
- Hocking D.R. et al (2014) Gait profiles as indicators of domain-specific impairments in executive control across neurodevelopmental disorders. *Research in Developmental Disabilities* 35(1):203-214
- Hocking D.R. et al (2011) A kinematic analysis of visually-guided movement in Williams syndrome. *Journal of the Neurological Sciences* 301(1):51-58
- Hocking, D R et al (2011) Gait adaptation during obstacle crossing reveals impairments in the visual control of locomotion in Williams syndrome. *Neuroscience* 197:320-329
- Hocking D.R. et al (2013) The interplay between executive control and motor functioning in Williams syndrome. *Developmental Science* 16(3): 428-442
- King, J. et al (1997). Dissociation of visually guided action from visual judgement in Williams Syndrome children. *Perception* 26(6):762.

Cognition-language

- D'Souza D. et al (2015) Concurrent relations between face scanning and language: A cross-syndrome infant study. *PLoS ONE*: 10(10)
- Krishnan S. et al (2015). Williams syndrome: A surprising deficit in oromotor praxis in a population with proficient language production. *Neuropsychologia* 67:82-90

Bibliography continued...

(papers selected for review by the Williams Syndrome Guideline Development Group, and considered in the formulation of management recommendations)

Cognition- language continued...

- Luyster R.J.et al (2011) Identifying early-risk markers and developmental trajectories for language impairment in neurodevelopmental disorders. *Developmental Disabilities Research Reviews* 17(2):151-159
- Purser H.R. et al Definitions versus categorization: assessing the development of lexico-semantic knowledge in Williams syndrome. *International Journal of Language & Communication Disorders / Royal College of Speech & Language Therapists* 46(3):361-373
- Santos A., Deruelle C. (2008). Verbal Peaks and Visual Valleys in Theory of Mind Ability in Williams Syndrome. *J Autism Dev Disord*

Cognition - social & behaviour

- Barak B., Feng G (2016) Neurobiology of social behaviour abnormalities in autism and Williams syndrome. *Nature Neuroscience* 19 (6):647-655
- Dimitriou D. et al (2015) Atypical development of configural face recognition in children with autism, Down syndrome and Williams syndrome. *Journal of Intellectual Disability Research* 59(5):422-438
- Isaac L., Lincoln A. (2011) Featural versus configural face processing in a rare genetic disorder: Williams Syndrome. *Intellectual Disability Research* 55(11):1034-42
- Jarvinen A.et al (2013) The social phenotype of Williams syndrome. *Current Opinion in Neurobiology* 23(3):414-422
- Klein-Tasman B.P. et al (2011) Honing in on the social phenotype in Williams syndrome using multiple measures and multiple raters. *Journal of Autism and Developmental Disorders* 41(3):341-351
- Klein-Tasman B.P. et al (2015) Parent and teacher perspectives about problem behaviour in children with Williams syndrome. *Am J Intellectual Developmental Disabilities* 120(1):72-86
- Lough E. et al (2015) Violations of Personal Space in Young People with Autism Spectrum Disorders and Williams Syndrome: Insights from the Social Responsiveness Scale. *Journal of Autism and Developmental Disorders* 45(12):4101-4108
- Martinez-Castilla P. et al (2015) Facial emotion recognition in Williams syndrome and Down syndrome: A matching and developmental study. *Child Neuropsychology* 21(5):668-692
- Ng R. et al (2014) Toward a deeper characterization of the social phenotype of Williams syndrome: The association between personality and social drive. *Research in Developmental Disabilities* 35(8):1838-1849
- Ng R. et al (2014) Characterising associations and dissociations between anxiety, social and cognitive phenotypes of Williams Syndrome. *Research in Developmental Disabilities* 35(10):2403-15
- Riby D.M. et al (2014) The interplay between anxiety and social functioning in Williams syndrome. *Journal of Autism and Developmental Disorders* 44(5):1220-1229
- Riby D.M. et al (2014) Stranger danger awareness in Williams syndrome. *Journal of Intellectual Disability Research* 58(6):572-582
- Rice L.J. et al (2015) The developmental trajectory of disruptive behaviour in Down syndrome, fragile X syndrome, Prader-Willi syndrome and Williams syndrome. *American Journal of Medical Genetics* 169(2):182-187
- Richards C. et al (2015) Prevalence of autism spectrum disorder phenomenology in genetic disorders: A systematic review and meta-analysis. *The Lancet Psychiatry* 2(10):909-916

Dental

- Axelsson, S. et al. (2003). "Dental characteristics in Williams syndrome: a clinical and radiographic evaluation." *Acta Odontol Scand* 61(3): 129-36.
- Axelsson, S. (2005). "Variability of the cranial and dental phenotype in Williams syndrome." *Swed Dent J Suppl*(170): 3-67.
- Fearn, J. "Dental Advice for Children with Williams Syndrome." UNPUBLISHED - from Williams Syndrome Foundation website:
www.williams-syndrome.org.uk

Bibliography continued...

(papers selected for review by the Williams Syndrome Guideline Development Group, and considered in the formulation of management recommendations)

Dental continued...

- Habersack K. et al. (2007). Orthodontic orthognathic surgical treatment of a subject with Williams Beuren syndrome a follow-up from 8 to 25 years of age. *Eur J Orthod* 29(4):332-7.
- Hertzberg J. et al. (1994). Williams syndrome--oral presentation of 45 cases. *Pediatr Dent* 16(4): 262-7.
- Joseph C. et al. (2008). Periodontal conditions in Williams Beuren syndrome: a series of 8 cases. *Eur Arch Paediatr Dent* 9(3):142-7.
- Kashyap A. S. et al. (2000). Dental anomalies in Williams syndrome. *Postgrad Med J* 76(901):712.
- Moskovitz M. et al. (2005). Medical considerations in dental treatment of children with Williams syndrome. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 99(5):573-80.
- Tarjan I. et al. (2003). Facial and dental appearance of Williams syndrome. *Postgrad Med J* 79(930): 241.
- www.gov.uk/publications/delivering-better-oral-health Delivering better oral health; an evidence based toolkit for prevention

Endocrine and Thyroid

- Bini, R. and I. Pela (2004). "New case of thyroid dysgenesis and clinical signs of hypothyroidism in Williams syndrome." *Am J Med Genet A* 127A(2): 83-5.
- Cambiaso, P. et al. (2007). "Thyroid morphology and subclinical hypothyroidism in children and adolescents with Williams syndrome." *J Pediatr* 150(1): 62-5.
- Selicorni A. et al. (2006). Thyroid anomalies in Williams syndrome: investigation of 95 patients. *Am J Med Genet A* 140(10): 1098-101.
- Stagi S. et al. (2008). Thyroid Hypoplasia as a Cause of Congenital Hypothyroidism in Williams Syndrome. *Horm Res* 70(5): 316-318.

Gastrointestinal & Feeding

- Giannotti, A., G. Tiberio, et al. (2001). "Coeliac disease in Williams syndrome." *J Med Genet* 38(11): 767-8.
- Ignacio RC et al. (2012) Diverticulitis in a child with Williams syndrome: A case report and review of the literature. *J Paed Surgery* 47(9):E33-5
- O'Reilly M. F., Lancioni G.E. (2001). Treating food refusal in a child with Williams syndrome using the parent as therapist in the home setting. *J Intellect Disabil Res* 45(1):41-6.
- Partsch CJ et al. (2005). Sigmoid diverticulitis in patients with Williams-Beuren Syndrome. Relatively high prevalence and complication rates in young adults with the syndrome. *Am J Med genet* 137A:52-4.
- Stagi S et al. (2010). Incidence of diverticular disease and complicated diverticular disease in young patients with Williams Syndrome. *Paed Surgery Int* 26:943-4.

Growth, Puberty and Sexual Health

- Cherniske E. M. et al. (1999). Early puberty in Williams syndrome. *Clin Dysmorphol* 8(2):117-21.
- Douchi T. et al. (1999). Precocious puberty in a Williams syndrome patient. *Obstet Gynecol* 94(5): 860.
- Kaplan A. S. et al. (1998). Body composition, energy expenditure, and energy intake in patients with Williams syndrome. *J Pediatr* 132(2): 223-7.
- Kotzot D. et al. (1995). Phenotype of the Williams-Beuren syndrome associated with hemizygosity at the elastin locus. *Eur J Pediatr* 154(6):477-82.
- Kuijpers G. M. et al. (1999). Growth hormone treatment in a child with Williams-Beuren syndrome: a case report. *Eur J Pediatr* 158(6): 451-4.
- Martin N. D. T. et al. (2007). New height, weight and head circumference charts for British children with Williams syndrome. *Arch Dis Child* 92(7):598-601.
- Nicholson W. R., Hockey K.A. (1993). Williams syndrome: a clinical study of children and adults. *J Paediatr Child Health* 29(6):468-72.
- Pankau R. et al. (1994). Natural history of body mass index in Williams-Beuren syndrome. *Am J Med Genet* 52(1): 51-4.
- Pankau R. et al. (1994). Head circumference of children with Williams-Beuren syndrome. *Am J Med Genet* 52(3): 285-90.

Bibliography continued...

(papers selected for review by the Williams Syndrome Guideline Development Group, and considered in the formulation of management recommendations)

Growth, Puberty & Sexual Health continued...

- Partsch C. J. et al. (1994). Hormonal regulation in children and adults with Williams-Beuren syndrome. *Am J Med Genet* 51(3): 251-7.
- Partsch C. J. et al. (1999). Longitudinal evaluation of growth, puberty, and bone maturation in children with Williams syndrome. *J Pediatr* 134(1):82-9.
- Partsch C. J. et al. (2002). Central precocious puberty in girls with Williams syndrome. *J Pediatr* 141(3): 441-4.
- Scothorn D. J., Butler M.G. (1997). How common is precocious puberty in patients with Williams syndrome? *Clin Dysmorphol* 6(1): 91-3.
- Utine G. E. et al. (2006). Central precocious puberty in a girl with Williams syndrome: the result of treatment with GnRH analogue. *Eur J Med Genet* 49(1):79-82.
- Yau E. K. et al. (2004). Williams-Beuren syndrome in the Hong Kong Chinese population: retrospective study. *Hong Kong Med J* 10(1):22-7.

Mental Health

- Ashworth A. et al (2013). Cross syndrome comparison of sleep problems in children with Down syndrome and Williams syndrome. *Research in developmental disabilities*, 34(5), 1572-1580.
- Davies M. et al. (1998). Adults with Williams syndrome. Preliminary study of social, emotional and behavioural difficulties. *Br J Psychiatry* 172:273-6
- Dykens E. M. (2000). Psychopathology in children with intellectual disability. *J Child Psychol Psychiatry* 41(4): 407-17.
- Dykens E. M. (2003). Anxiety, fears, and phobias in persons with Williams syndrome. *Dev Neuropsychol* 23(1-2): 291-316.
- Dykens E. M., Hodapp, R.M (1997). Treatment Issues in Genetic Mental Retardation Syndromes. *Professional Psychology: Research and Practice* 28(3): 263-270.
- Einfeld S. L. et al. (1997). Behavioral and emotional disturbance in individuals with Williams syndrome. *Am J Ment Retard* 102(1):45-53.
- Green T. et al (2012). Phenotypic psychiatric characterization of children with Williams syndrome and response of those with ADHD to methylphenidate treatment. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 159(1), 13-20.
- Hahn L. J. et al (2014). Adaptive behavior and problem behavior in young children with Williams syndrome. *American journal on intellectual and developmental disabilities*, 119(1), 49-63.
- Hocking D. R. et al (2015). Characterising the Profile of Everyday Executive Functioning and Relation to IQ in Adults with Williams Syndrome: Is the BRIEF Adult Version a Valid Rating Scale?. *PloS one*, 10(9), e0137628.
- Janes E. et al (2014). Exploring the prevalence and phenomenology of repetitive behaviours and abnormal sensory processing in children with Williams Syndrome. *Journal of Intellectual Disability Research*, 58(8), 746-757.
- Järvinen A. et al (2015). Autonomic response to approachability characteristics, approach behavior, and social functioning in Williams syndrome. *Neuropsychologia*, 78, 159-170.
- Leyfer O. T. et al. (2006). Prevalence of psychiatric disorders in 4 to 16-year-olds with Williams syndrome. *Am J Med Genet B Neuropsychiatr Genet* 141B(6):615-22.
- Martens M. A. (2012). Parent report of antidepressant, anxiolytic, and antipsychotic medication use in individuals with Williams syndrome: Effectiveness and adverse effects. *Research in developmental disabilities*, 33(6), 2106-2121.
- Martens M. A. (2013). Caregiver survey of pharmacotherapy to treat attention deficit/hyperactivity disorder in individuals with Williams syndrome. *Research in developmental disabilities*, 34(5), 1700-1709.
- McGrath L. M. (2016). Attention Bias to Emotional Faces Varies by IQ and Anxiety in Williams Syndrome. *Journal of autism and developmental disorders*, 46(6), 2174-2185.
- Mervis C. B., John, A. E. (2010, May). Cognitive and behavioral characteristics of children with Williams syndrome: implications for intervention approaches. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics* 154(2): 229-248.
- Miodrag N. et al (2013). A pilot study of a mindfulness intervention for individuals with Williams syndrome: Physiological outcomes. *Mindfulness*, 4(2), 137-147.

Bibliography continued...

(papers selected for review by the Williams Syndrome Guideline Development Group, and considered in the formulation of management recommendations)

Mental health continued.....

- Royston R. et al (2016). Anxiety Disorders in Williams Syndrome Contrasted with Intellectual Disability and the General Population: A Systematic Review and Meta-Analysis. *Journal of Autism and Developmental Disorders*, 1-13.
- Stinton C. et al. (2008). Physical and mental health of adults with Williams syndrome. *J Intellect Disabil Res* 52(10):813.
- Zarchi O. et al (2014). A comparative study of the neuropsychiatric and neurocognitive phenotype in two microdeletion syndromes: Velocardiofacial (22q11.2 deletion) and Williams (7q11.23 deletion) syndromes. *European Psychiatry*, 29(4), 203-210.

Neurology

- Mercuri, E. et al (1997). Chiari I malformation in asymptomatic young children with Williams Syndrome: Clinical and MRI study. *Europ. J. Paediatric Neurol.* 5/6:177-181.
- Pober B.R., Foliano J.J. (1995) Association of Chiari I malformation and Williams syndrome. *Pediatric Neurology* 1995; 12: 84-8

Orthopaedic

- Cohen D. B., Quigley M.R. (2006). Thoracolumbar syrinx in association with Williams syndrome. *Pediatrics* 118(2): e522-5.
- Franceschini P. et al. (1996). The Williams syndrome: an Italian collaborative study. *Minerva Pediatr* 48(10):421-8.
- Kaplan, P. et al. (1989). Contractures in Patients With Williams Syndrome. *Pediatrics* 84(5): 895-899.
- Nicholson W. R., Hockey K.A. (1993). Williams syndrome: a clinical study of children and adults. *J Paediatr Child Health* 29(6):468-72.
- Osebold, W. R., King H.A. (1994). Kyphoscoliosis in Williams Syndrome. *Spine* 19(3):367-

71. Renal & Hypertension

- Adams GN et al. (2012) The Williams-Beuren Syndrome - A window into genetic variants leading to the development of cardiovascular disease. *PLoSGenet* 8(2):e1002479
- Aggoun Y. et al. (2000). Mechanical properties of the common carotid artery in Williams syndrome. *Heart* 84(3): 290-3.
- Amenta S. et al. (2005). Clinical manifestations and molecular investigation of 50 patients with Williams syndrome in the Greek population. *Pediatr Res* 57(6):789-95.
- Bastianon V. (1996). Pseudohypertension and Williams syndrome. *Pediatr Cardiol* 17(2):132.
- Bedeschi MF et al. (2011). Clinical follow up of young adults affected by Williams syndrome: Experience of 45 Italian patients. *Am J Med Genet* 155:353-9.
- Bouchireb K et al. (2010). Clinical features and management of arterial hypertension in children with Williams-Beuren syndrome. 25:434-8.
- Broder K. et al. (1999). Elevated ambulatory blood pressure in 20 subjects with Williams syndrome. *Am J Med Genet* 83(5): 356-60.
- Courtel et al. (1998). Percutaneous transluminal angioplasty in children. *Pediatr Radiol* 28:59-66
- De Ferrari M. E. et al. (1997). Type IV renal tubular acidosis and uric acid nephrolithiasis in William's syndrome--an unusual mode of renal involvement." *Nephrol Dial Transplant* 12(7):1484-6.
- Del Campo M. et al. (2006). Hemizygosity at the NCF1 gene in patients with Williams-Beuren syndrome decreases their risk of hypertension." *Am J Hum Genet* 78(4):533-42.
- Ergul Y et al. (2012). Cardiovascular abnormalities in Williams syndrome: 20 years' experience in Istanbul. *Acta Cardiologica* 67(6)649-55
- Eronen M et al. (2002). Cardiovascular manifestations in 75 patients with Williams Syndrome. *J Med Genet* 39:554-55.
- Giordano U. et al. (2001). Exercise testing and 24-hour ambulatory blood pressure monitoring in children with Williams syndrome. *Pediatr Cardiol* 22(6): 509-11.
- Ichinose M. et al. (1996). Williams syndrome associated with chronic renal failure and various endocrinological abnormalities. *Intern Med* 35(6): 482-8.

Bibliography continued...

(papers selected for review by the Williams Syndrome Guideline Development Group, and considered in the formulation of management recommendations)

Renal & hypertension continued....

- Ingelfinger JR et al. (1991). Spectrum of renal anomalies in patients with Williams syndrome. *J Paediatr* 119:771-3.
- Kozel BA et al. (2014). Williams syndrome predisposes to vascular stiffness modified by antihypertensive use and copy number changes in NCF1. *Hypertension* 63:74-9.
- Lacolley P. et al. (2002). Disruption of the elastin gene in adult Williams syndrome is accompanied by a paradoxical reduction in arterial stiffness. *Clin Sci (Lond)* 103(1):21-9.
- Lopez-Rangel E et al. (1992). Williams syndrome in adults. *Am J Med genet* 44:720-2
- Lurbe E et al. (2016) 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescent. *J Hypertens* 34(10):1887-920.
- Morris CA et al. (1988). Natural history of Williams syndrome. Physical characteristics. *J Paediatr* 113:318-26.
- Narasimhan C. et al. (1993). Pseudohypertension in a child with Williams syndrome. *Pediatr Cardiol* 14(2): 124-6.
- Panayiotopoulos Y. P. et al. (1996). Mid-aortic syndrome presenting in childhood. *Br J Surg* 83(2): 235-40.
- Pankau R. et al. (1996). Incidence and spectrum of renal abnormalities in Williams-Beuren syndrome. *Am J Med Genet* 63(1): 301-4.
- Pober B. R. et al. (1993). Renal findings in 40 individuals with Williams syndrome. *Am J Med Genet* 46(3):271-4.
- Radford D. J., Pohlner P.G. (2000). The middle aortic syndrome: an important feature of Williams syndrome. *Cardiol Young* 10(6): 597-602.
- Rose C. et al. (2001). Anomalies of the abdominal aorta in Williams-Beuren syndrome--another cause of arterial hypertension. *Eur J Pediatr* 160(11): 655-8.
- Roux n et al. (2012) A rare case of visceral arterial stenosis in Williams-Beuren syndrome. *Ann Vasc Surg* 26(4):573.
- Salaymeh, K. J., Banerjee A. (2001). Evaluation of arterial stiffness in children with Williams syndrome: Does it play a role in evolving hypertension? *Am Heart J* 142(3):549-55.
- Sammour Z. M. et al. (2006). Voiding dysfunction and the Williams-Beuren syndrome: a clinical and urodynamic investigation. *J Urol* 175(4):1472-6.
- Schulman S. L. et al. (1996). Increased prevalence of urinary symptoms and voiding dysfunction in Williams syndrome. *J Pediatr* 129(3): 466-9.
- Sforzini C. et al. (2002). Renal tract ultrasonography and calcium homeostasis in Williams-Beuren syndrome. *Pediatr Nephrol* 17(11): 899-902.
- Sugayama S. M. et al. (2004). Renal and urinary findings in 20 patients with Williams-Beuren syndrome diagnosed by fluorescence in situ hybridization (FISH). *Rev Hosp Clin Fac Med Sao Paulo* 59(5):266-72.
- Wessel A et al. (1997). Arterial hypertension and blood pressure profile in patients with Williams-Beuren syndrome. *Z Kardiol* 86:251-7.

Social Vulnerabilities

- Doyle T. F. et al (2004). "Everybody in the world is my friend" - hypersociability in young children with Williams syndrome. *American Journal of Medical Genetics* 124A(3):263-273.
- Fisher M. H. et al (2012). Vulnerability and experiences related to social victimization among individuals with intellectual and developmental disabilities. *Journal of mental health research in intellectual disabilities* 5(1): 32-48
- Fisher M. H. et al (2013). Differences in social vulnerability among individuals with autism spectrum disorder, Williams syndrome, and Down syndrome. *Research in autism spectrum disorders*: 7(8):931-937
- Fisher M.H. et al (2013). Teaching young adults with intellectual and developmental disabilities to respond appropriately to lures from strangers. *Journal of Applied Behavior Analysis* 46: 528-533.
- Fisher M. H. (2014). Evaluation of a stranger safety training programme for adults with Williams Syndrome. *Journal of Intellectual Disability Research*, 58(10),903-914.
- Frigerio E. et al. (2006). Is everybody always my friend? Perception of approachability in Williams syndrome. *Neuropsychologia* 44(2): 254-259.
- Jarvinen-Pasley A. et al. (2010). Affiliative behavior in Williams syndrome: Social perception and real-life social behavior. *Neuropsychologia* 48(7): 2110-2119.

Bibliography continued...

(papers selected for review by the Williams Syndrome Guideline Development Group, and considered in the formulation of management recommendations)

Social Vulnerabilities continued...

- Järvinen A. et al (2013). The social phenotype of Williams syndrome. *Current Opinion in Neurobiology* 23: 414-422.
- Jawaid A. et al (2012). 'Too withdrawn' or 'too friendly': considering social vulnerability in two neuro-developmental disorders. *Journal of Intellectual Disability Research* 56(4):335-350
- Jones, W. et al (2000). Hypersociability in Williams syndrome. *Journal of Cognitive Neuroscience* 12: 30-46.
- Little K. et al (2013). Heterogeneity of social approach behaviour in Williams syndrome: The role of response inhibition. *Research in Developmental Disabilities* 34: 959-967.
- Lough E. et al (2016). Parent insights into atypicalities of social approach behaviour in Williams syndrome. *Journal of Intellectual Disability Research* 60:1097-1108.
- Lough E. et al (2015). Violations of personal space in young people with ASD and Williams syndrome. *Journal of Autism & Developmental Disorders* 45:4101-4108.
- Lough E. et al (2015). Mapping real-world to online vulnerability in young people with developmental disorders: Illustrations from autism and Williams syndrome. *Review Journal of Autism and Developmental Disorders* 2: 1-7
- Lough E. et al (2016). Personal space regulation in Williams syndrome: The effect of familiarity. *Journal of Autism and Developmental Disorders* 10: 3207-3215.
- Mervis C. B. et al (2003). Attentional Characteristics of Infants and Toddlers with Williams Syndrome during Triadic Interactions. *Developmental Neuropsychology* 23:243-268.
- Plesa-Skwerer D. et al (2006). Perceiving facial and vocal expressions of emotion in individuals with Williams syndrome. *American Journal on Mental Retardation* 111:15-26.
- Porter M.A. et al (2007). The neuropsychological basis of hypersociability in Williams and Down syndrome. *Neuropsychologia* 45(12): 2839-2849
- Riby D. M., Hancock P. J. B. (2008) Viewing it differently: social scene perception in Williams syndrome and autism. *Neuropsychologia* 46: 2855 - 2860.
- Riby D.M., Hancock P. J. B. (2009). Looking at Movies and Cartoons: Eye-tracking evidence from Williams syndrome and Autism. *Journal of Intellectual Disability Research* 53: 169-181.
- Riby D. M., Hancock P. J. B. (2009). Do faces capture the attention of individuals with Williams syndrome or Autism? Evidence from tracking eye movements. *Journal of Autism and Developmental Disorders* 39:421-431.
- Riby D M. et al. (2014). The Interplay between Anxiety and Social Functioning in Williams Syndrome. *Journal of Autism and Developmental Disorders* 44(5):1220-1229.
- Riby D. M. et al (2014). Stranger Danger Awareness in Williams syndrome, *Journal of Intellectual Disability Research* 58: 572-58
- Searcy Y.M. et al (2004). The relationship between age and IQ in adults with Williams syndrome. *American Journal on Mental Retardation* 109: 231-236.
- Tager-Flusberg H., Sullivan K. (2000) A componential view of theory of mind: evidence from Williams syndrome. *Cognition* 76: 59 - 90.
- Van der Fluit F. et al (2012) Social cognition in Williams syndrome: Relations between performance on the social attribution task and cognitive and behavioral characteristics. *Frontiers in Developmental Psychology* 3:197

Bibliographycontinued...

(papers selected for review by the Williams Syndrome Guideline Development Group, and considered in the formulation of management recommendations)

Vision

- Adoh T.O, Woodhouse J.M. (1994) The Cardiff Acuity Test used for measuring visual acuity development in toddlers. *Vision Res* 14:1063-6
- Anker S. et al (1989). The use of the Cambridge Crowding Cards in preschool vision screening programmes, ophthalmic clinics and assessment of children with multiple disabilities. *Ophthalmic and Physiological Optics* 9(4): 470.
- Anker S., Atkinson, J. (1997). Visual acuity measures in a sample of Williams Syndrome. *Perception* 26(6):763.
- Atkinson J. et al (1988). Visual acuity testing of young children with the Cambridge Crowding Cards at 3 and 6 metres. *Acta Ophthalmologica* 66: 505-508.
- Atkinson J. et al (2001). Visual and visuo-spatial development in young Williams Syndrome children. *Developmental Medicine & Child Neurology* 43: 330-337.
- Atkinson J. et al (2003). Neurobiological models of visuospatial cognition in children with Williams Syndrome: Measures of dorsal-stream and frontal function. *Developmental Neuropsychology* 23(1/2): 139-172.
- Bohning M. et al. (2002). Audiovisual speech perception in Williams syndrome. *Neuropsychologia* 40(8): 1396-406.
- Castelo-Branco M. et al. (2007). Visual phenotype in Williams-Beuren syndrome challenges magnocellular theories explaining human neurodevelopmental visual cortical disorders. *J Clin Invest* 117(12):3720-9.
- Eckert M. A. et al. (2006). The neurobiology of Williams syndrome: cascading influences of visual system impairment? *Cell Mol Life Sci* 63(16):1867-75.
- Farran EK et al (2013) Colour discrimination and categorisation in Williams syndrome. *Res in Dev Disabilities* 118 (3) 201 - 10
- Kapp M. E. et al. (1995). Strabismus in Williams syndrome. *Am J Ophthalmol* 119(3):355-60.
- Olitsky S. E. et al. (1997). Subnormal binocular vision in the Williams syndrome. *J Pediatr Ophthalmol Strabismus* 34(1): 58-60.
- Sadler L. S. et al. (1996). Reduced stereoacuity in Williams syndrome. *Am J Med Genet* 66(3):287-8.
- Sarpal D. et al. (2008). A Genetic Model for Understanding Higher Order Visual Processing: Functional Interactions of the Ventral Visual Stream in Williams Syndrome. *Cereb. Cortex* 18(10):2402-2409.
- Van der Geest J. N. et al. (2005). Visual depth processing in Williams-Beuren syndrome. *Exp Brain Res* 166(2):200-9.
- Weber SL et al (2014) Williams syndrome: ophthalmological examination and review of systemic manifestations. *J Ped Ophthalmology and Strabismus* 51(4):209-13
- Winter M. et al. (1996). The spectrum of ocular features in the Williams-Beuren syndrome. *ClinGenet* 49(1): 28-31.

Summary of Investigations for Children with Williams Syndrome

The table below lists the tests and screening which should be carried out in children with Williams Syndrome, and specifies at what age and how often they should be undertaken. For clinical management and follow up recommendations, please see the full set of UK Clinical Management Guidelines for Williams Syndrome, available from the Williams Syndrome Foundation website : www.williams-syndrome.org.uk.

Test/Screening	Age/Frequency			
	At diagnosis	Neonates & Infants (0–1)	Children (2–11)	Adolescents (11–18)
Cardiac screening	Cardiac assessment, 4 limb BP, oxygen saturation, ECG and Echocardiography	Cardiac assessment, 4 limb BP, oxygen saturation, ECG and Echocardiography	Cardiac assessment until 4 years and 5 yearly in childhood	Cardiac assessment 5 yearly
Hyperclacemia / hypercalcuria screening	Blood calcium and urine calcium : creatinine ratio	Blood calcium and urine calcium : creatinine ratio	Blood calcium if symptomatic	Blood calcium if symptomatic
Genitourinary tract examination	Examination, blood creatinine, electrolytes and urinary tract ultrasound	Examination, blood creatinine, electrolytes and urinary tract ultrasound	Creatinine and electrolytes every 2 - 4 years and investigate if symptomatic.	Investigate if symptomatic.
Hypertension screening	Plasma renin activity and renal artery Doppler	Plasma renin activity and renal artery Doppler	Annual BP in both arms	Annual BP in both arms
Inguinal hernia examination	Examination	Examination	Annual general examination.	Annual general examination.
Gastrointestinal examination	Coeliac screen and growth assessment	Coeliac screen and growth assessment	Coeliac screen at 3 years and annual general examination.	Coeliac screen at 3 years and annual general examination.
Endocrine & growth screening	Thyroid Function Tests (TFTs)	Thyroid Function Tests (TFTs)	Annual growth assessment and measure TFTs if symptomatic.	Annual growth assessment and sexual health assessment

Summary of Investigations for Children with Williams Syndrome continued...

The table below lists the tests and screening which should be carried out in children with Williams Syndrome, and specifies at what age and how often they should be undertaken. For clinical management and follow up recommendations, please see the full set of UK Clinical Management Guidelines for Williams Syndrome, available from the Williams Syndrome Foundation website: www.williams-syndrome.org.uk.

Test/Screening	Age/Frequency			
	At diagnosis	Neonates & Infants (0–1)	Children (2–11)	Adolescents (11–18)
Musculo skeletal screening	Examination and radiology as indicated.	Examination and radiology as indicated.	Annual general examination.	Annual general examination.
Dental screening	Referral to oral healthcare programme	Referral to oral healthcare programme	Annual dental examination	Annual dental examination
Developmental screening	Referral for multidisciplinary assessment	Referral for multidisciplinary assessment	Annual developmental assessment	
Auditory screening	Audiology review.	Referral to newborn hearing screening programme.	Audiology review if speech is delayed.	Assessment at 11 and 18 years for high frequency hearing loss
Visual screening	Referral to community orthoptist/optometrist	Referral to community orthoptist/optometrist	Visual screening at school entry by community orthoptist/optometrist.	Assessment by local optometrist as indicated.
Mental Health screening			Behavioural coaching and clinical psychology assessment as indicated	Assessment by local services as indicated.
Educational screening			Input by appropriate professionals to EHCP	Review of EHCP at 11 and 16 years.

Other Resources

- **Personal Health Record for Williams Syndrome (Blue Book)**

All babies in the UK are issued with a red book to record their health, growth and development. Similar Blue Books have been developed for several rare conditions requiring multi-disciplinary management. As part of this project a Blue Book has been designed for people with WS. The primary aim of the Blue Book is to empower patients and their families, giving them more information about and ultimately more control over their health. It will also benefit the healthcare professionals involved in managing these patients, by facilitating inter-speciality communication, educating non-specialists and allied healthcare professionals, providing a readily accessible summary 'snapshot' of a patient's condition, and they can also be used as a tool for clinical audit and research. They are available from the Williams Syndrome Foundation patient (see below).



- **The Williams Syndrome Foundation UK (www.williams-syndrome.org.uk)**

The Williams Syndrome Foundation is run for parents by parents. They aim to be the first point of contact for individuals with Williams Syndrome, their families, and professionals needing support and information regarding the Syndrome. The Foundation actively supports research into the educational, behavioural, social, scientific and medical aspects of the Syndrome, and seeks to organise their financial and personnel resources so as to achieve their mission on a sustainable basis.

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