










Clinical practice guidelines for the care of girls and women with Turner syndrome

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The guidelines have been endorsed by the European Society for Endocrinology, European Reference Network on Rare Endocrine Conditions, the European Society of Human Reproduction and Embryology, the Society for Endocrinology, by the societies of the International Consortium of Pediatric Endocrinology: the Arab Society for Pediatric Endocrinology and Diabetes, the Asia Pacific Pediatric Endocrine Society, the Australia and New Zealand Society for Pediatric Endocrinology and Diabetes, The Japanese Society for Pediatric Endocrinology and the Pediatric Endocrine Society.

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Abstract

Turner syndrome (TS) affects 50 per 100 000 females. TS affects multiple organs through all stages of life, necessitating multidisciplinary care. This guideline extends previous ones and includes important new advances, within diagnostics and genetics, estrogen treatment, fertility, comorbidities, and neurocognition and neuropsychology. Exploratory meetings were held in 2021 in Europe and United States culminating with a consensus meeting in Aarhus, Denmark in June 2023. Prior to this, eight groups addressed important areas in TS care: (1) diagnosis and genetics, (2) growth, (3) puberty and estrogen treatment, (4) cardiovascular health, (5) transition, (6) fertility assessment, monitoring, and counselling, (7) health surveillance for comorbidities throughout the lifespan, and (8) neurocognition and its implications for mental health and well-being. Each group produced proposals for the present guidelines, which were meticulously discussed by the entire group. Four pertinent questions were submitted for formal GRADE (Grading of Recommendations, Assessment, Development and Evaluation) evaluation with systematic review of the literature. The guidelines project was initiated by the European Society for Endocrinology and the Pediatric Endocrine Society, in collaboration with members from the European Society for Pediatric Endocrinology, the European Society of Human Reproduction and Embryology, the European Reference Network on Rare Endocrine Conditions, the Society for Endocrinology, and the European Society of Cardiology, Japanese Society for Pediatric Endocrinology, Australia and New Zealand Society for Pediatric Endocrinology and Diabetes, Latin American Society for Pediatric Endocrinology, Arab Society for Pediatric Endocrinology and Diabetes, and the Asia Pacific Pediatric Endocrine Society. Advocacy groups appointed representatives for pre-meeting discussions and the consensus meeting.

Keywords: Turner syndrome, hypogonadism, cardiovascular health, transition, infertility, co-morbidity, neurocognition

Summary of recommendations

The recommendations (R) are worded as *recommend* (strong recommendation) and *suggest* (weak recommendation). We formally graded only the evidence underlying recommendations for therapeutic choices. The quality of evidence behind the recommendations is classified as very low (⊕○○○), low (⊕⊕○○), moderate (⊕⊕⊕○), and strong (⊕⊕⊕⊕). See further section “Summary of methods used for guideline development”.

1. Diagnosis and genetics

- **R 1.1** We recommend considering a diagnosis of Turner syndrome (TS) in individuals with female phenotype with a karyotype containing one X chromosome and complete or partial absence of the second sex chromosome, associated with one or more typical clinical manifestations of TS (⊕⊕⊕⊕).
- **R 1.2** We recommend against considering a diagnosis of TS in individuals with one X chromosome and a deletion distal to Xq24 on the other X chromosome, and in women over the age of 50 years with less than 5% 45,X mosaicism (⊕⊕○○).
- **R 1.3** We recommend that the new general surveillance management guideline applies to TS individuals with any karyotype (⊕⊕⊕○).
- **R 1.4** We recommend that the surveillance guidelines also apply to individuals with 45,X/46,XY mosaicism with either ambiguous or male external genitalia, regardless of sex of rearing (⊕⊕⊕○).
- **R 1.5** We recommend testing for TS in a female individual with typical signs of TS (⊕⊕⊕⊕).
- **R 1.6** When testing for TS, we recommend that a minimum of 30 metaphases be counted on a chromosome analysis as the first-line test. When a rapid test result is needed (eg, prenatally, newborn) other methods can be used as a first-line test (eg, microarray, fluorescence in situ hybridization (FISH), polymerase chain reaction (PCR)), with chromosome analysis as a second line confirmatory test (⊕⊕⊕○).
- **R 1.7** We recommend that fetal echocardiography be performed in case of prenatal diagnosis of TS (⊕⊕⊕○).
- **R 1.8** We recommend that prenatal diagnosis of TS should be confirmed by postnatal karyotyping on blood (⊕⊕⊕⊕).
- **R 1.9** We recommend that when sex chromosomes are included as part of noninvasive prenatal testing (NIPT),

counseling should include information about the clinical validity/performance (⊕⊕⊕○).

- **R 1.10** If NIPT indicates a high risk for TS, we recommend thorough non-directive genetic counselling (informed decision-making) (⊕⊕⊕○).
- **R 1.11** If NIPT indicates a high risk for TS, we recommend that a detailed ultrasound be performed, and invasive diagnostic testing be offered (⊕⊕⊕○).
- **R 1.12** In case of a high-risk NIPT result for TS and a normal fetal ultrasound where invasive diagnostic testing is not performed or shows a normal result, we recommend offering the pregnant woman karyotyping for maternal sex chromosome aneuploidies (⊕⊕⊕○).
- **R 1.13** We recommend that preimplantation testing be offered to individuals with TS who want to use their own oocytes for pregnancies. TS individuals with mosaicism (45,X/46,XX) who become pregnant spontaneously, should be offered prenatal diagnostic testing (⊕⊕⊕○).
- **R 1.14** We recommend screening for Y chromosomal material by PCR or other molecular method in TS individuals with a 45,X karyotype and signs of virilization (⊕⊕○○).
- **R 1.15** We suggest that ethical issues, phenotypic variability, methodological limitations, and feasibility of appropriate genetic counseling be considered prior to adopting newborn screening platforms that identify TS (⊕○○○).

2. Growth disorders and their management

- **R 2.1** We recommend offering growth hormone (GH) treatment early, because growth failure in TS starts before birth and is rapid during the first years of life, and early GH treatment can prevent further loss of height potential. Treatment may be offered from as young as 2 years of age in the following circumstances: evidence of growth failure (rate of growth below normal or declining), short stature, or likelihood of short stature. GH treatment may be offered later, as long as epiphyses remain open (⊕⊕⊕○).
- **R 2.2** We suggest that GH treatment may be continued until little growth potential remains (bone age ≥ 14 years and/or height velocity < 2 cm year⁻¹). There is no physiological rationale for continuing GH treatment into the transition period after epiphyseal closure (⊕⊕⊕○).
- **R 2.3** We recommend a starting GH dose of 45–50 $\mu\text{g kg}^{-1} \text{ day}^{-1}$ or (1.3–1.5 mg m⁻² day⁻¹) in most

instances, increasing to a maximum of $68 \mu\text{g kg}^{-1} \text{day}^{-1}$ ($2.0 \text{ mg m}^{-2} \text{day}^{-1}$) if response is suboptimal and/or adult height potential remains substantially compromised ($\oplus\oplus\oplus\circ$).

- **R 2.4** We recommend monitoring the response to growth-promoting treatment by measurement of height at a minimum every 6 months and plotting on a standard (reference female population) and/or TS-specific height chart. Maintenance of height percentile equivalent to, or greater than, the pre-treatment height percentile on a female population-based growth chart or increasing percentile on a TS-specific height chart, provides evidence of treatment effect ($\oplus\oplus\oplus\circ$).
- **R 2.5** We recommend monitoring GH therapy by measurement of IGF-I at least annually. We suggest generally maintaining IGF-I within the normal range for age, pubertal stage, and sex. GH dose reduction may be warranted for persistently high IGF-I values ($\oplus\circ\circ\circ$).
- **R 2.6** We suggest not to routinely add very low-dose estrogen supplementation in the prepubertal years to further promote growth ($\oplus\oplus\circ\circ$).

3. Puberty and sex hormone treatment

- **R 3.1** We recommend measuring luteinizing hormone (LH), follicle stimulating hormone (FSH) and anti-Müllerian hormone (AMH) at 8-9 years and yearly until 11-12 years to enable timely referral for fertility preservation if appropriate ($\oplus\oplus\oplus\circ$).
- **R 3.2** We recommend initiation of low dose estrogen replacement between 11 and 12 years of age, if FSH is elevated on at least two sequential measurements. Estrogen dosage should be increased slowly to adult replacement dosage over 2-4 years ($\oplus\oplus\oplus\circ$).
- **R 3.3** In individuals with a later diagnosis (>12 years) who have short stature and remaining growth potential, we suggest initiating treatment with low dose 17β -estradiol (E2) simultaneously with GH ($\oplus\circ\circ\circ$).
- **R 3.4** We suggest E2 transdermal (TD) route when possible, with oral E2 as second choice. Ethinyl estradiol has more risks but is better than no treatment ($\oplus\oplus\circ\circ$).
- **R 3.5** We recommend adding cyclic progesterone once breakthrough bleeding occurs (mostly this will be after about 18-24 months of unopposed estrogen exposure but this can occur later based on pubertal stage, serum E2 and uterine growth, endometrial thickness, and estrogen dose). The preferred option is micronized progesterone 200 mg for 10-12 days per month ($\oplus\oplus\oplus\oplus$).
- **R 3.6** We suggest combined sequential E2 and progesterone dosing in young women to avoid experiencing abnormal uterine bleeding. A combined continuous regimen is an option when the endometrium is more stable ($\oplus\circ\circ\circ$).
- **R 3.7** To optimize uterine growth during puberty and bone health in adulthood, we suggest multiple assessments of treatment effect, to include: breast development, height, uterine ultrasound, bone density, serum E2 concentrations, with the goal to achieve E2 concentrations of $100\text{-}150 \text{ pg mL}^{-1}$ ($350\text{-}500 \text{ pmol L}^{-1}$) at full adult replacement ($\oplus\circ\circ\circ$).

- **R 3.8** We suggest using measurements of endometrial thickness and serum E2 concentrations in adolescents or women experiencing abnormal uterine bleeding to inform adjustments to E2 and/or progesterone doses ($\oplus\circ\circ\circ$).
- **R 3.9** We recommend continuing cyclic estrogen and progesterone treatment until the usual age of menopause (approximately 50-55 years old) and then re-evaluate for possible continued lower dose of E2 and progesterone ($\oplus\oplus\circ\circ$).
- **R 3.10** We recommend individualized E2 + progesterone replacement, taking account of patient preference, to aid adherence with their management plans ($\oplus\oplus\circ\circ$).

4. Cardiovascular health

- **R 4.1** We recommend that if TS is highly suspected or has been confirmed prenatally, a fetal echocardiogram should be performed ($\oplus\oplus\oplus\circ$).
- **R 4.2** We recommend that diagnosis of left-sided congenital heart disease (CHD) in a female fetus or child should prompt a genetic evaluation that includes testing for TS ($\oplus\oplus\oplus\circ$).
- **R 4.3** We recommend that a pediatric cardiologist should be included in the multidisciplinary care team when CHD is detected prenatally in a fetus with TS to provide counseling regarding the anatomy and physiology of the specific defect, the recommended site and mode of delivery, and postnatal cardiovascular management ($\oplus\oplus\circ\circ$).
- **R 4.4** We recommend that a newborn with prenatally diagnosed or suspected TS be examined with transthoracic echocardiography (TTE) at day 2 to day 3 of life, sooner if CHD is suspected, even if the fetal echocardiogram or postnatal clinical examination was normal ($\oplus\oplus\oplus\circ$).
- **R 4.5** In settings where postnatal TTE prior to discharge after birth is not available, we recommend clinical cardiac evaluation with 4-extremity blood pressure, pulse oximetry, palpation of femoral pulses, cardiac auscultation, and ECG prior to discharge followed by outpatient TTE within the first weeks of life ($\oplus\oplus\oplus\circ$).
- **R 4.6** We recommend that visualization of the origin and proximal course of coronary arteries to identify potential coronary anomalies should be included in the cardiovascular assessment of all individuals with TS ($\oplus\oplus\circ\circ$).
- **R 4.7** We recommend that TTE should be performed at the time of diagnosis in all children and adults with TS, even when a fetal echocardiogram or postnatal clinical examination was normal ($\oplus\oplus\oplus\circ$).
- **R 4.8** We recommend that in the absence of significant cardiovascular disease (hypoplastic left heart syndrome, Shone's complex, aortic coarctation, bicuspid aortic valve (BAV), aortic dilation, or cardiac shunt) at the initial comprehensive screening, TTE should be performed at age 9-11 years, after growth completion or at transition to adult care, and at least every 5-10 years in adults. ($\oplus\oplus\circ\circ$).
- **R 4.9** If the heart and aorta are completely visualized and are normal in an infant or child without symptoms that could be attributable to cardiovascular disease, an initial cardiovascular magnetic resonance (CMR) scan is still

- recommended but can be delayed until it can be performed without general anesthesia (⊕⊕○○).
- **R 4.10** CMR should be performed, in addition to or instead of initial screening echocardiography, in all adolescents and adults newly diagnosed with TS. Imaging should ideally be completed within 12 months, with the exact interval based on initial echocardiography findings (if echocardiography completed first), presence of additional risk factors, and clinical judgement (⊕⊕○○).
 - **R 4.11** Computed tomography (CT) is a reasonable alternative when CMR is not tolerated or available. Both CT and CMR scans should include electrocardiogram (ECG)-gated or ECG-triggered assessment of the thoracic aorta (⊕⊕○○).
 - **R 4.12** We recommend that individuals with TS, especially with aortic dilation or BAV, should be counseled to seek prompt evaluation if they experience acute symptoms consistent with aortic dissection, such as chest, neck, shoulder, back, or flank discomfort, particularly if it is sudden in onset and severe (⊕⊕○○).
 - **R 4.13** Individuals with TS require lifelong cardiovascular surveillance at a frequency that should be determined by their risk factors for aortic dissection (⊕○○○).
 - **R 4.14** For children <15 years old, aortic dilation may be categorized by calculating the TS-specific Z-score (Z). For adults and adolescents >15 years old, aortic dilation may be categorized by calculating the aortic height index (AHI), the aortic size index (ASI), the TS-specific Z-score, or the general population Z-score.
 - **R 4.15** For adults with TS, we recommend informed, individualized decision-making about the timing of elective aortic surgery, considering risk factors for aortic dissection, including moderate aortic dilation (AHI > 23 mm m⁻¹, ASI > 2.3 cm m⁻², or Z > 3.5) with at least one additional risk factor: BAV, aortic coarctation, hypertension, or a rapid increase in aortic diameter (>3 mm year⁻¹). Dissection risk probably increases if more than one additional risk factor is present. Severe aortic dilation (AHI > 25 mm m⁻¹, ASI > 2.5 cm m⁻², or Z > 4) as a single risk factor should prompt an evaluation for elective aortic surgery (⊕○○○).
 - **R 4.16** For children with TS, the risk of aortic dissection is much lower than in adults. We recommend informed, individualized decision-making about the timing of elective aortic surgery, considering risk factors for aortic dissection including moderate aortic dilation (age < 15 years: Z > 3.5; age ≥ 15 years: AHI ≥ 23 mm m⁻¹, ASI > 2.3 cm m⁻², or Z > 3.5) and hypertension, aortic coarctation, BAV, or a rapid increase in aortic diameter (>3 mm year⁻¹ or >1 Z year⁻¹) (⊕○○○).
 - **R 4.17** We recommend annual assessment of blood pressure, preferably using ambulatory blood pressure monitoring (ABPM), and initiation of medical therapies if hypertension is confirmed, for all individuals with TS (⊕⊕○○).
 - **R 4.18** We recommend treatment with a beta-blocker, an angiotensin receptor blocker, or both for individuals with TS who have hypertension and have a dilated aorta (age < 15 years: Z ≥ 2.5; age ≥ 15 years: AHI ≥ 20 mm m⁻¹, ASI > 2.0 cm m⁻², or Z > 2.5) (⊕⊕○○).
 - **R 4.19** We suggest that treatment with a beta-blocker, an angiotensin receptor blocker, or both should be considered for individuals with TS who have a dilated aorta (age < 15 years: Z ≥ 2.5; age ≥ 15 years: AHI ≥ 20 mm m⁻¹, ASI > 2.0 cm m⁻², or Z > 2.5), even if they are not hypertensive (⊕○○○).
 - **R 4.20** We recommend that medical treatment of hypertension for all individuals with TS who do not have a dilated aorta (age < 15 years: Z < 2.5; age ≥ 15 years: AHI < 20 mm m⁻¹, ASI < 2.0 cm m⁻², or Z < 2.5) should be based on the appropriate pediatric or adult guidelines for medical management of hypertension (⊕⊕○○).
 - **R 4.21** We do not recommend routine screening for blood clotting disorders before initiation of female sex hormone replacement therapy (HRT). The diagnosis, surveillance, and treatment of blood clotting disorders in TS should be based on the appropriate pediatric or adult clinical guidelines for the general population (⊕○○○).
 - **R 4.22** We recommend that an initial lipid profile should be obtained no later than the age of initial screening recommended by country-specific guidelines or at transition and repeated every 3 years. The diagnosis and treatment of hyperlipidemia in TS should be based on the appropriate pediatric or adult clinical guidelines for the general population (⊕⊕○○).
 - **R 4.23** We recommend that new onset chest pain, regardless of age, should be assessed by a cardiologist. The diagnosis, surveillance, and treatment of coronary artery disease in TS should be based on the appropriate pediatric or adult clinical guidelines for the general population (⊕⊕○○).
 - **R 4.24** We recommend that a resting ECG should be performed at the time of diagnosis to assess for findings consistent with CHD, an arrhythmia, or conduction abnormality. Follow up ECGs should be obtained and reviewed by a cardiologist at intervals deemed appropriate based on baseline findings, underlying CHD, and clinical course (⊕⊕⊕⊕).
 - **R 4.25** We suggest, given prior concern for QTc prolongation in persons with TS, that the QTc should be routinely calculated, ideally using Hodges formula, whenever an ECG is performed on a patient with TS. However, newer research suggests that QTc prolongation is not more prevalent in persons with TS compared to the general population when defining prolongation as QTc >450 ms in girls (up to 15 years old) and >460 ms in women and when using Hodges formula (⊕⊕○○).
 - **R 4.26** We recommend that standard guidelines for the general population should apply to individuals with TS if QTc prolongation >480 ms by Hodges formula has been detected on at least two serial ECGs. In those circumstances, consultation with a cardiologist, possibly an electrophysiologist, should be completed (⊕⊕⊕⊕).
 - **R 4.27** We recommend regular aerobic physical activities as part of a heart healthy lifestyle for all individuals with TS (⊕○○○).
 - **R 4.28** We recommend that the function of the aortic valve, the presence of any other congenital heart lesions, and hypertension should be considered in determining athletic participation recommendations for the individuals with TS and aortic dilation (⊕○○○).
 - **R 4.29** We suggest that for individuals with normal aortic size (age < 15 years: Z < 2.5; age ≥ 15 years: AHI < 20 mm m⁻¹, ASI < 2.0 cm m⁻², or Z < 2.5), it is reasonable to participate in all sports (⊕○○○).

- **R 4.30** We suggest that for individuals with a mild to moderately dilated aorta (age < 15 years: Z 2.5-3.5; age \geq 15 years: AHI 20-23 mm m^{-1} , ASI 2.0-2.3 cm m^{-2} , or Z 2.5-3.5), participation in low and moderate static and dynamic competitive sports may be acceptable but intense weight-training should be avoided ($\oplus\circ\circ\circ$).
 - **R 4.31** We suggest that individuals with a moderately to severely dilated aorta (age < 15 years: $Z > 3.5$; age \geq 15 years: $AHI > 23$ mm m^{-1} , $ASI > 2.3$ cm m^{-2} , or $Z > 3.5$) should be advised not to participate in any competitive sports, intense weight-training, or physical activities with risk of contact injury to the chest ($\oplus\circ\circ\circ$).
 - **R 4.32** We recommend that cardiovascular imaging, ideally CMR or CT, should be performed at least once within 2 years before planned pregnancy or assisted reproductive methods and repeated closer to pregnancy if recommended by a cardiovascular specialist ($\oplus\oplus\circ\circ$).
 - **R 4.33** In the presence of aortic dilation ($AHI > 20$ mm m^{-1} , $ASI > 2.0$ cm m^{-2} , or $Z > 2.5$) or at least one other risk factor for dissection (BAV, aortic coarctation, hypertension, rapid aortic diameter increase), we recommend informed, individualized peripartum cardiovascular care by a multidisciplinary team that ideally should include a maternal-fetal medicine specialist and a cardiologist with expertise in managing women with TS, preferably in a center with expertise in aortic surgery and TS ($\oplus\circ\circ\circ$).
 - **R 4.34** In the presence of severe aortic dilation ($AHI > 25$ mm m^{-1} , $ASI > 2.5$ cm m^{-2} , or $Z > 4$) and especially when other risk factors for aortic dissection are present (previous aortic surgery, previous aortic dissection, or rapid aortic diameter increase (>3 mm $year^{-1}$), BAV, hypertension, or aortic coarctation), we suggest that assisted reproductive technologies or spontaneous conception should be avoided ($\oplus\circ\circ\circ$).
 - **R 4.35** We recommend tight blood pressure control to a target of less than 130/80 mm Hg during the peripartum period. Antihypertensive therapies and low dose aspirin for the prevention of adverse pregnancy outcomes due to preeclampsia and related hypertensive disorders should be administered according to current clinical practice guidelines ($\oplus\oplus\circ\circ$).
 - **R 4.36** We recommend obtaining a TTE at least once during pregnancies in low-risk women ($AHI < 20$ mm m^{-1} , $Z < 2.5$, $ASI < 2.0$ cm m^{-2} and no BAV, aortic coarctation, hypertension, or rapid aortic diameter increase), ideally around 20 weeks of gestation ($\oplus\oplus\circ\circ$).
 - **R 4.37** In the presence of aortic dilation ($AHI > 20$ mm m^{-1} , $ASI > 2.0$ cm m^{-2} , or $Z > 2.5$) or at least one other risk factor (BAV, aortic coarctation, hypertension, rapid aortic diameter increase), we suggest TTE at least once every 12 weeks during pregnancy, or more frequently on an individualized basis. Consideration of an additional imaging study in the early third trimester is reasonable and is strongly encouraged if there is any concerning change noted on the second trimester TTE ($\oplus\circ\circ\circ$).
 - **R 4.38** We recommend that CMR (without contrast medium) should be performed during pregnancy when TTE raises suspicion of rapid aortic dilation. If aortic segments previously known to be dilated cannot be adequately visualized, or if new dilation is suspected, CMR should be used for confirmation ($\oplus\oplus\circ\circ$).
 - **R 4.39** We suggest that rapid aortic diameter increase (>3 mm compared to pre-conception imaging) should lead to renewed risk assessment and discussion in an expert center with a multidisciplinary team to determine potential modifications of maternal risk factors for aortic dissection, delivery, and postpartum planning, including consideration of prophylactic aortic replacement ($\oplus\circ\circ\circ$).
 - **R 4.40** We recommend the mode of infant delivery should be based on the safest method to prevent aortic and obstetric complications, individual preferences, and local professional expertise. Preventive measures (epidural anesthesia, expedited second stage of labor) that reduce the risk of aortic dissection should be considered, but are especially recommended in the presence of aortic dilation ($AHI > 20$ mm m^{-1} , $ASI > 2.0$ cm m^{-2} , or $Z > 2.5$) or additional risk factors for aortic dissection (BAV, aortic coarctation, hypertension, rapid aortic diameter increase). Cesarean section is preferred for individuals with severe aortic dilation ($AHI > 25$ mm m^{-1} , $ASI > 2.5$ cm m^{-2} , or $Z > 4$) or a history of aortic dissection ($\oplus\circ\circ\circ$).
 - **R 4.41** We recommend postpartum cardiac imaging and cardiology consultation due to the continued risk of aortic dissection. For individuals with severe aortic dilation ($AHI > 25$ mm m^{-1} , $ASI > 2.5$ cm m^{-2} , or $Z > 4$) or a history of aortic dissection, the initial postpartum visit should occur 2-6 weeks after delivery with at least one additional follow up cardiology visit. For individuals with less severe aortic disease, one postpartum visit 4-6 months after delivery may be sufficient before resuming routine follow up intervals ($\oplus\circ\circ\circ$).
 - **R 4.42** We recommend that individuals who can become pregnant and have left-sided obstructive lesions (sub-aortic stenosis, aortic valve stenosis, or coarctation) should have regular aortic imaging and cardiovascular follow up with consideration for intervention before pregnancy ($\oplus\circ\circ\circ$).
 - **R 4.43** We recommend that individuals with severe sub-aortic or aortic valve stenosis or significant valve disease and reduced cardiac function should be advised against pregnancy ($\oplus\circ\circ\circ$).
- ## 5. Transition from pediatric to adult care
- **R 5.1** We recommend an intentional, defined, individualized pathway to transition from pediatric to adult care for adolescents with TS beginning in early adolescence ($\oplus\oplus\circ\circ$).
 - **R 5.2** We suggest a formal assessment of transition readiness at multiple timepoints of the individual and/or caregiver/support person to identify specific needs and barriers to successful transition ($\oplus\circ\circ\circ$).
 - **R 5.3** We suggest that developmentally appropriate, organ systems-based assessment and counseling occurs during transition, ensuring that these elements are documented upon transfer ($\oplus\oplus\circ\circ$).
 - **R 5.4** We suggest that pediatric health care teams transition individuals with TS to adult providers with expertise to manage TS comorbidities ($\oplus\oplus\circ\circ$).

6. Fertility assessment, monitoring, and counselling

- **R 6.1** We recommend developmentally appropriate disclosure of the potential for reduced fertility in individuals with TS. We recommend disclosing that the probability to conceive is primarily associated with the presence of a 46, XX cell line and spontaneous menarche, and that there is increased risk of maternal and fetal complications in pregnancy compared to the general population (⊕⊕⊕○).
- **R 6.2** We recommend counselling of TS girls and parents, as early as possible after diagnosis, by the primary care provider, pediatric endocrinologist, or gynecologist, as appropriate, regarding family building options such as fertility preservation, foster care, adoption, surrogacy, egg or embryo donation or the choice to remain childless (⊕⊕○○).
- **R 6.3** We recommend offering a referral to a fertility specialist with specific expertise in TS care to all individuals with TS (or their parents/guardians), when developmentally appropriate, at the time of diagnosis and intermittently over time (⊕⊕○○).
- **R 6.4** We recommend offering AMH measurements to all individuals with TS from diagnosis. AMH should be monitored annually if fertility preservation is considered, along with pre- and post-test fertility counselling (⊕○○○).
- **R 6.5** We recommend thorough cardiac screening and appropriate counselling by a maternal–fetal medicine specialists and cardiologists with expertise in managing women with TS prior to planning a pregnancy, especially if oocyte or embryo donation is considered. (⊕⊕⊕⊕)
- **R 6.6** We recommend controlled ovarian stimulation and oocyte cryopreservation, in females with a fertility potential, as the primary fertility preservation option in post-menarche individuals of appropriate psychological maturity, in centers with sufficient expertise in managing women with TS and the availability of psychosocial support (⊕⊕⊕○).
- **R 6.7** We recommend that controlled ovarian stimulation and oocyte cryopreservation not be offered to premenarcheal children or individuals not mature enough to understand and undergo the procedure (⊕○○○).
- **R 6.8** We recommend in all TS, including minors who cannot make their own decision, that ovarian tissue cryopreservation only be offered in the context of an institutional/ethics board approved research study or with clinical ethics board approval (⊕○○○).
- **R 6.9** We suggest shared decision-making when addressing fertility preservation and fertility treatment for individuals with TS (Good Practice Statement).

7. Health surveillance for comorbidities throughout the lifespan

- **R 7.1** We recommend delivery of a fetus with known or suspected TS occur in a facility equipped to provide neonatal care (⊕○○○).
- **R 7.2** We recommend a comprehensive physical examination with particular attention to hip stability and lymphedema, echocardiography, and renal ultrasonography be obtained regardless of prenatal imaging results, ideally prior to discharge (⊕⊕○○).

- **R 7.3** We recommend monitoring pre-feeding blood glucose levels in the first 48 h of life and ensure that the infant is euglycemic prior to discharge. We suggest heightened awareness for symptoms of hypoglycemia in the early years of life (⊕○○○).
- **R 7.4** We recommend counseling on, and monitoring for, feeding difficulties and poor weight gain in the first year of life, with collaborative evaluation and treatment by the primary care provider and/or specialists based on the concern and available resources (⊕○○○).
- **R 7.5** We recommend expectant and new parents/caregivers be offered genetic counseling, referred to specialists in TS care, and be provided resources for local support and advocacy groups (⊕○○○).
- **R 7.6** We recommend a comprehensive ophthalmologic examination between 6 and 12 months of age, or at the time of diagnosis if older (⊕⊕○○).
- **R 7.7** We recommend follow-up ophthalmologic examinations if the initial examination is abnormal or if new visual or ocular concerns arise (⊕⊕○○).
- **R 7.8** We recommend otoscopy evaluation for detection of middle ear disease, including effusion and cholesteatoma, annually in childhood and with symptoms (⊕⊕○○).
- **R 7.9** We recommend newborn hearing screening be completed, and if this is normal, age-appropriate behavioral audiometric evaluation be conducted every 2-3 years in childhood and adolescence starting as soon as developmentally able (1-2 years of age), every 5 years in adults, and any time decreased hearing is suspected (⊕⊕⊕○).
- **R 7.10** We recommend annual tympanometry up to 5 years of age where clinically available (⊕⊕○○).
- **R 7.11** We recommend antibiotic treatment should be administered for acute bacterial otitis media per local treatment guidelines (as for a high-risk population) and a repeat examination should be done to ensure resolution (⊕⊕○○).
- **R 7.12** We suggest placement of tympanostomy tubes at the early stages of chronic or recurrent middle ear disease in childhood (as for a high-risk population) (⊕⊕○○).
- **R 7.13** We recommend rapid intervention with tympanostomy tube insertion or hearing aids for conductive hearing loss due to middle ear disease in childhood (⊕⊕○○).
- **R 7.14** We recommend rehabilitation with hearing aids or cochlear implantation for sensorineural hearing loss (⊕⊕○○).
- **R 7.15** We recommend counseling on, and monitoring for, balance and vestibular problems in adults with sensorineural hearing loss, and referral to appropriate specialists for vestibular testing and compensatory training if concerns are identified (⊕○○○).
- **R 7.16** We recommend at least annual dental care from first tooth eruption throughout the lifespan, with particular attention to periodontal health (⊕⊕⊕○).
- **R 7.17** We suggest orthodontic evaluation after permanent tooth eruption for initial consultation and anticipatory management (⊕○○○).
- **R 7.18** We suggest screening for obstructive sleep-disordered breathing through history and/or validated instruments throughout the lifespan (⊕○○○).

- **R 7.19** We recommend annual skin assessment (⊕○○○).
- **R 7.20** We suggest use of compression garments, lymphatic massage, and referral to specialists in lymphedema care for any compromising lymphedema (⊕○○○).
- **R 7.21** We recommend a renal ultrasound at time of diagnosis to identify congenital anomalies of the kidney and urinary tract (⊕⊕⊕⊕).
- **R 7.22** We recommend performing laboratory testing or repeat imaging if there are new renal or urinary concerns, such as urinary tract infections and hypertension. Annual urinalysis for proteinuria is indicated in all individuals with renal agenesis, bilateral hypoplasia, or horseshoe kidney (⊕⊕○○).
- **R 7.23** We recommend promotion of healthy lifestyles including exercise to address modifiable risk factors of cardiovascular disease (⊕⊕○○).
- **R 7.24** We recommend screening for diabetes with measurement of hemoglobin A1c or fasting glucose every 1-2 years starting at age 10-12 years or sooner with symptoms of diabetes (⊕⊕○○).
- **R 7.25** We recommend assessment of diabetes autoantibodies at diagnosis of diabetes in girls and women with TS to determine the type of diabetes as it is not easy to differentiate Type 1 and Type 2 diabetes in this population (⊕⊕⊕⊕).
- **R 7.26** We recommend measuring liver enzymes (alanine aminotransferase (ALT) at minimum) in childhood and every 1-2 years starting at the age of 10 and continuing throughout the lifespan. Aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP) should be added in adults (⊕⊕○○).
- **R 7.27** We suggest that if liver enzymes are elevated at least twice the normal upper limit, reassessment is recommended as fluctuation is common. Persistent liver function abnormalities (LFA) warrant further investigation and referral to a gastroenterologist (⊕⊕⊕⊕).
- **R 7.28** We suggest that in adults with LFA, the fibrosis-4 (FIB-4) score and/or liver elastography is useful for evaluating the severity of liver damage (⊕○○○).
- **R 7.29** We recommend that HRT should be continued in the presence of LFA (⊕⊕⊕⊕).
- **R 7.30** We recommend screening for celiac disease by measuring tissue transglutaminase antibodies (TTG IgA with total IgA) in asymptomatic individuals starting at age 2 years, and subsequently every 2-5 years (⊕⊕○○).
- **R 7.31** We recommend screening for celiac disease if there are gastrointestinal symptoms, poor growth, weight loss, osteoporosis, skin changes, anemia and/or other symptoms present at any age (⊕⊕○○).
- **R 7.32** We suggest measurement of complete blood count to evaluate for anemia every 1-2 years in adolescents and adults (⊕⊕○○).
- **R 7.33** We recommend that all individuals should be counseled on healthy lifestyle measures including dietary intake of calcium and vitamin D, weight-bearing activity, and the role of estrogen replacement for bone health (⊕⊕○○).
- **R 7.34** We recommend routine screening for vitamin D deficiency using a serum 25 (OH) vitamin D level concentration between 9 and 11 years of age and every 2-3 years ongoing and treating with standard vitamin D supplement as necessary (⊕⊕○○).
- **R 7.35** We recommend obtaining a dual energy X-ray absorptiometry (DXA) scan after completion of growth but prior to 21 years of age and every 5-10 years throughout adulthood (⊕⊕○○).
- **R 7.36** We recommend using serial DXA scans to monitor BMD in high-risk women (fractures, inadequate hormone replacement, celiac disease, and other comorbidities) and once reaching menopause or discontinuing estrogen therapy (simulating menopause) (⊕⊕○○).
- **R 7.37** We recommend physical examination to identify scoliosis at diagnosis and then at least annually until skeletal maturation (⊕○○○).
- **R 7.38** We suggest screening for orthopedic anomalies (such as scoliosis, genu valgum, Madelung deformity) which in severe cases, may lead to pain and improve with intervention (⊕○○○).
- **R 7.39** We recommend adhering to generally accepted population screening guidelines for cancer surveillance in TS (⊕⊕⊕⊕).
- **R 7.40** We recommend individualized decision-making about gonadectomy/salpingo-oophrectomy in girls and women with TS and Y chromosome material identified on standard karyotyping or FISH analysis. This also includes a discussion of the timing of the procedure weighing risk of gonadoblastoma/dysgerminoma against the potential benefit of gonadal function and fertility (⊕⊕○○).
- **R 7.41** We recommend screening for hypothyroidism with measurement of TSH every 1-2 years starting at 2 years of age and continuing through adulthood, and with new symptoms. If TSH is elevated, we suggest testing for anti-thyroid antibodies (⊕⊕○○).
- **R 7.42** We recommend counseling on and screening for symptoms of other autoimmune conditions, such as vitamin B12 deficiency, celiac disease, psoriasis, vitiligo, and inflammatory bowel diseases (⊕○○○).
- **R 7.43** We recommend the clinical care recommendations herein be implemented on an individual basis with consideration of both patient- and system-level factors (Good Practice Statement).
- **R 7.44** We recommend all individuals with TS receive care from specialists with expertise in genetics (and/or genetic counseling), cardiology, endocrinology, reproductive medicine, audiology/otolaryngology, ophthalmology, neurodevelopment and mental health. Additional subspecialists should be involved as needed, such as dermatology, gastroenterology, nephrology, orthopedics, podiatry, nutrition, and speech/occupational/physical therapy (⊕⊕⊕⊕).
- **R 7.45**, We recommend that girls and women with TS attend specialist interdisciplinary or multidisciplinary clinics, when available, for health surveillance in addition to their primary care provider (⊕⊕○○).
- **R 7.46** We suggest that the TS care team provide resources for additional education, self-advocacy, and connecting with other affected individuals such as through TS support and advocacy organizations (⊕⊕○○).
- **R 7.47** We suggest telehealth may supplement medical and/or psychosocial care if it is available and improves access to TS specialists (⊕○○○).

8. Neurocognition and its implications for mental health and well-being

- **R 8.1** We recommend that cognitive/neuropsychological evaluations and behavioral/social/emotional screenings be integrated into the care of individuals with TS across the lifespan (⊕⊕⊕○).
- **R 8.2** We recommend surveillance of generic risk factors associated with chronic medical conditions that can threaten well-being and quality of life (QoL) (Ungraded Good Practice Statement).
- **R 8.3** We recommend that evidence-based interventions for cognitive or psychosocial problems in the general population be adapted to meet the needs of girls/women with TS (⊕⊕⊕○).
- **R 8.4** We recommend that a “support plan” be prepared by the patient’s specialist providers as a tool to empower individuals and their caregivers in advocating for all necessary supports, outside the medical environment (eg, schools, community), to achieve optimal educational and socioemotional development (Ungraded Good Practice Statement).
- **R 8.5** We recommend counseling regarding TS that emphasizes personal understanding and meaning of the features associated with TS (Ungraded Good Practice Statement).
- **R 8.6** We recommend that girls and women with TS receive counseling regarding sexual health and sexual well-being (Ungraded Good Practice Statement).
- **R 8.7** We suggest that individuals with TS and their caregivers be encouraged to network with local/regional/national TS peer support organizations (⊕○○○).

The purpose of the guidelines

These guidelines were developed to ensure that girls and women with TS receive optimal, evidence-based care that meets their needs and improves their health. Building on the 2017 Clinical Practice Guidelines for the care of girls and women with TS,¹ these new guidelines have been updated and expanded to areas not previously addressed, including partnership in care and empowerment of women with TS. Personal characteristics, preferences, culture, social determinants of health, and values are all considered, in addition to resource availability in different settings. The guidelines are offered in support of girls, women and families living with TS and their healthcare providers to optimize diagnosis, assessment, and management of TS.

Introduction

Turner syndrome (TS) affects 25-50 per 100 000 female individuals and can involve multiple organ systems through all stages of life, necessitating a multidisciplinary approach to care. Previous guidelines have already addressed this, but numerous important advances have been noted since their publication.¹⁻³ These advances cover all specialty fields involved in the care of girls and women with TS. This paper is based on an international effort that started with exploratory virtual meetings in 2021, and culminated with a Consensus Meeting held in Aarhus, Denmark in June 2023. Prior to this meeting, eight groups each addressed important areas in TS care: (1) diagnosis and genetics, (2) growth, (3) puberty and estrogen treatment, (4) cardiovascular health, (5) transition, (6) fertility assessment, monitoring, and counselling, (7) health

surveillance for comorbidities throughout the lifespan, and (8) neurocognition and its implications for mental health and well-being. These groups produced proposals for the present guidelines. Additionally, four pertinent questions were submitted for formal GRADE (Grading of Recommendations, Assessment, Development and Evaluation) evaluation with a separate systematic review of the literature.⁴ These four questions related to the efficacy and most optimal treatment of short stature, infertility, hypertension, and HRT. These guidelines were initiated and developed by members of the European Society of Endocrinology (ESE) in Europe, and by the Pediatric Endocrine Society (PES) in the USA, with important contributions from members from the European Society of Human Reproduction and Embryology (ESHRE), the European Society for Cardiology, the American Heart Association (AHA), the Society for Endocrinology, the European Society for Pediatric Endocrinology, Japanese Society for Pediatric Endocrinology, Australasian Pediatric Endocrine Group, Latin American Society for Pediatric Endocrinology (SLEP), Arab Society for Pediatric Endocrinology and Diabetes, and Asia Pacific Pediatric Endocrine Society.

Funding bodies should recognize that although TS is a relatively rare condition, it presents with multi-system effects and therefore deserves diversified and increased efforts to support research in the years to come.

Methods

Guideline development consensus working group

The work on these guidelines was sponsored primarily by ESE and co-sponsored by European Society for Paediatric Endocrinology and the European Reference Network on Rare Endocrine Conditions (Endo-ERN), Project ID No 101084921, co-funded by the European Union within the framework of the EU4H Programme. Endo-ERN Reference Centre (RC) individual contributions is acknowledged. Furthermore, PES supported their own delegates for the meeting, and additional support was obtained from an unconditional grant from Novo Nordisk and a gift from Ascendis Pharma, as well as certain TS advocacy groups (Turner Syndrome Support Society of the United Kingdom, Turner Syndrome Center Denmark). The chairs of the consensus working group, Claus H. Gravholt and Philippe F. Backeljauw, were confirmed by the ESE Clinical Committee and PES, respectively. Other members of the working and writing group were: Niels H. Andersen (adult cardiologist), Sophie Christin-Maitre (adult endocrinologist), Shanlee Davis (pediatric endocrinologist), Anthonie Duijnhouwer (adult cardiologist), Aneta Gawlik (pediatric endocrinologist), Andrea T. Maciel Guerra (clinical geneticist), Iris Gutmark-Little (pediatric endocrinologist), Kathrin Fleischer (gynecologist and fertility specialist), David Hong (child psychiatrist), Karen O. Klein (pediatric endocrinologist), Siddharth Prakash (adult cardiologist), Roopa Kanakatti Shankar (pediatric endocrinologist), David E. Sandberg (health psychologist), Theo C.J. Sas (pediatric endocrinologist), Anne Skakkebaek (clinical geneticist), Kirstine Stochholm (adult endocrinologist), and Janielle A. van der Velden (pediatric endocrinologist). The working group had one in-person meeting (June 2023 where all participants were present) and numerous virtual meetings. Consensus was reached upon discussion; minority positions were considered in the rationale behind the recommendations. Some working groups included members from the TS advocacy community. These

individuals provided a valuable and nuanced perspective. All participants completed conflict-of-interest forms (Appendix S1).

A draft of the guideline was submitted for external review and commentary with/without endorsement by the professional societies. All comments and suggestions were discussed and implemented as appropriate by the working/writing group. Responses to the comments are summarized in Appendix S2.

Target group

This guideline document is developed for all health-care providers of individuals with TS, ie, both primary care providers (pediatricians, family doctors, internal medicine specialists), as well as sub-specialists, such as various specialist pediatricians, geneticists, endocrinologists, cardiologists, gynecologists and fertility specialists, clinical psychologists, and neuropsychologists.

Aims

The overall purpose of the updated guidelines is to provide practical clinical recommendations for TS care, with focus on daily management across the lifespan. We also aimed to address health-care issues not previously addressed.

Summary of methods used for guideline development

The methods used have previously been described in greater detail.³ In short, the guidelines used GRADE as a methodological base for four clinical questions. The first step was to define these questions followed by a systematic literature search. After including relevant articles, we: (1) estimated an average effect for specific outcomes (if possible); and (2) rated the quality of the evidence. Formal evidence syntheses were performed and graded only for these questions.

For the GRADE questions we considered: (1) quality of the evidence, (2) balance of desirable and undesirable outcomes, and (3) values and preferences (patient preferences, goals for health, costs, management inconvenience, feasibility of implementation, etc.). Additional recommendations based on good practice were graded based on expert opinion.

All other recommendations were derived from majority consensus of the guideline development working group, but, if members had substantive disagreements, this is acknowledged in the manuscript. For transparency, all recommendations provided are accompanied by a text explaining why specific recommendations were made. The recommendations are worded as *recommend* (strong recommendation) and *suggest* (weak recommendation). The quality of evidence behind the recommendations is classified as very low (⊕○○○), low (⊕⊕○○), moderate (⊕⊕⊕○) and strong (⊕⊕⊕⊕).⁵ This approach was used for all other recommendations as well. For “all other classifications” not formally submitted for GRADE, the recommendations were proposed by selected members of the working group and accepted by the remaining members of that working group, and as such represent good clinical practice based on the limited available evidence, but still supported by individuals with considerable expertise in TS care.

Clinical questions, endpoint definitions, and eligibility criteria

The guideline panel formulated four clinical questions for which a separate systematic literature search was performed,

and for which available evidence was synthesized. For each question, the eligibility criteria, endpoint definition, search strategy, and main findings are described below.

What is the effect of growth promoting treatment in TS? (GRADE question 1)

Short stature, present in most individuals with TS, has been treated with growth hormone (GH), with or without oxandrolone (a non-aromatizable androgen), with the main outcome objective to increase adult height. We systematically searched for randomized clinical trials (RCTs) published after 1990 on the effects of GH with or without the addition of oxandrolone. The following outcomes were considered: height change and adult height outcome, QoL, mortality, cardiovascular side effects, and masculinization (due to oxandrolone treatment). The following studies were not eligible: non-randomized studies, studies not reporting height, studies only comparing different doses of one drug, and cross-over trials.

What is the probability of achieving viable pregnancy after oocyte donation in TS? (GRADE question 2)

TS is usually accompanied by infertility due to premature ovarian insufficiency. Women with TS can be offered oocyte donation if they desire pregnancy. We searched for studies that reported on the probability of a live birth or viable pregnancy after oocyte donation in TS. Outcomes considered important were live-born children, risk of miscarriage, and complications (eg, pre-eclampsia and aorta dissection). We also searched for studies that compared the effectiveness of achieving a viable pregnancy with different protocols for oocyte donation.

What are the effects of blood pressure treatment on clinical outcomes in TS? (GRADE question 3)

TS is often accompanied by hypertension, which has been linked to the development of aortic dilation or dissection, both observed with strikingly increased frequency in TS. Some experts have advocated for stricter blood pressure control in individuals with TS. Therefore, two questions were formulated: (1) At what blood pressure threshold should hypertension in TS be treated? (2) What anti-hypertensive treatment is most effective in TS? We searched for studies comparing different blood pressure targets and different blood pressure treatments. Cardiovascular disease and mortality were considered relevant endpoints. Randomized as well as non-randomized studies were considered; cohort studies without control arm and case series were ineligible.

What is the optimal approach to estrogen replacement in TS (GRADE question 4)

TS is usually accompanied by hypergonadotropic hypogonadism and primary or secondary amenorrhea. Most TS individuals will therefore need HRT—first for induction of puberty and later for maintaining secondary sex characteristics, attaining peak bone mass, normalizing uterine growth (for possible pregnancy later). This leads to the following question: What is the optimal HRT, mainly focusing on dosing throughout adolescence and adulthood?

Description of search and selection of literature

In cooperation with a trained librarian, a search strategy was composed for seven of the subgroups, specifically to include any research published since the last guideline meeting in 2016. The following databases were searched: PubMed, Embase (OVID-version), and COCHRANE Library. The number of articles retrieved are shown in the flowchart (Figure S1). Screening and exclusion of articles were carried out by the individual subgroups. Three of these subgroups opted to use Covidence software for systematic reviews (<https://www.covidence.org/>) for this process. For the newly added transition group, literature published before 2016 was also included. This group conducted their own search. A complete list of the literature reviewed is available upon request.

Guideline recommendations with rationale

1. Diagnosis and genetics

1.1 Definition and Diagnosis

- **R 1.1** We recommend considering a diagnosis of TS in individuals with female phenotype with a karyotype containing one X chromosome and complete or partial absence of the second sex chromosome, associated with one or more typical clinical manifestations of TS (⊕⊕⊕⊕).
- **R 1.2** We recommend against considering a diagnosis of TS in individuals with one X chromosome and a deletion distal to Xq24 on the other X chromosome, and in women over the age of 50 years with less than 5% 45,X mosaicism (⊕⊕○○).
- **R 1.3** We recommend that the new general surveillance management guideline applies to TS individuals with any karyotype (⊕⊕⊕⊕).
- **R 1.4** We recommend that the surveillance guidelines also apply to individuals with 45,X/46,XY mosaicism with either ambiguous or male external genitalia, regardless of sex of rearing (⊕⊕⊕⊕).
- **R 1.5** We recommend testing for TS in a female individual with typical signs of TS (⊕⊕⊕⊕).
- **R 1.6** When testing for TS, we recommend that a minimum of 30 metaphases be counted on a chromosome analysis as the first-line test. When a rapid test result is needed (eg, prenatally, newborn) other methods can be used as a first-line test (eg, microarray, fluorescence in situ hybridization (FISH), polymerase chain reaction (PCR)), with chromosome analysis as a second line confirmatory test (⊕⊕⊕⊕).

1.1.1 Definition

TS is a sex chromosome disorder that affects phenotypic *female individuals* who have one intact X chromosome and complete or partial absence of the second sex chromosome (Table 1) in association with one or more clinical manifestations.¹ The traditional definition of TS implies the presence of physical

Table 1. Type and frequency of karyotypes associated with TS.

Karyotype	Frequency (%)	Description
45,X	40-50	Monosomy X
45,X/46,XX	15-25	Mosaicism with 46,XX
45,X/47,XXX;45,X/46,XX/47,XXX	3	Mosaicism with 47,XXX
45,X/46,XY	10-12	Mosaicism with 46,XY
45,X/46,X,r(X)	Rare	Ring X chromosome
46,X,i(Xq); 46,X,idel(Xp)	15	Isochromosome Xq; Isodicentric Xp;
46,XX,del(p11)		Proximal deletion of Xp
X-autosome trans, unbalanced	Rare	Various

Table 2. Karyotypes *not* associated with TS.

Karyotype	Description
46,XX,del(p22.3)	Distal deletion Xp22.3 (Leri-Weill syndrome) (SHOX)
46,XX,del(q24)	Premature ovarian insufficiency
46,X,idel(X)(q24)	Isodicentric Xq24

features such as the characteristic facial appearance, with neck webbing and peripheral lymphedema.^{5,6} However, the 2017 Guidelines¹ broadened the clinical manifestations of TS to include features such as linear growth failure (short stature), ovarian insufficiency (pubertal delay), early sensorineural hearing loss, distinctive congenital cardiovascular, skeletal and renal anomalies, a particular neurodevelopmental profile, and a constellation of other conditions with a higher prevalence in TS including hypothyroidism and celiac disease.

As stated in the 2017 TS guidelines, smaller X chromosome deletions may cause distinct features, which are not included in the definition of TS (Table 2). Female individuals with small distal deletions of the short arm of the X chromosome (Xp22.33) where the *SHOX* (short stature homeobox) gene resides, frequently have short stature and other TS-associated skeletal anomalies associated with a *SHOX* deletion,^{7,8} but do not appear to have a higher risk for cardiac anomalies, neurocognitive issues, or ovarian insufficiency.⁹ Those who have a deletion distal to Xq24 frequently have primary or secondary amenorrhea without short stature or other TS features and should be referred to as having premature ovarian insufficiency. In addition, a diagnosis of TS should not be used in women over the age of 50 years with less than 5% 45,X cells in case of symptoms, because 45,X mosaicism may develop in older women due to age-related loss of one of the X chromosomes.¹⁰ In women less than 50 years of age, there has been no specific lower limit for 45,X that defines TS, although many have used 5%.^{11,12} In addition, it has not been determined whether there is a “cut-off” point of the percentage of 45,X below which surveillance does not apply.¹³ Individuals with 45,X/46,XY mosaicism who do not have typical female external genitalia are also excluded from the diagnosis, although we recommend that the guidelines also apply to these individuals due to a similar comorbidity profile (see below).

Table 3. Indications for genetic testing to diagnose TS.*As the only clinical feature:*

Fetal cystic hygroma, or hydrops, especially when severe
 Unexplained short stature
 Left-sided outflow congenital heart defects (excluding BAV)^a
 Unexplained delayed puberty/menarche, failure to progress puberty or secondary amenorrhea
 Infertility
 Characteristic physical features^b

As least two of the following:

Renal anomaly (horseshoe, absence, or hypoplasia)
 Madelung deformity
 Neuropsychologic problems, and/or psychiatric issues
 Multiple typical or melanocytic nevi
 Dysplastic or hyperconvex nails
 Other congenital heart defects (including BAC)^c
 Hearing impairment <40 years of age together with short stature

^aCoarctation; aortic stenosis; mitral valve anomalies; hypoplastic left heart syndrome.

^bDown-slanted palpebral fissures; epicanthal folds; low-set anomalous pinnae; micrognathia; narrow palate; short broad neck; webbing of the neck.

^cPartial anomalous pulmonary venous return/connection; atrial septal defect, secundum type; ventricular septal defects, muscular or membranous; BAV (bicuspid aortic valves).

1.1.2 Indication for testing

Certain features alone would prompt chromosome analysis, including fetal cystic hygroma or hydrops, unexplained short stature, left-sided outflow congenital heart defects (excluding BAV), unexplained delayed puberty/menarche, failure to progress puberty or secondary amenorrhea, characteristic facial and physical features, and infertility (Table 3). Combinations of other features (at least two) are also an indication for testing. These include early sensorineural hearing loss together with short stature, Madelung deformity, renal abnormalities, neurocognitive problems and/or psychiatric issues, multiple typical and/or melanocytic nevi, dysplastic or hyperconvex nails, and other congenital heart defects (including BAV).^{3,14-17}

1.1.3 Diagnostic strategy

Karyotyping is the gold standard test to diagnose TS. We recommend that a minimum of 30 metaphases be counted on a chromosome analysis as the first-line test which can detect approximately 10% mosaicism with 95% confidence limits, consistent with the original 2010 ACMG (American College of Medical Genetics and Genomics) laboratory guideline¹⁸ and the European guidelines for constitutional cytogenomic analysis (2019).¹⁹ TS may also be diagnosed using newer methods such as microarray, and exome- and genome sequencing. Microarray can provide better resolution compared to karyotyping, but has limitations in detecting low level 45,X mosaicism (<10%, though studies show detection as low as 5%),²⁰ and in interpreting structural variants (ie, mosaic isodicentric Xp chromosome). Exome/genome sequencing have the potential to detect mosaicism as low as 5% and the ability to detect smaller Y-chromosome material, as current methods use SRY or centromeric markers.

1.1.4 Karyotype-phenotype analysis

TS is associated with significant phenotypic variability ranging from individuals with classic traits to individuals without apparent observable traits. This clinical heterogeneity constitutes a diagnostic challenge to clinicians. Comparative

studies of karyotype-phenotype in TS are challenged by relatively small cohorts, differences in patient ages, variability in the definition of the clinical features, and general uncertainty regarding the extent of mosaicism in different tissues.¹ It has been hypothesized that all individuals with TS with a 45,X karyotype who survive to birth must have some degree of cryptic mosaicism for a normal cell line in the body, although there is no conclusive evidence for this.²¹⁻²⁴ Although phenotypic heterogeneity exists also within the different karyotype subgroups, some general karyotype-phenotype associations have been established.

- Overall, individuals with TS and a 45,X karyotype have a significantly higher frequency of comorbidities and a higher mortality compared to individuals with other TS karyotypes.²⁵⁻²⁹
- In general, individuals with TS and a 45,X/46,XX mosaic karyotype present with a milder phenotype with left-sided congenital heart defects, obesity and hypertension being less frequent, age at menarche being near-normal and are more likely to experience spontaneous menarche and pregnancies compared to individuals with TS and 45,X.^{26,30}
- In general, individuals with TS and 45,X/47,XXX karyotype also have a milder external and cardiovascular phenotype compared to 45,X, but neurodevelopmental disabilities and mental health domains remain a concern.³¹
- Overall, individuals with TS and isochromosome Xq present with an intermediate phenotype regarding left-sided congenital heart defects and spontaneous menarche, and also seem to have a lower incidence of aortic coarctation.^{26,30}
- Individuals with TS and with 45,X/46,XY seem to have the lowest incidence of autoimmune thyroid disease and severe hearing loss and a low incidence of aortic coarctation.²⁶
- TS individuals with a ring X chromosome *without* functional loss of *XIST* seem to have an increased risk of metabolic syndrome compared with TS individuals with 45,X but in contrast, they appear to have the lowest risk of BAV.²⁶ In TS individuals with a ring X chromosome *and* functional loss of *XIST*, a more severe cognitive phenotype may be seen.

1.1.4.1 45,X/46,XY mosaicism with either ambiguous or male external genitalia.

Although several high-quality studies and reviews³²⁻³⁶ were available at the 2016 Cincinnati Conference, they did not address management of individuals with 45,X/46,XY with atypical female or male external genitalia. 45,X/46,XY mosaicism and its variants (45,X/47,XXY, structural abnormalities of the Y chromosome) have an estimated prevalence of 3-15 per 100 000 newborns,^{37,38} with new data showing a prevalence of 5.6 per 100 000 live-born phenotypically male infants and 2.1 per 100 000 live-born phenotypically female infants. Diagnosis is delayed to a median age of 29 years (male individuals) and 13 years (female individuals),³⁹ and these karyotypes are associated with various phenotypes, accompanied by elevated morbidity⁴⁰ and mortality.³⁹ In most cases, which may remain undiagnosed, there are bilateral testes and a male phenotype. There may also be bilateral streak gonads and a female phenotype, leading to the diagnosis of TS, or a streak gonad with a

contralateral testis, or bilateral testes associated with atypical genitalia.⁴¹ In the latter, patients are classified as having mixed gonadal dysgenesis.⁴² Regardless of the gonadal and genital phenotype, the presence of a 45,X cell line may be associated with short stature and anomalies which are typically seen in TS, including cardiovascular, renal, and autoimmune disorders (Tables S1-S4). However, studies have shown that individuals with 45,X/46,XY mosaicism and ambiguous or male genitalia are less likely to receive appropriate counseling and assessments, highlighting disparities in clinical practice.^{43,44} In addition, when this form of mosaicism is associated with genital ambiguity, there are a series of issues related to gender assignment, surgical procedures, risk of gonadal neoplasms, puberty, hormone replacement, and fertility that have been studied within the scope of DSD⁴² and that are outside the scope of these guidelines.

1.2 Prenatal diagnosis

- **R 1.7** We recommend that fetal echocardiography be performed in case of prenatal diagnosis of TS (⊕⊕⊕○).
- **R 1.8** We recommend that prenatal diagnosis of TS should be confirmed by postnatal karyotyping on blood (⊕⊕⊕⊕).

The availability of screening for TS and screening modalities varies in different countries. TS can be suspected prenatally by abnormal ultrasound, as a secondary finding of abnormal combined first trimester screening low pregnancy associated plasma protein-A (PAPP-A)/increased nuchal translucency, abnormal ductus venosus flow, or high-risk NIPT for TS. The diagnosis of TS can be confirmed prenatally by chorionic villous sampling, amniocentesis, or cordocentesis. If the parents decline invasive testing, the diagnosis should be confirmed postnatally on newborn blood. Regardless of the indication, test procedure, or specific result, genetic counseling by a geneticist, genetic counselor, or pediatric endocrinologist should be offered before and after any prenatal test procedure.

Even though fetuses with TS may exhibit no abnormality on prenatal imaging, ultrasonography plays an essential role in prenatal diagnosis of TS. Abnormalities can be present already in the first trimester and may regress with advancing gestational age.⁴⁵ In the first trimester, markedly increased nuchal translucency (especially in cases of associated cardiac anomalies) is common in fetuses with TS, but is also observed in other genetic conditions, especially chromosome abnormality syndromes and RASopathies, or with fetal structural anomalies.⁴⁶⁻⁵⁰ However, the presence of a frank cystic hygroma increases the likelihood of diagnosing TS.^{46,51} Other ultrasound findings suggestive of TS include left-sided cardiac anomalies, partial anomalous pulmonary venous return/connection and persistent left superior vena cava, renal anomalies, small omphalocele, short femur and fetal growth restriction.^{45,50-54} Depending on fetal TS karyotype, cardiac anomalies are described in 7.8%-72% of prenatal series.⁵⁰⁻⁵³ Due to this high prevalence, fetal echocardiogram should be performed timely after the prenatal diagnosis of TS. Although non-mosaic 45,X fetuses with

marked cystic hygroma and/or fetal hydrops often result in miscarriage, these findings are also compatible with delivery of a viable newborn.⁵⁵ In the absence of ultrasound anomalies, fetuses with mosaic TS diagnosed prenatally as an incidental finding are expected to have a milder phenotype than the ones ascertained postnatally.⁵⁶⁻⁵⁸ Abnormal results in prenatal serum screening (PAPP-A as part of combined first trimester screening, triple or quadruple test) even though not specifically intended to screen for TS, may also suggest this condition.^{59,60} However, these tests may be normal together with normal nuchal translucency thickness.⁵⁹ Up to 42% of TS fetuses are being detected prenatally by first trimester screening.⁵⁹

1.2.1 Non-invasive prenatal testing

- **R 1.9** We recommend that when sex chromosomes are included as part of NIPT, counseling should include information about the clinical validity/performance (⊕⊕⊕○).
- **R 1.10** If NIPT indicates a high risk for TS, we recommend thorough non-directive genetic counseling (informed decision-making) (⊕⊕⊕○).
- **R 1.11** If NIPT indicates a high risk for TS, we recommend that a detailed ultrasound should be performed, and invasive diagnostic testing be offered (⊕⊕⊕○).
- **R 1.12** In case of a high-risk NIPT result for TS and a normal fetal ultrasound where invasive diagnostic testing is not performed or shows a normal result, we recommend offering the pregnant woman karyotyping for maternal sex chromosome aneuploidies (⊕⊕⊕○).

NIPT has had an enormous impact on the field of prenatal diagnosis and is currently the first prenatal screening test to also include TS and other sex chromosome abnormalities. It will potentially increase the number of cases with TS incidentally diagnosed in utero. A recent meta-analysis showed that for TS sensitivity is 98.8% and specificity is 99.4%,⁶¹ whereas positive predicted value (PPV) varies widely (range: 9%-85.2%; mean: 25.4%). However, with an abnormal ultrasound the PPV may be over 85%. The PPV for TS is generally lower than for other SCAs, due to factors such as confined placental mosaicism, maternal constitutional or somatic mosaicism and vanishing twin.^{62,63} Professional medical societies or organizations have provided guidelines regarding the use of NIPT (Table S5) including the ACMG, which has recently recommended screening for sex chromosome abnormalities for patients with singleton pregnancies.⁶⁴ However, all societies emphasize the importance of qualified pre- and posttest counselling and recognize the complexity of prenatal counseling (Table S5).

Important aspects that are specific to NIPT for TS include the limited test validity/performance, and the possibility of incidental detection of a maternal sex chromosome abnormality. Parental emotional distress may result from a false positive result as well as limited predictability of postnatal

phenotype.⁶⁵ The high number of false positive results leads to an undesirable increase in invasive testing.⁶⁶ NIPT should always be offered in conjunction with a detailed ultrasound scan.^{66,67} In case of fetal anomalies or increased nuchal thickness, diagnostic genetic tests should be offered and NIPT should only be considered after extensive counseling or parental demand.⁶⁸

Counseling should emphasize that NIPT is a screening test, and not a diagnostic test. When TS is suspected by circulating free DNA, the possible interpretations may include confined placental mosaicism, TS in the fetus, or TS in the mother⁶⁹⁻⁷¹ and co-twin demise of a fetus with TS. Additional diagnostic genetic testing should be offered after extensive genetic counselling and may include chorionic villous sampling in the setting of a fetal anomaly and early NIPT, or amniocentesis in case of a normal ultrasound and maternal karyotype.^{62,63,66,72,73} Because constitutional karyotype of individuals with prenatally diagnosed TS are uncertain, especially in patients with mosaicism, postnatal confirmation by standard chromosome analysis performed on a peripheral blood sample is indicated, irrespective of prenatal ascertainment.

1.2.2 Pre-implantation genetic testing

- **R 1.13** We recommend that preimplantation testing can be offered to individuals with TS who want to use their own oocytes for pregnancies. TS individuals with mosaicism (45,X/46,XX), who become pregnant spontaneously, should be offered prenatal diagnostic testing (⊕⊕⊕○).

Pre-implantation genetic testing is currently offered to women with recurrent pregnancy loss or repetitive implantation failure after in vitro fertilization procedures although the clinical benefit is an ongoing topic of discussion.^{74,75} Pre-implantation genetic testing can be offered in case of a women with TS and the desire to have children.⁷⁶ However, a sufficient ovarian reserve to obtain sufficient embryos for testing is a prerequisite for applying pre-implantation genetic testing.

1.2.3 Prenatal diagnosis of TS and genetic counselling

When TS is diagnosed prenatally, decision-making about pregnancy continuation can be difficult, and it is critical that the best available information is provided to parents. Physicians and genetic counselors involved in pre- and post-diagnostic counseling need to be fully informed about the prognosis, complications, and quality of life (QoL) of individuals affected with TS, as well as of recent advances in management.^{77,78} The input of a physician with experience in the long-term follow-up of individuals with TS will be valuable to put management of the different comorbidities in perspective. The discussion should include the known variability of the TS clinical features, even within a particular genotype. Of course, the discussion should be tailored to the specific findings of the fetus because decisions regarding termination are often influenced by the presence and severity of an abnormal phenotype.^{53,79} Discussion with support groups, families of girls and women with TS can be very helpful. This is often accomplished through contact with TS support organizations.

1.2.4 Decisions on pregnancy termination

Legislation on termination of pregnancy varies considerably between countries and lack of consensus regarding choice of termination for TS among fetal medicine experts within countries have been reported,⁸⁰ highlighting the existence of ethical and cultural differences. In countries where termination of pregnancy is allowed, rates of termination of pregnancy following prenatal diagnosis of TS vary between 15.4% and 100%.^{59,81,82} Several factors have been found to influence the prospective parents' decision to continue or terminate a pregnancy with a TS fetus. These include fetal ultrasound abnormalities, incidental findings, presence or absence of mosaicism, gestational age at diagnosis, parental age, number of previous children, possibility of infertility, parents' fear/anxiety, parents' socioeconomic status and religious background, ethnicity, but also genetic expertise of the health care provider and the mode, delivery, and explanation of the results,^{81,83,84} pointing to the importance of a balanced and comprehensive non-directive counseling.

1.3 Postnatal diagnosis

- **R 1.14** We recommend screening for Y chromosomal material by PCR or other molecular method in TS individuals with a 45,X karyotype and signs of virilization (⊕⊕○○).

Individuals with suspected TS should have a standard 30-metaphase karyotype as the first-line test (see R.1.6 and section 1.1.3 diagnostic strategy). In cases where the chromosome analysis is normal, and when mosaicism is suspected, additional metaphases should be analyzed. Usually, karyotyping is performed on a peripheral blood sample; however, if blood karyotype reveals 46,XX, but there is a high clinical suspicion of TS based on the phenotype, karyotyping or FISH analysis of a second tissue (eg, skin, buccal epithelium, urine) is indicated.

If a rapid postnatal test result is needed (eg, newborn) other methods than standard karyotyping can be used as a first-line test (eg, microarray, FISH, PCR), with chromosome analysis as a second line confirmatory test (see R.1.6 and section 1.1.3 diagnostic strategy).

In 10%-12% of individuals with TS, a normal or structurally abnormal Y chromosome can be detected by karyotyping, FISH using Y-chromosome probes, PCR with Y-specific probes, or array-comparative genomic hybridization (array-CGH). An abnormal Y chromosome can initially be described as a marker chromosome and may require additional analysis. PCR is more sensitive in detecting Y material than FISH and should therefore be performed in TS individuals with a 45,X karyotype and signs of virilization. Searching for Y chromosome material in all 45,X individuals is not endorsed.¹

1.3.1 Newborn screening

- **R 1.15** We suggest that ethical issues, phenotypic variability, methodological limitations, and feasibility of appropriate genetic counseling be considered prior to adopting newborn screening platforms that identify TS (⊕○○○).

Although there seems to be a tendency towards earlier diagnosis, missed and delayed diagnoses of TS continues to be a challenge. Despite the widespread use of NIPT, this does not routinely include screening for sex chromosome abnormalities necessitating postnatal recognition and testing. When girls with TS are not identified in infancy by characteristic features such as lymphedema and webbed neck, the diagnosis is often made years after growth failure ensues, and sometimes little or no growth potential remains.^{28,85-88} In general, the later GH therapy is initiated, the larger the growth deficit and the lower the likelihood of normal adult stature. This can also delay age-appropriate initiation of therapies for pubertal development. Early diagnosis can also improve QoL by allowing for timely screening and intervention for complications such as strabismus, hearing loss, renal and cardiac abnormalities, hypothyroidism, celiac disease and neurodevelopmental disabilities and mental health concerns. It may also allow for improved fertility in some individuals with TS by enabling earlier oocyte or ovarian tissue harvesting before too many follicles are lost. Greater recognition of the disorder through education and/or population screening is required to encourage earlier diagnosis.

Optimally, existing newborn screening programs would include TS. While karyotyping is the gold-standard technique for diagnosing TS, it has major limitations as a screening tool. This requires specialized personnel and entails a long processing time and greater expense. Alternatively, several molecular methods have been proposed for neonatal screening of TS, the most promising of which thus far are pyrosequencing and real-time PCR.⁸⁹ According to a recent study, real-time PCR testing for TS detection costs \$15 per test. Employing PCR of the *ARSE* and *MAGEH1* genes, all but one patient with TS was detected (albeit only 10 patients with mosaicism were tested) for a detection sensitivity of 95%, and only 0.6% of the newborns required recall for karyotypes.⁹⁰ Subsequently, reverse transcription PCR (RT-PCR) of the combination of *SHOX*, *SRY*, and *VAMP7* was evaluated.⁹¹⁻⁹³ Sensitivity and specificity for detection of *SRY* was 100%, with *SHOX* and *VAMP* being important in detection of structural anomalies and *SRY* for karyotypes with Y material.⁹¹ The technique was determined to be highly reliable for all sex chromosome abnormalities.⁹³ Whole-exome sequencing has also been shown to accurately diagnose TS, including cases with low-level mosaicism, isochromosome Xq, and cryptic Y material.⁹⁴ If molecular screening for TS is offered, positive findings will need prenatal or postnatal confirmation with a karyotype. Like other disorders diagnosed on newborn screening, it will be crucial to develop infrastructure for follow-up, treatment, and support of the newborns diagnosed with TS. A potential downside to screening includes the likelihood that some girls identified with TS will have mild or no apparent TS features and experience minor or no clinical consequences. This may result in unnecessary stigmatization or concern. In the process of screening for TS, other sex chromosome abnormalities, such as Klinefelter syndrome (if both phenotypic male and female individuals are tested), may also be diagnosed and will also need appropriate follow-up.

In the United States, nomination of a condition to the Recommended Uniform Newborn Screening Panel requires a high certainty that screening for the targeted condition would lead to a significant net benefit, that screening has high-to-moderate feasibility and that most state screening programs would be able to implement screening within 3 years.⁹⁵ Studies are needed to evaluate the benefits of newborn screening

for TS. The optimal molecular techniques for diagnosis likewise need to be established. We conclude that prior to considering newborn screening for TS, additional improvements in methodology and systems will be required.

1.3.2 Improving postnatal diagnosis

Improved diagnostics will result from pediatricians, family physicians, and pediatric specialists becoming more aware of TS as a diagnosis. After the 2007 TS guidelines¹ were published in part to optimize the screening for TS, the median age at diagnosis has remained high.^{96,97} The 2017 TS guidelines were developed for a pediatric specialty audience and focusing on general pediatricians as well as neonatologists may improve time to diagnosis. Furthermore, counseling of otolaryngologists to achieve an increased awareness for dysmorphic signs of the external ear and the increased prevalence of hearing impairment due to both conductive and sensorineural hearing loss in TS might also allow for an earlier diagnosis. Given that the most common indication for diagnosis in children is short stature,⁹⁶ a guideline addressing growth disorders for primary care physicians may be helpful as noted in a recent Dutch publication.⁹⁸ It remains to be seen whether an automated population-based screening will allow earlier detection of TS-characteristic growth disturbances. In addition, TS can be recognized in the newborn period by features of lymphedema/neck-webbing, cardiac anomalies, and renal anomalies. It is important that these are recognized, and that chromosomal testing be ordered promptly to ensure that the appropriate medical monitoring and follow up be initiated.

In resource limited countries, facial analysis technology has proven effective in diagnosing TS. Kruszka et al.⁹⁹ used the DeepGestalt model¹⁰⁰ to differentiate TS from unaffected controls and controls with Noonan syndrome in diverse populations.

Clinical recognition of signs and symptoms has been the traditional method of diagnosis for rare diseases; however, as noted in TS, clinicians frequently miss diagnoses. A potential solution is using the data in patient records to identify undiagnosed individuals with TS. One study¹⁰¹ used an algorithm-driven electronic health record approach to search for girls with TS who were initially diagnosed with idiopathic short stature. The algorithm successfully found that 6% of girls with microarray data available had newly diagnosed TS, and that only 62% of girls with idiopathic short stature ever had a karyotype performed. In addition to algorithm-driven electronic health record searches, deep learning/artificial intelligence searches have been successful in finding undiagnosed patients with genetic conditions.¹⁰²

1.3.3 Convincing governments to increase diagnostic measures

Many children throughout the world receive their health care from government-funded programs. These often may not provide coverage for genetic testing. Anecdotal data and our personal practice expertise have shown the importance of early diagnosis and monitoring and prevention of complications such as cardiac events and hearing loss. However, additional studies gathering data to document these benefits is crucial to gaining government support for diagnostic testing.

1.4 New developments in genomics

Over the past decade, new methods and approaches for understanding the genomic nature of TS have become increasingly available, which have contributed to an advanced and refined

picture of the genomics, a highly complex picture, with many layers, pathways, and interactions we do not yet fully understand. The current model indicates that subtle changes in the genome, transcriptome and proteome play in concert, rather than a single gene model explaining all specific phenotypic traits. In addition, gene association studies and pharmacogenetic studies have started to emerge, proposing genetic variants related to specific phenotypic traits and treatment response. In this section, we will highlight recent advances in the genomic field.

1.4.1 The methylome, transcriptome, and proteome in TS

Although there is currently no evidence to support methylation and transcription analysis in TS for the purpose of clinical management, these studies are informative in understanding the biology of TS and its phenotypes.

There is evidence of a unique and tissue-specific genome-wide methylation and transcription landscape in TS extending to both the X chromosome and the autosomes.¹⁰³⁻¹⁰⁹ In general, an overall hypomethylation and gene downregulation is seen in TS across tissues,¹⁰³ and integrative analysis of the methylome and transcriptome have demonstrated several genes with a complementary pattern being both differentially methylated and differentially expressed.¹⁰³ There is also evidence that sex chromosome dosage sensitive genes on the X chromosome regulate specific networks of autosomal genes, indicating an organized regulatory gene network of genes on the X chromosome and autosomes.^{107,110} *ZFX* and *KDM6A* have been highlighted as possible key regulators in these networks,^{103,107,110} as have *AKAP17A*, *CD99*, *DHRX*, *EIF2S3*, *GTPBP6*, *JPX*, *PP2R3B*, *PUDP*, *SLC25A6*, *TSIX*, *XIST*, *ZBED1*, *BDNF*.^{103,110} Enrichment analysis of the differentially expressed genes has revealed enrichment for terms related to the phenotype seen in TS (eg, immune system, coagulation, otologic disorders, liver disease, bone differentiation, glucose metabolism, gonadal, and neural development),^{103,104,111,112} highlighting these genomic changes' involvement in the phenotype of TS. Several candidate genes for different phenotypic traits have been suggested,^{103,106,112-115} but conclusive evidence is still missing, except for *SHOX*, known to be associated with the decreased height in TS¹¹⁶ (for review see Gravholt et al. 2023¹⁷).

The expression of non-coding ribonucleic acid (RNA), including micro-RNAs, circular RNAs and long non-coding RNAs, have been found to be affected in TS.^{104,106,117-120} A relation between specific micro-RNAs and congenital heart defects, aortic deformation, and arterial distensibility may exist.^{117,118} Further studies are needed to elucidate a possible impact of noncoding RNAs in the phenotype of TS.

1.4.2 Gene association studies and pharmacogenetics

Over the past 15 years, efforts have been made to identify genetic variants (single-nucleotide polymorphisms, indels, copy number variations, haplotypes) involved in the phenotypic variability seen in TS. Genetic variants associated with traits such as low BMD,^{121,122} thyroiditis,¹²¹ heart^{121,123-125} and renal¹²¹ malformations, autoimmunity,¹²⁶ obesity,¹²⁷ insulin resistance,¹²⁸ and thrombophilia¹²⁹ have been reported in single studies. Much larger sample sizes are required both from single center and multi-center studies to validate and replicate these findings.

In addition to the above-mentioned studies, a few studies have also emerged with the aim of identifying genetic markers related to growth response to recombinant human GH (rhGH) therapy,

as the growth response varies significantly across individuals. Deletion of exon 3 (d3) in *GHR* (encoding the GH receptor) has been proposed as a genetic marker for predicting response to rhGH. However, the results from studies of girls with TS are contradictory with some finding a significant effect on height velocity, total gain in height and adult height in girls with TS carrying one or two d3 alleles.¹³⁰⁻¹³² Other studies did not find an effect.¹³³⁻¹³⁵ Recently, a large prospective multicenter study assessing the association between genomic markers and short- and long-term rhGH responsiveness identified potential genetic markers and expression profiles for rhGH-induced growth response in children with TS.¹³⁶ However, these findings need to be validated in other larger cohorts of children with TS before being applied in clinical practice.

2. Growth disorders and their management

2.1 Spontaneous growth and the etiology of growth disturbances

Short stature is a common feature and often the presenting concern leading to the diagnosis of TS. Growth failure in TS begins early, often in utero, characterized by mild intrauterine growth restriction,¹³⁷ and with lower placental weight,⁵⁹ resulting in average birth weight ~300-1000 grams and length 1-2 cm below mean values for healthy infants of similar gestational age and country of birth.^{59,138,139} The decline in growth rate, resulting in downward trend across percentiles, is particularly rapid during the first 2 years of life, with an established height deficit by 3 years of age.^{140,141} Linear growth remains suboptimal in childhood and the estrogen-mediated pubertal growth spurt is minimal or absent, resulting in an average adult height ranging from 138 to 147 cm, depending on the country; this represents a deficit of ~20 cm (−3 SD) compared with population means for many countries.^{139,142,143} Country-specific reference standards for growth curves have been compiled for TS¹⁴⁴ (Table S6).

Absence of the *short stature homeobox-containing (SHOX)* gene in the pseudo-autosomal regions of the X chromosome is primarily responsible for the short stature and skeletal dysplasia in TS.^{7,145} However, perturbations in GH and insulin-like growth factor-I (IGF-I) physiology,^{146,147} including resistance to IGF-I,¹⁴⁸⁻¹⁵⁰ and estrogen deficiency¹⁵¹ may also contribute to impaired linear growth. Short stature in TS affects the limbs more significantly than the trunk, resulting in disproportionate growth, with a longer trunk than legs (increased sitting height to height ratio).^{152,153} TS is also associated with increased prevalence of skeletal anomalies, including scoliosis, kyphosis, cubitus valgus, genu valgum, Madelung deformity of the wrist and short fourth and fifth metacarpals and metatarsals.^{154,155}

2.2 Growth hormone treatment

- **R 2.1** We recommend offering GH treatment early, because growth failure in TS starts before birth and is rapid during the first years of life, and early GH treatment can prevent further loss of height potential. Treatment may be offered from as young as 2 years of age in the following circumstances: evidence of growth failure (rate of growth below normal or declining), short stature, or likelihood of

short stature. GH treatment may be offered later, as long as epiphyses remain open (⊕⊕⊕○).

- **R 2.2** We suggest that GH treatment may be continued until little growth potential remains (bone age ≥ 14 years and/or height velocity < 2 cm year⁻¹). There is no physiological rationale for continuing GH treatment into the transition period after epiphyseal closure (⊕⊕⊕○).

The purpose of growth-promoting therapy in TS is to prevent progressive growth failure, facilitate the attainment of height during childhood that allows puberty to begin at a similar age to peers, and to result in adult height that minimizes physical and potential psychosocial barriers. GH, the primary therapeutic agent, increases height velocity and results in modest increases in adult height for most patients.¹⁵⁶ Furthermore, as most girls with TS will require estrogen therapy to either initiate or complete puberty prior to completion of linear growth, the estrogen route, dose, and tempo of dose escalation will have an impact on pubertal growth and, therefore, on AH. While GH may be continued until adult height is attained, treatment may be individualized with the option to discontinue GH if the individual is satisfied with her height or attains a height within the normal range for the adult female population.

Although GH treatment is considered standard, growth promotion itself, or early treatment initiation, may not be appropriate for every child. We therefore recommend that the initiation of GH be individualized, and the potential advantages, disadvantages and burdens of treatment be discussed to allow shared decision-making. GH is available in many countries around the world (Table S7).

2.2.1 Effectiveness of GH treatment

Despite numerous studies of GH treatment in TS, only six randomized, controlled trials (RCTs) have compared GH treatment with a concurrent non-treatment or placebo control for at least one year¹⁵⁷⁻¹⁶² and only two of these trials have followed non-GH-treated participants to adult height.^{158,160} Based on three studies published between 1998 and 2005,^{158,159,161} a 2007 Cochrane Center review¹⁵⁶ concluded that girls treated with GH grew 3 cm year⁻¹ more than untreated girls in the first 12-18 months of therapy; after 2 years of treatment height velocity was ~ 2 cm year⁻¹ greater for treated than untreated girls in the study that continued the control arm long term.¹⁵⁸ Since publication of the Cochrane review, a double-blind, placebo-controlled trial to adult height¹⁶⁰ and a 2-year RCT evaluating the impact of GH initiation before age 4 years¹⁶² followed by a 10-year extension study to adult height¹⁶³ have been published. Individuals with TS treated to (near-) adult height had average gains compared with randomized concurrent non-treatment¹⁶⁴ or placebo,¹⁶⁰ baseline predicted^{165,166} or projected height^{159,164,167*} ([*Baseline predicted adult height is typically calculated using the patient's baseline height, age, and bone age (eg, according to the methods of Bayley and Pinneau). Baseline projected adult height is calculated by extrapolating the patient's baseline Turner-specific height SDS to adult height SDS using the same Turner standard.]), or historical

controls,¹⁶⁷ ranging from ~ 5 to 8 cm over periods of 5.5 to 7.6 years.^{159,160,164,167} A subsequent meta-analysis concluded a similar effect of GH therapy, reporting mean adult height gain of 7.2 cm,¹⁶⁸ based on data from the two RCTs that followed non-GH-treated subjects to adult height.^{158,160} Two European studies using high GH doses at young ages have demonstrated much more dramatic gains of 15-17 cm (mean) vs baseline projected adult height.¹⁶⁹⁻¹⁷¹ Although there is marked variability in response to treatment, in aggregate, there appears to be approximately 1 cm of gain in height for every year of GH treatment. In the two clinical trials that maintained long-term untreated/placebo controls, adult height was within the normal range for 40%-50% of treated individuals vs. 4%-16% percent of non-GH treated individuals.^{158,160} Results from large observational studies have confirmed similar short term growth improvement (average height SDS increase of 0.8 ± 0.7 after an average of 3.2 ± 2 year of treatment)¹⁷² and adult height gain (median near adult height gain $+1.07$ SDS over baseline height SDS)¹⁷³ but with significant individual variability.

In summary, if catch-up growth brings height within the normal range within the first 2 years of treatment, and height velocity subsequently is maintained close to the mean for age, adult height is likely to fall within the lower normal range for most GH-treated individuals.^{163,174} Caution should be exercised interpreting height SDS changes during the typical time for puberty, as absent or minimal pubertal growth spurt often results in partial loss of the relative pre-pubertal height SDS gain.¹⁷⁴

2.2.1.1 Factors influencing the effectiveness of GH treatment.

Various factors are associated with long-term height outcomes following GH treatment, including intrinsic (non-modifiable) factors, and extrinsic aspects of treatment that may be subject to management decisions. Overall, factors predictive of taller adult height include taller baseline height prior to GH initiation, tall parental heights (ie, mid-parental height), younger age at initiation of therapy, longer duration of treatment (especially pre-pubertal treatment duration) and higher GH dose.^{162,171,175,176} Because of the wide variability of adult height outcomes following GH treatment, mathematical prediction models have been developed with the goal of providing accurate information for long-term outcomes (height gained and height attained).¹⁷⁷ However, the complexity of these models has impeded their use in clinical practice. Additional intrinsic genetic variations^{132,178} are also associated with GH responsiveness in TS but such detailed genetic analyses are not currently available for routine clinical use. Characteristics such as the patient's baseline height and mid-parental height, while not modifiable, may provide useful information to facilitate realistic expectations of treatment outcomes. Modifiable factors that impact GH treatment outcomes include age at initiation of treatment, GH dosing strategies and management of pubertal induction with low-dose estrogen.

2.2.1.2 Age at GH initiation.

Younger age at treatment initiation,^{158,162,163} including at least 4 years of treatment prior to puberty,^{175,179,180} is associated with greater GH treatment effect. Early GH treatment in TS prevents further growth failure^{162,163,180} and provides the opportunity to maintain height within the age-appropriate normal range. In the long-term

extension of the Toddler Turner Study, the early treated girls were taller at all key childhood timepoints and at puberty.¹⁶³ Early treatment (around 2-6 years of age) is likely to result in greater height gains during childhood and facilitate pubertal induction at an age closer to that of typical female puberty,¹⁸¹ such that the goals for both greater adult stature and near-normal timing of puberty can both be achieved.¹⁷⁴ Although early GH treatment is optimal, late initiation of GH therapy may nevertheless result in meaningful height gains for individuals whose diagnosis is delayed,^{182,183} particularly in those with delayed bone age.¹⁸² However, such gains were at the expense of markedly late puberty,^{174,183} and the height gain was negatively correlated with age at GH initiation.¹⁸²

2.2.1.3 GH dose.

- **R 2.3** We recommend a starting GH dose of 45-50 $\mu\text{g kg}^{-1} \text{ day}^{-1}$ or (1.3-1.5 $\text{mg m}^{-2} \text{ day}^{-1}$) in most instances, increasing up to a maximum of 68 $\mu\text{g kg}^{-1} \text{ day}^{-1}$ (2.0 $\text{mg m}^{-2} \text{ day}^{-1}$) if response is suboptimal and/or adult height potential remains substantially compromised ($\oplus\oplus\oplus\circ$).

GH therapy for TS is generally recommended to be initiated at a dose of 45-50 $\mu\text{g kg}^{-1} \text{ day}^{-1}$ or (1.3-1.5 $\text{mg m}^{-2} \text{ day}^{-1}$) administered daily, although there are regional variations in GH regimens for TS guided by regulatory limitations. Higher GH doses are not routinely recommended, but following careful discussion of potential risks and benefits, such as possible mild, reversible dose-dependent higher insulin concentration with normal glucose,^{169,184} an increase in GH dose up to 68 $\mu\text{g kg}^{-1} \text{ day}^{-1}$ (within the authority-approved dose range) may be considered in individuals with very poor height prognosis, or inadequate response to standard GH dosage.

Optimal GH dosing is important, especially during the first year of therapy when the most rapid catch-up growth response occurs. Despite initial catch-up growth, the overall height gain is gradual and incremental, and it is important to set realistic expectations of adult height outcomes. Families should also be advised of the importance of treatment adherence. Observational data¹⁸⁵⁻¹⁸⁸ show reduced efficacy when prescribed doses are lower than recommended doses. Similarly, titration of GH dose based on IGF-I values may result in a suboptimal weight-based dosing of GH, with reduced height gain and adult height outcomes. Poor adherence¹⁸⁹ to prescribed doses and early treatment discontinuation¹⁹⁰ may also result in lower height gain.

2.2.2 Safety of GH treatment

Data on safety of GH treatment in TS in long-term prospective clinical and observational trials have generally been reassuring with respect to blood pressure and risk factors for cardiovascular disease,^{173,185,186,188,191-199} carbohydrate and lipid metabolism,^{192,200-202} body composition,^{192,202} bone mineralization,^{203,204} body proportions,^{191,205,206} and prevalence of otitis media and hearing loss²⁰⁷ relative to cohorts of non-GH treated individuals with TS. However, it is important to recognize that clinical trials are not powered for safety endpoints, hence caution should be exercised in their interpretation. Large observational studies that have adequate patient numbers

to detect rare adverse outcomes^{173,198,199,208-213} provide more robust assessment of the longer-term safety of GH. However, the interpretation of safety data is complicated by use of varying comparator groups (concurrent TS, historical TS, other GH-treated non-TS, general population) and statistical methodologies.

2.2.2.1 Intracranial hypertension and skeletal issues.

Individuals with TS appear to be at increased risk of intracranial hypertension and slipped capital femoral epiphysis²⁰⁸ as well as scoliosis^{173,198,208} during GH treatment compared with children with idiopathic GH deficiency or idiopathic short stature. Scoliosis is common in TS regardless of GH therapy, and may be exacerbated by the rapid increase in linear growth stimulated by GH,²¹⁴ but two studies demonstrated no increased risk of developing scoliosis or worsening existing scoliosis with GH therapy^{160,215} in TS. Improvement of skeletal disproportion in some individuals with TS was reported with GH therapy in one study.²⁰⁶

2.2.2.2 Lymphedema. In one retrospective study, a higher prevalence of lymphedema was seen in individuals with TS treated with GH compared to untreated individuals, likely reflecting a more severe phenotype in those treated,²¹⁶ but no data were provided on the impact of GH therapy on prevalence or acute worsening of lymphedema.

2.2.2.3 Neoplasia. Although neoplasia has been reported rarely in GH-treated and non-GH-treated individuals with TS,²¹⁷⁻²²¹ data from GH registries provide no evidence of an increase in risk of neoplasia with treatment.^{173,208,222-224} Although there is no reported evidence for an effect of GH treatment on risk for development or progression of nevi in girls with TS, the product labeling for somatotropin (GH) in the USA advises that patients should be monitored for increased growth or potential malignant changes of pre-existing nevi.

2.2.2.4 Mortality. No overall increase in mortality due to GH relative to other GH-treated pediatric populations has been reported in individuals with TS followed in the GH registries.^{173,197,208,225} Although one multinational European registry study (SAGhE consortium) described an increase in standardized mortality ratio for moderate risk group of GH-treated children (which included patients with TS along with other genetic syndromes like Prader Willi syndrome, Noonan syndrome, multiple pituitary hormone deficiencies, Cushing syndrome, benign pituitary tumors, severe craniofacial malformations, and severe chronic pediatric diseases), these patient groups were compared to the general population instead of untreated controls, and there was no association with daily or cumulative GH dose, suggesting that the excess mortality may not be related to a GH treatment effect.²¹¹

2.2.2.5 Carbohydrate metabolism. Patients with TS are inherently at increased risk of disorders of carbohydrate metabolism^{226,227} and have a specific defect in glucose-stimulated insulin secretion.^{227,228} Although alterations of glucose/insulin metabolism have been reported during or following GH treatment in TS,^{169,184} no permanent negative effects of GH treatment on insulin sensitivity or beta-cell secretory capacity have been observed.^{229,230} One observational study reported

an increase in type 2 diabetes compared with rates in the general population,²³¹ but no increases were reported in analyses from other observational databases.^{173,199,208,210} Furthermore, no increase in the prevalence²¹⁰ or incidence²¹⁶ of type 1 or insulin-requiring diabetes has been reported. Improvements in body composition, abdominal adiposity, lipid profile and blood pressure resulting from GH therapy may have a beneficial effect on cardiometabolic status.²¹⁶

2.2.2.6 Aortic disease. The risk of aortic dissection in TS is increased in those with increased aortic diameter.²³² Studies examining the effect of GH exposure on aortic diameter have yielded conflicting results²³³⁻²³⁶ and their clinical implications remain unclear. This is an area that warrants further investigation. Presently there is insufficient evidence that GH treatment increases the risk for aortic disease or dissection in TS.

2.2.3 IGF-I: physiology in TS and role in monitoring GH treatment

- **R 2.4** We recommend monitoring the response to growth-promoting treatment by measurement of height approximately every 6 months and plotting on a standard (reference female population) and/or TS-specific height chart. Maintenance of height percentile equivalent to, or greater than, the pre-treatment height percentile on a female population-based growth chart or increasing percentile on a TS-specific height chart, provides evidence of treatment effect (⊕⊕⊕○).
- **R 2.5** We recommend monitoring GH therapy by measurement of IGF-I at least annually. We suggest generally maintaining IGF-I within the normal range for age, pubertal stage, and sex. GH dose reduction may be warranted for persistently high IGF-I values (⊕○○○).

Published guidelines by professional societies have recommended monitoring IGF-I and adjusting GH therapy to keep IGF-I concentrations generally within the normal ranges for age and sex in children with various growth disorders.²³⁷ However, the evidence for this approach in TS is questionable, both from an efficacy perspective and a safety standpoint. IGF-I values in non-GH-treated girls with TS are generally in the low-normal range^{146,150,162} and multiple lines of evidence have demonstrated relative IGF-I resistance in girls with TS.^{148-151,162} IGF-I values more than 2 SD above the mean for age and sex are common during GH treatment¹⁹⁹ suggesting that these patients likely require supranormal circulating IGF-I concentrations to elicit an adequate growth response to GH treatment. Modest correlations between growth response and GH-treated IGF-I values have been reported in some studies^{162,238} but not others.²³⁹ In addition to the variability of IGF-I responses to GH in TS, and significant intra-individual variation in IGF-I values, there are methodological challenges associated with measurement of IGF-I in general²⁴⁰⁻²⁴² and significant disparity among IGF-I assays, particularly at the upper end of the IGF-I concentration

range.²⁴³ These challenges raise questions regarding the validity of assigning an IGF-I value of +2 or +3 SDS as a flag for GH dosage reduction and warrant further study in TS. To mitigate the impact of intra-individual and inter-laboratory variation, IGF-I should preferably be measured consistently at the same reference laboratory, and attention should be paid to factors that may increase IGF-I variability, such as time of day, pubertal stage, nutritional status or obesity, and presence of intercurrent illness.²⁴⁰

Although concerns have been raised regarding associations between elevated IGF-I and neoplasia in epidemiologic studies of adult populations,²⁴⁴ there is no evidence for such an association in TS. Nevertheless, because the potential long-term risk remains unresolved, we suggest a cautious approach by monitoring IGF-I approximately annually and considering dosage adjustment for values persistently above the normal range for age when measured under consistent conditions, with individualization of treatment goals.

2.3 Concomitant treatment with the anabolic steroid oxandrolone

Addition of oxandrolone, which has been used off-label for decades, produces synergistic increases in growth response during GH treatment,²⁴⁵⁻²⁴⁹ and systematic reviews^{250,251} confirm a positive effect on adult height gain (2-4 cm). To minimize unwanted effects of delayed breast development and dose-dependent virilization,²⁴⁵ previous guidelines recommended adding oxandrolone for those TS patients with a poor height prognosis or suboptimal response to GH alone, only around the age of 10 years, initiated at a dose of 0.03 mg kg⁻¹ day⁻¹ and maintained at no greater than 0.05 mg kg⁻¹ day⁻¹. Oxandrolone therapy was associated with a lower HDL cholesterol,²⁵² but no negative impact on body composition, skeletal disproportion,²⁵² hearing²⁵³ or neurocognition.²⁴⁷ However, oxandrolone has been unavailable in many countries, and the US Food and Drug Administration (FDA) withdrew marketing approval for oxandrolone in 2023 based on adverse event reporting (<https://www.federalregister.gov/documents/2023/06/28/2023-13733/gemini-laboratories-llc-et-al-withdrawal-of-approval-of-one-new-drug-application-for-oxandrin> [federalregister.gov]).

Although there is no information indicating whether these adverse event issues were related to the use of oxandrolone in girls with TS, based on the position taken by the FDA, the Guidelines Committee no longer recommends the use of oxandrolone in TS at this time. However, physicians who choose to prescribe this medication in jurisdictions outside the USA may do so according to local guidelines, with discussion of efficacy and safety, and with full disclosure of the benefits and risks.

2.4 Concomitant treatment with prepubertal ultra-low dose estrogen

- **R 2.6** We suggest not to routinely add very low-dose estrogen supplementation in the prepubertal years to further promote growth (⊕⊕○○).

One double-blind, placebo-controlled trial using ultra-low-dose oral ethinyl estradiol as a growth-promoting agent

during the prepubertal period combined with GH, followed by a standardized incremental pubertal induction regimen, demonstrated a modest synergistic increase in adult height, normalization of the timing of thelarche for about one-quarter of the girls, and modest improvements in cognition and memory within specific developmental windows.^{160,181,254,255} An additional RCT that used a similar regimen but with higher ethinyl estradiol doses found no long-term growth benefit from prepubertal estrogen treatment.¹⁶¹ The formulation, route, and dosing of childhood estrogen have not been optimized. Hence, until further studies are undertaken, the addition of prepubertal very-low-dose estrogen replacement as a growth-promoting therapy is currently not recommended.

2.5 Other growth promoting therapies

Long-acting GH preparations have been approved for the treatment of GH deficiency²⁵⁶ and several trials in children with TS are underway (<https://clinicaltrials.gov/>). A single 2-year retrospective study showed that pegylated GH was comparable to daily GH injections in terms of growth promotion, without unexpected serious adverse effects.²⁵⁷ Though encouraging, these preliminary, non-randomized data are insufficient to recommend long-acting GH for the treatment of short stature in girls with TS, and data from registration studies are not yet available.

Limited studies^{258,259} have shown that limb-lengthening procedures (distraction osteogenesis) can result in substantial height increase in women with TS. However, the complication rates for these procedures are still unacceptably high²⁵⁸ and therefore this treatment is not recommended.

2.6 Short stature and quality of life

Height is only one of many factors that affect QoL in TS. The methodology to assess impact of GH treatment on QoL in TS is not robust and the data are inconsistent or inconclusive.²⁶⁰⁻²⁶² Hence the decision to offer GH treatment for a child with TS should involve a candid discussion of the advantages and disadvantages, risks and benefits, knowns and unknowns of GH therapy and incorporate the patient's and family's values and preferences to facilitate shared decision-making.

3. Puberty and sex hormone treatment

3.1 Introduction

TS is usually accompanied by hypergonadotropic hypogonadism due to gonadal dysgenesis and ensuing primary or secondary amenorrhea. The risk and timing of premature ovarian insufficiency in TS varies. More than one third of girls with TS develop signs of puberty, in non-45,X patients this is twice as common. Only one in five girls has spontaneous menarche, and the chance for spontaneous pregnancy is about 10%, again more common in women with mosaic karyotype.^{11,263-267} This means that most girls and women with TS require or will require HRT at various times and for various reasons.

Literature review and expert opinion of current knowledge about puberty and approaches to HRT in TS are presented. A summary of the issues discussed, and questions raised are presented in [Figure 1](#).

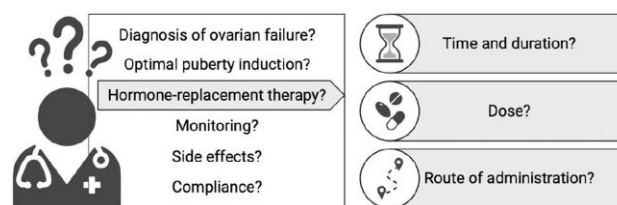


Figure 1. Summary of the issues discussed and questions raised in relation to puberty and HRT.

3.2 Laboratory and ultrasound markers of ovarian function

- R 3.1** We recommend measuring Luteinizing hormone (LH), follicle stimulating hormone (FSH) and anti-Müllerian hormone (AMH) at 8-9 years and yearly until 11-12 years to enable timely referral for fertility preservation if appropriate (⊕⊕⊕○).

LH and FSH are basic markers in the assessment of ovarian function. Circulating concentrations of both FSH and LH present a biphasic pattern in TS individuals with hypogonadism: elevated after birth, declining to values similar to girls with normal ovarian function during mid-childhood, and rising again in the peripubertal years, or at the time of loss of ovarian function.²⁶⁶⁻²⁶⁸ We recommend measuring FSH and LH at 8-9 years old to have time to track changes and allow timely referral for fertility preservation if appropriate. If gonadotropins are normal for age, we recommend continued observation for spontaneous puberty, with future replacement therapy if gonadal failure occurs. FSH values ≥ 6.7 IU L⁻¹ in 6-10-year-old girls have been reported to reflect a higher rate of ovarian insufficiency.²⁶⁷

Low AMH and undetectable inhibin B can also be used to predict ovarian insufficiency in TS, and we recommend measuring AMH along with FSH and LH during assessments.^{266,269-271} Measurable AMH concentration are positively associated with spontaneous breast development and spontaneous menarche.²⁷² AMH <4 pmol L⁻¹ has been shown to suggest absence of puberty.^{270,273}

A higher frequency of primary amenorrhea is more common in individuals with 45,X than compared to those with 45,X/46,XX.^{26,274-276} Despite this evidence, it is also true that the correlation between karyotype and phenotype is highly variable as evidenced by cases of repeated pregnancies in multiple patients with 45,X.

The results of pelvic ultrasound in girls with TS have not yet proven useful as a marker of spontaneous puberty. Both ultrasound ovarian visualization²⁶⁷ and uterine volume in comparison to prepubertal controls²⁷⁷ did not help predict spontaneous puberty. Because very low concentrations of serum E2 in healthy prepubertal girls seem to have minimal impact on uterine growth, this suggests that ultra-low-dose E2 may also not be beneficial to uterine growth during the prepubertal period in girls with TS.

3.3 Estrogen replacement therapy

- **R 3.2** We recommend initiation of low dose estrogen replacement between 11 and 12 years of age, if FSH is elevated on at least two sequential measurements. Estrogen dosage should be increased slowly to adult replacement dosage over 2-4 years (⊕⊕⊕○).
- **R 3.3** In individuals with a later diagnosis (>12 years) with short stature and continued growth potential, we suggest initiating treatment with low dose 17β-estradiol (E2) simultaneously with GH (⊕○○○).

Most girls and women with TS will require HRT for initiation or progression of puberty and/or maintaining the female endocrine milieu. The goal of pharmacologic puberty induction in TS should be to mimic physiology as closely as possible to support longitudinal growth and to gradually induce physiological estrogen-dependent development at an age and at a tempo within normal range for girls without TS. Continuous information and guidance adapted to the girl/woman's needs should be given by the health care provider(s). If gonadotropins (FSH in particular) in repeated samples (two or more) measured yearly from age 8-9 years are clearly elevated without any pubertal signs on physical exam, the girl with TS will need HRT. Information and discussion on "how" and "when" can preferably start at age 10 years, anticipating actual E2 start will not take place for another 1-2 years. Being well prepared and informed contributes to the sense of security and confidence in girls with TS and their caregivers.

Pubertal induction should start between 11 and 12 years old if there is evidence of gonadal failure based on repeatedly elevated FSH and no spontaneous thelarche. Pubertal induction should start with very low doses of E2 to allow continued linear growth, followed by increasing doses at a tempo mimicking serum E2 values in girls without TS.²⁷⁸ In addition to the psychosocial advantage of reaching puberty concurrently with peers, using physiological age as a guide to the initiation of HRT supports normal bone mineral accrual (discussed below). Recommended dosing and schema for tempo of increasing dosage are discussed below.

Some girls with TS are not diagnosed until they fail to enter puberty or have secondary amenorrhea. In these situations, if there is still linear growth potential and open epiphyses, GH treatment can be initiated at the same time as low dose estrogen treatment. This recommendation can be theoretically justified but has not yet been scientifically evaluated in this age group. Caution is needed to not give too high an estrogen dose and thereby cause too rapid bone maturation hampering remaining growth potential. For girls with TS who are diagnosed later and have completed their growth, estrogen dosing does not have to start as low and can increase more quickly.

3.4 Type, dose, and route of estrogen(s) administration for HRT

- **R 3.4** We suggest E2 transdermal (TD) route when possible, with oral E2 as second choice. Ethinyl estradiol has more risks but is better than no treatment (⊕⊕○○).

3.4.1 Type of estrogen

17β-estradiol (E2) is the natural physiological form of estrogen and is the preferred option. It has been shown to be effective in maintaining and improving BMD, increasing uterine size and has some beneficial effects on endpoints relating to cardiovascular outcomes. In addition, it tends to lower BP, improve liver function tests, and increase HDL cholesterol in women with TS.²⁷⁹⁻²⁸¹ Estradiol valerate may also be used because it is quickly converted to E2 in the gut and liver and provides stable serum E2 concentrations.²⁸²

Other estrogens include ethinyl estradiol and conjugated equine estrogens. Conjugated equine estrogens are no longer recommended because they increase the risk of venous thromboembolism, they are a non-standardized mixture of many different estrogens and metabolites, and there are more physiological alternatives.²⁸³ Ethinyl estradiol is a potent synthetic E2 analogue, widely used in the combined oral contraceptive pill and, historically, has been used as HRT in women with premature ovarian insufficiency including those with TS. It is long-acting; therefore, it cannot mimic the typical diurnal variation seen in early puberty, and serum concentration of E2 cannot be measured meaningfully while on ethinyl estradiol. It also has an adverse cardiovascular and metabolic profile and, pertinent for women with TS, it tends to increase blood pressure and is linked with an increased risk of venous thromboembolism.²⁸³ Nevertheless, the combined oral contraceptive pill may be more attractive to younger women needing HRT because it is peer-friendly and user-friendly, inexpensive, accessible, gives good cycle control and provides contraception for those with residual ovarian function who wish to avoid pregnancy.²⁸¹ If contraception is required, combined oral contraceptive pills containing estradiol valerate are now available. An example is Qlaira® (estradiol valerate 3 mg → 1 mg + dienogest). Theoretically, this should provide good estrogen replacement as well as contraception.

3.4.2 Route of administration

There have been few studies comparing the efficacy of oral and transdermal (TD) E2 and minimal evidence to guide choice of formulation.²⁸⁴ E2 is available for both transdermal and oral use. The transdermal route is the most physiological form and is recommended for replacement therapy, based on the risk of potentially harmful liver metabolites when the oral route is used. A RCT comparing the metabolic impact of oral E2 versus TD E2, found that oral administration resulted in a disproportionate, significant accumulation of genotoxic estrogens compared with TD administration.²⁸⁵ Genotoxic estrogens are mutagenic metabolites which have been linked to breast carcinogenesis in post-menopausal women. Additionally, the TD route resulted in E2, estrone, and bioestrogen concentrations closer to normal compared to oral HRT.²⁸⁶ However, TD patches may fail to adhere well in girls with skin conditions such as eczema and they may also cause skin irritation, both limiting their use. This can be alleviated by replacing a patch on a new site (see options under "Dose of estrogen" below). Distribution problems from the drug companies have been a recent problem. Patch doses have primarily been adapted to postmenopausal women, making off-label use necessary even though cutting matrix patches into smaller pieces has been shown to work nicely.^{287,288}

The oral route has long been used and reports on satisfying development of secondary sex characteristics and growth are

available.^{289,290} However, a drawback is that tablets are available in fixed doses, and it is difficult to divide into smaller doses. The lowest dose available is 0.5 mg but is only available in a few countries. Even though the transdermal route is theoretically attractive, it has not been shown scientifically whether any route is superior to the other in a lifelong replacement situation in TS or in any other hypogonadal group. An initiative to gather and share data from TS girls worldwide through an ESPE-supported registry is in process.²⁹¹ A large recent review showed the effect of E2 was superior to ethinyl estradiol and conjugated equine estrogens for BMD without difference according to route of administration. However, oral E2 gave rise to a greater increase in HDL cholesterol than TD E2 indicating a potential cardioprotective effect, but this would need to be balanced against the pro-thrombotic effects in a large-scale long-term prospective trial.²⁸⁰

Taken together, there is not strong evidence against oral E2 and perhaps some benefit to HDL cholesterol but based on the more physiologic route of TD E2 and the potential for lower dosing during puberty, we continue to suggest preference for the TD route and encourage ongoing longer term prospective studies. However, we also stress the importance of patient preference in the decision to increase adherence to treatment. We acknowledge that different formulations may not be available in all countries.

3.4.3 Dose of estrogen

The challenge for pubertal induction with both routes is to start with a low enough E2 dose. For girls without spontaneous puberty, initial dosing needs to be low and dose increments can be individually increased over 2-2.5 years to a serum concentration corresponding to reference range for an adult woman.²⁹² A physiological tempo is the goal, which can be more rapid in an older girl to support her psychological and social wellbeing.

In early puberty there is a diurnal variation with E2 serum concentrations increasing first during night-time and very early morning. In mid-puberty, the diurnal variation ceases, and serum E2 concentrations increase until menarche followed by the estradiol–progesterone cyclic variation of the adult fertile woman. Several schemes for dosing have been published over the last few years to mimic this diurnal variation and require multiple dose changes and patch applications.²⁹¹⁻²⁹³

Low dose is important for two reasons. First, to mimic typical pubertal progression. Second, to allow adequate time for linear growth because estrogen has a dual effect on the growth plate: initially stimulatory but also leading to physeal fusion at higher concentrations. Even ethinyl estradiol, generally not recommended for puberty induction, but used in ultra-low doses and gradually increased, resulted in favorable adult height.^{160,181,294}

While no rigorous long-term prospective study to adult height has been performed comparing E2 preparations (oral vs. TD), using doses that reach the same plasma concentrations of E2, one observational cross-sectional analysis suggested that the impact on adult height of these E2 regimens used for pubertal induction was comparable.²⁹⁵ Additional studies are needed to evaluate the optimal routes and dosages of estrogen replacement for pubertal induction in TS.

For girls with arrested pubertal maturation, E2 replacement starting dose should mimic a serum concentration corresponding to her spontaneous puberty stage.²⁸⁷ Even if a

physiological tempo is the goal, in an older girl a higher dose increment tempo may support her psychological and social wellbeing.

Ethinyl estradiol is not recommended for pubertal induction. For estrogen replacement after attainment of pubertal induction, ethinyl estradiol has been shown to be inferior to E2 for bone health, and therefore higher doses may be beneficial. In healthy older adolescents taking the combined oral contraceptive pill for contraception, a dose of >20 mcg ethinyl estradiol is advised to allow ongoing bone mass accrual.²⁹⁶ This means that combined oral contraceptive pill containing 30 mcg ethinyl estradiol is advised, at least until peak bone mass has been achieved. It is useful to remember that a standard oral contraceptive pill is taken for 21/28 days and that a woman with TS will therefore be hypoestrogenic during the pause. It is possible that modern extended regimens, without a pause, would be more effective for BMD. Following this, the dose will depend on other outcomes and variables such as blood pressure and lipid profile. Based on the literature and expert opinion, to mimic physiology, to individualize the approach, and be familiar with different situations and dose availability worldwide, we recommend the following E2-dose escalation protocol for puberty induction in girls with TS (Table 4). It is practically important to integrate each of the variables in Table 7 to optimize decisions about treatment. Note that if a patch falls off or is removed from the skin prior to the previously prescribed dosing interval, it can be replaced as soon as possible/practical as an effect is only present while patch is in place. If skin problems occur, patch can be removed before the prescribed interval and a new patch is attached on another site. Dose delivery is dependent on contact time and more frequent changes of patch does not result in an increased dose. Additionally, some patches are designed to be applied twice weekly and some weekly. It is important to check patient knowledge of regimen and product provided to ensure the estrogen delivery is as desired.

3.5 Progesterone replacement therapy

- **R 3.5** We recommend adding cyclic progesterone once breakthrough bleeding occurs (mostly this will be after about 18-24 months of unopposed estrogen exposure but this can occur later based on pubertal stage, serum E2 and uterine growth, endometrial thickness, and estrogen dose). The preferred option is micronized progesterone 200 mg for 10-12 days per month (⊕⊕⊕⊕).
- **R 3.6** We suggest combined sequential E2 and progesterone dosing in young women since they are more likely to experience abnormal uterine bleeding. A combined continuous regimen is an option when the endometrium is more stable (⊕○○○).

Progesterone or a synthetic progestin is added towards the end of pubertal induction. The primary indication for adding progesterone is endometrial protection. This allows the proliferative endometrium, stimulated by estrogen, to become secretory, avoiding hyperplasia, a forerunner of endometrial

Table 4. Recommended 17 β -estradiol (E2)-dose escalation for puberty induction in girls with TS.

Timing early onset or late onset with growth potential ^a Initiation 11-12 years old (if FSH high)	Timing late diagnosis without growth potential	TD E2 dose ^a	Oral E2 dose ^b	Breast stage goal	Serum E2 goal (measure 2 days after patch placed if TD)	Uterine size Endometrium ^c (ultrasound)
Year 1 (1-12 m)		7 μ g ($1/2$ of 14 μ g or $1/4$ of 25 μ g patch)	0.025 mg d ⁻¹	Stage 2 by end of time period	<50 pmol L ⁻¹ (13 pg mL ⁻¹)	1.6 cm ³
Year 2 (13-24 m)	1-4 m	12.5-14 μ g d ⁻¹ (based on available patch)	0.5 mg d ⁻¹	Stage 3	50-150 pmol L ⁻¹ (12-30 pg mL ⁻¹)	10 cm ³
Year 3 (25-36 m)	4-12 m	25-37.5 μ g d ⁻¹	1 mg d ⁻¹	Stage 4	150-450 pmol L ⁻¹ (30-120 pg mL ⁻¹) ^c	
Year 4 (37-48 m)	12-24 m	50-200 μ g d ⁻¹	2-4 mg d ⁻¹	Stage 4-5	375 pmol L ⁻¹ (100 pg mL ⁻¹)	50 cm ³

Abbreviation: TD, transdermal.

^aUse this regimen for late onset with growth potential. ^bMore or less based on serum E2 and breast stage (for ethinylestradiol 20-30 mcg d and only after year 4).

^cAdd progesterone if spontaneous bleed AND > 2 year on E2 OR endometrial stripe > 4-8 mm if < 2 years on E2. If endometrial stripe < 4 mm and E2 time > 2 years, we recommend checking serum E2 and increasing E2 dose, prior to adding progestin.

carcinoma.²⁹⁷ Secondly, the addition of progesterone administered in a cyclic regimen with estrogen allows regular, controlled, predictable episodes of withdrawal bleeding or “periods”. Progesterone has other effects being crucially important for the implantation of the fertilized ovum, the maintenance of pregnancy,²⁹⁸ and some psychopharmacological actions including anxiolytic, antidepressant, and analgesic effects.

3.5.1 Type of progesterone and synthetic progestins

Progesterone itself has its major effects on the progesterone receptor (PR) with negligible effects on the glucocorticoid receptor (GR), androgen receptor (AR), and it is an antagonist of the mineralocorticoid receptor (MR).^{298,299} All synthetic progestins bind to the PR effectively but differ in their binding affinities and effects on the GR, AR, and MR giving rise to different profiles of actions and side effects.²⁹⁸

Natural progesterone has poor oral bioavailability but this can be greatly improved by micronizing.²⁹⁸ Micronized progesterone confers adequate endometrial protection when administered as part of a cyclic combined regimen (200 mg daily for 12 days each month) or as a continuous combined regimen of 100 mg per day. In postmenopausal women, this dose seems to be devoid of adverse effects on BP, lipid profile, breast cancer risk, and thrombotic risk.³⁰⁰

Medroxyprogesterone acetate has been widely used in HRT because its bioavailability orally is >90%, it has high potency and its half-life is 24 h, allowing for daily dosing.²⁹⁸ It is effective at providing endometrial protection. However, although it primarily acts on the PR, it also acts on the GR giving rise to potential glucocorticoid-like adverse effects, not shared with natural progesterone, including an increased risk for breast cancer in non-TS populations and stroke in postmenopausal women. Other progestins are listed in Table 5 with notes regarding use.

3.5.2 Route of administration of progesterone and progestins

Oral administration is generally attractive to young women but progesterone and progestins vary in their oral bioavailability. Although E2 is well absorbed via the TD route, only norethisterone acetate (NET) and levonorgestrel are available TD as part of a combined hormone regimen. Progesterone can be

administered vaginally and exerts good endometrial protective effects at low serum concentrations, although there is limited evidence assessing the efficacy and optimal regimen.³⁰⁰ The levonorgestrel intra-uterine device (LNG-IUS 52) is licensed for endometrial protection and contraception. It has minimal side effects and lasts for 5 years. Women who have never been sexually active may need brief general anesthesia for insertion.

3.5.3 Which one to choose?

Based on available data, theoretical concerns, and expert opinion, we recommend oral natural micronized progesterone (MP) or dydrogesterone, being a stereoisomer of natural progesterone, as first line therapy since these provide the most physiological replacement, allow regular withdrawal bleeding, and have lower risk for adverse health effects. The availability of different preparations differs widely between countries.

3.5.4 Dosing of progesterone and progestins

Because the main function of progesterone is to prevent endometrial hyperplasia caused by unopposed estrogen, it is prudent to note that evidence shows a consistent association between level of risk and duration and strength of the estrogen dose.²⁹⁸ Many young women with TS benefit from a higher dose of estrogen than their older peers, that is, exceeding 2 mg E2 orally or 50 mcg TD. This is particularly important for achieving maximal uterine growth and development as options for fertility treatment increase.³⁰⁰⁻³⁰³ As the dose of estrogen increases, a higher dose of progesterone is needed to balance this.³⁰⁴

Dosing schedules are clear for micronized progesterone and medroxyprogesterone acetate³⁰⁰ but there is a lack of evidence for other progestins. It is agreed that the duration of the average luteal phase should be matched, providing physiological replacement, so that progesterone should be given for 12 days each month as part of a sequential combined regimen.³⁰⁴ In general, endometrial protection is better in those women using a continuous combined regimen.³⁰⁵ However, such a regimen is designed to avoid withdrawal bleeding which may not be attractive to young women and may also give rise to erratic vaginal bleeding, especially in those women using TD preparations. A continuous combined regimen gives rise to an atrophic endometrium, and it is unclear whether this is a

Table 5. Recommended progesterone/progestins preparations and dosing.

Progesterone/Progestins	Sequential combined HRT—Std dose	Sequential combined HRT—High dose	Continuous combined HRT—Std dose	Continuous combined HRT—High dose	Notes
Micronized progesterone (oral/per vagina) (mg)	200	≥200	100	≥200	
Dydrogesterone (oral) (mg)	10	20	5	10	Devoid of androgenic properties, does not induce metabolic side effects but confers a high degree of endometrial protection
Medroxyprogesterone acetate (oral) (mg)	5	10	2.5	5	
Norethisterone acetate (oral) (mg)	2.5-5	2.5-10	1.25-2.5	5	Absorbed well orally and TD, significant binding to AR giving rise to unwanted acne, oily skin and weight gain
Desogestrel (oral) (mcg)	150	n/a	n/a	n/a	“Not inferior” to MPA for endometrial protection, high affinity for the PR and little effect on AR, GR and MR
Levonorgestrel (oral) (mcg)	50-250	n/a	n/a	n/a	Some androgenic effects but no effect on the GR, excellent endometrial protection and can be administered orally, TD or intra-uterine
(TD) (mcg)	10/24 h	n/a	7/24 h	n/a	
Intra-uterine (IUD)(mcg)	n/a	n/a	20/24 h	20/24 h	
<i>E2/Progesterone/Progestins combined regimens</i>					
E2/Micronized Progesterone (oral) (mg)	1-2/100-200	>2/>200	1-2/100-200	3-4/300-400	
E2/norethisterone acetate (TD) (µg/24 h)	25-50/85-170	75-100/255-340	25-50/85-170	75-100/255-340	
E2/dydrogesterone (oral) (mg)	1-2/10	3-4/20	0.5-1/2.5-5	3-4/7.5-10	
E2/norethisterone (oral) (mg)	1-2/1	3-4/2-4	0.5-2/0.1-1	3-4/1.5-2	

Abbreviations: E2-17β-estradiol; Std, standard; mg, milligrams; TD, transdermal; IUD, intra uterine device; PR, progesterone receptor; AR, androgen receptor; GR, glucocorticoid receptor; MR, mineralocorticoid receptor.

Table 6. What is new with progesterone treatment?

Use of micronized progesterone or dydrogesterone as first-line product
Dosing—to use progesterone for at least 12 days in every month (or daily)
Doses of progesterone should be proportionate to the dose of E2
Studies of adherence and acceptability of different approaches and regimens are needed in view of reports of poor concordance with HRT ³⁰⁶
Intra-uterine device with levonorgestrel is licensed for endometrial protection and contraception and has minimal side effects and lasts for 5 years. Non-sexually active women may need a brief general anesthesia for its insertion.

Abbreviation: E2, 17β-estradiol.

disadvantage in the short- or medium-term in women planning an oocyte-donated pregnancy.

Micronized progesterone confers adequate endometrial protection when administered as part of a cyclic combined regimen (200 mg daily for 12 days each month) or as a continuous combined regimen of 100 mg per day. Higher doses of estrogen need higher doses of micronized progesterone (300 mg daily for 12 days per month or 200 mg daily).³⁰⁵ It is important not to underdose progesterone as that leads to more abnormal uterine bleeding. It is also important to remember that as the dose of estrogen increases, the dose of progesterone may need to increase (Table 6). Recommended doses for progestins are given in Table 5.³⁰⁰

3.5.5 When to add progesterone during pubertal induction

Progesterone is unnecessary until uterine growth and development is approaching maturity. In girls undergoing pubertal

induction, it is likely that progesterone will be needed after about 1.5-3 years of unopposed estrogen administration or after the first episode of vaginal bleeding. However, inter-individual variability in response to estrogen means that it is good practice to ensure that starting progesterone is appropriate by carrying out pubertal staging and, if possible, performing a pelvic US to review uterine dimensions and the presence of an endometrial stripe >4-8 mm.^{307,308} In cases where the uterus is relatively small and the endometrium is thin, progesterone treatment should be deferred, and more time or increased estrogen dose considered. This ensures maximum time for uterine and breast development with unopposed estrogen.³⁰⁹ Initial vaginal bleeding may be spotting only from an immature endometrium and does not necessarily indicate timing to start progesterone. Recent data suggest that girls with TS who initiate progesterone closer to 18 months into estrogen treatment may have less abnormal uterine bleeding.³¹⁰

There are very few good quality studies of progesterone/progestins in pubertal induction or HRT in adolescents and women with TS. This means that the results of studies in women with premature ovarian insufficiency are extrapolated to support decision-making in patients with TS. In practice, studies of premature ovarian insufficiency tend to include many subjects with TS and so this approach has some credence. Studies and trials describing the adverse effects of HRT invariably involve post-menopausal women. In these cases, extrapolation of results to young women with TS is much more dubious and results should be regarded with great caution. There are also very few studies addressing compliance with and acceptability of HRT medication. The most important factor when prescribing regular long-term medication is whether the patient is truly satisfied with taking it.

3.5.5.1. Results from recent literature search regarding TS and progesterone/progestins. There was only one study concerning progestins as hormone replacement in TS. This was a cross-sectional, non-controlled retrospective cohort study of 111 patients with TS who started estrogen at 15.8 years old. It was found that the prolonged use of medroxyprogesterone acetate, levonorgestrel or micronized progesterone showed no metabolic change (BP, lipid profile, fasting blood glucose, TSH, renal function) except for weight gain. The percentage of annual BMI increment was positive for all progestins used in TS women, but levonorgestrel seemed to best prevent weight gain over time.³¹¹

3.6 Note about world-wide availability of estrogens and progestins

The availability of estrogen and progesterone preparations varies greatly world-wide as determined by an online survey conducted by ESPE between May 2020 and October 2022 (unpublished data submitted to Hormone Research in Paediatrics). TD E2 was the most widely available preparation (90%) and was the preferred option for pubertal induction in 69% of respondents. Although oral E2 preparations were widely available (82% of respondents), the lower doses of 1 and 0.5 mg tablets were only available in 40% and <10% of centers, respectively. Low dose ethinyl estradiol (2 mcg tablets) was available in nearly 50% of centers but was the preferred preparation in only 2.8%.

In almost all countries, oral preparations of progesterone and progestins were available (95.9%). Dydrogesterone (67%) and/or medroxyprogesterone acetate (67%) were generally available with TD progestins in 25% of centers.

Availability in the Arab region has recently been published³¹² and showed that the most commonly available forms of estrogen were conjugated estrogen (29% of centers) followed by ethinyl estradiol (26%). The combined oral contraceptive pill was available in 32% centers. In the UK, it was recognized that access and availability to all treatment options was an important factor for shared decision-making which can improve medication adherence.³¹³ Social deprivation was a key influence on the availability of HRT treatment options but the reasons for this inequity are not understood. There are great disparities regarding the availability of HRT preparations between different countries/regions and even within countries. The availability of suitable low dose estrogen preparations for pubertal induction is extremely poor worldwide.

3.7 Monitoring during estrogen treatment

- **R 3.7** To optimize uterine growth during puberty and bone health in adulthood, we suggest multiple assessments of treatment effect, to include: breast development, height, uterine ultrasound, bone density, serum E2 concentrations, with the goal to achieve E2 concentrations of 100-150 pg mL⁻¹ (350-500 pmol L⁻¹) at full adult replacement (⊕○○○).

- **R 3.8** We suggest using measurements of endometrial thickness and serum E2 concentrations in adolescents or women experiencing abnormal uterine bleeding to inform adjustments to E2 and/or progesterone doses (⊕○○○).

We suggest multiple assessments for monitoring, all of which are based on limited data but years of expert experience and common pathophysiology. No rigorous studies have looked at all variables together to assess outcomes. We suggest measuring E2 concentrations when a highly sensitive assay is available. E2 values in typical menstruating women depend on phase of cycle with great variability between women and between cycles; with follicular and luteal mean E2 values around 183 and 521 pmol L⁻¹ (50 and 142 pg mL⁻¹), respectively.²⁸⁶ More detailed data coming from healthy adult women confirmed it as well: 100-181-730 pmol L⁻¹ (27-49-199 pg mL⁻¹) for early-mid-late-follicular phase and 386-599-395 pmol L⁻¹ (105-163-108 pg mL⁻¹) for early-mid-late-luteal phase, respectively³¹⁴ but with wide variability with some women showing values as high as 2500 pmol L⁻¹. Both untreated girls with TS with confirmed hypogonadism and post-menopausal women have E2 concentrations around 18 pmol L⁻¹ (5 pg mL⁻¹).³¹⁵ Viuff et al. reported that E2 concentrations during HRT in TS were comparable to controls only at early follicular phase suggesting that the current regimen does not fully normalize E2 concentrations in TS.³⁰³ References from women without TS can be used for guidance.²⁹² A suggested adult target is an E2 concentration of 350-500 pmol L⁻¹ (100-150 pg mL⁻¹).²⁸⁶ The wide individual variability leads to our suggestion to use multiple variables for assessment of treatment including: breast development, uterine ultrasound, serum E2, LH, FSH, and DXA with further adjustments for patient satisfaction. Serum concentrations may be used to monitor E2 dose at the start of treatment to ensure target concentrations are reached but, in the medium- to long-term, effects of HRT on specific outcomes such as BMD and uterine growth assume greater importance.³¹⁶ In contrast, in a study of 145 women with premature ovarian insufficiency, long-term TD E2 100 mcg daily restored mean BMD to normal ranges and there was no benefit of increasing the dose to 150 mcg.³¹⁷ A study with TD E2 compared with oral E2 showed that a higher dose corresponded to higher concentration of E2, however without linear correlation.²⁸⁶ TD E2 led to more effective feminization after 2 years compared with oral conjugated equine estrogen.³¹⁸

Very sensitive radioimmunoassays or mass spectrometry assays for E2 may be used with care taken to note differences in concentrations based on assay chosen.^{278,319,320} These assays may not be commercially available or not supported by insurance. Taken together, we suggest a goal of adult serum E2 as mentioned above once pubertal progression is complete, with caution that E2 concentrations vary by assay used. There is also variability in the metabolic clearance of E2 between women, which supports the importance of monitoring serum E2 concentrations during treatment and making decisions based on more than just one measurement.

Uterine growth observed after the first 6-12 months of estrogen therapy induction suggested that uterine volume measurement may be a useful monitoring marker for HRT

Table 7. Clinical, laboratory, and radiological markers of estrogenization.

Clinical	Laboratory	Radiological
<ul style="list-style-type: none"> • Breast development: every visit • Growth velocity: every visit till final height • Monitoring of vaginal bleeding/menstruation • Quality of life • Sexuality • Neurocognition 	<ul style="list-style-type: none"> • Serum E2 concentration in relation to E2 dose and treatment goal • FSH, LH are used by some 	<ul style="list-style-type: none"> • Ultrasound of uterus /endometrium: at first bleeding or when progesterone treatment is considered. At adult height—if uterus is still smaller than normal, a higher E2 dose for 5 years will not hamper her growth/height but stimulate uterine growth for³²¹ • Bone age X-ray rate of maturation • DXA and pQCT (estimation of peak bone mass) at last pediatric visit when adult height is attained (approx. age 18 years). As we do not have knowledge on when TS women attain their peak bone mass it may be wise to repeat DXA and pQCT at age 21 years.

Abbreviations: DXA, dual X-ray absorptiometry; E2, 17 β -estradiol; FSH, follicle-stimulating hormone; LH, luteinizing hormone; pQCT, peripheral quantitative CT.

efficacy.²⁷⁷ E2 dosage affects uterine volume initially but not in the long term.³²¹ It is important to note that uterine volume and endometrial assessments by ultrasound are operator dependent and more difficult to standardize, while MRI is superior in determining uterine volume, yet more expensive.³²² Uterine size during induction of puberty can be a proxy for sufficient estrogen exposure and therefore valuable in addition to serum E2, or when serum E2 cannot be assessed.³²³

Clinical assessment, patient satisfaction, patient age and often residual growth potential are the primary determinants for the timing of E2 dose increase. If potential for taller stature is still possible, girls may remain on lower estrogen doses longer. In older girls at initiation, the duration of time until adult dosing may be shortened. Serum concentrations may be used to monitor E2 dose—but, in the medium- to long term, outcomes such as BMD, uterine growth, QoL, neurocognition and sexuality are of greater importance.³¹⁶

As E2 sensitivity is variable within and between individuals, monitoring serum E2 is valuable, but following the biomarker(s) of individual estrogenization seems paramount. Table 7 provides guidelines for markers of treatment effect.

3.8 Hormone replacement therapy in adults with Turner syndrome

- **R 3.9** We recommend continuing cyclic estrogen and progesterone treatment until the usual age of menopause (approximately 50-55 years old) and then re-evaluate for possible continued lower dose of E2 and progesterone (⊕⊕○○).
- **R 3.10** We recommend individualized E2 + progesterone replacement, taking account of patient preference, to aid adherence with their management plans (⊕⊕○○).

After completing pubertal induction, maintenance HRT is continued until the expected age of natural menopause, about 50-55 years, but lower in some populations,^{324,325} aiming for a period of at least 42 years of exogenous estrogen exposure mimicking normal physiology of endogenous estrogen exposure. During adulthood the aim is to restore the physiological hormonal environment as closely as possible and HRT is

Table 8. Estrogen replacement therapy in adulthood—estrogen type, route, and dose.^{283,300,316,326}

Estrogen type	Route of administration	Dose
Estradiol	Patch (TD)	50-200 $\mu\text{g}/24\text{ h}$
	Gel sachet (TD)	1.5-3 mg day^{-1}
	Oral	2-4 mg day^{-1}
Ethinylestradiol	Patch (TD)	34 μg 24 h
	Oral	20-30 $\mu\text{g day}^{-1}$

Abbreviation: TD, transdermal.

important for continuing bone mass accrual to reach peak bone mass during the third decade and for further uterine growth and development.^{326,327} HRT may also help to improve QoL and to avoid the effects of estrogen deprivation including vasomotor symptoms, urogenital effects, low BMD with increased risk of fracture, cardiovascular disease with increased risk of ischemic heart disease and stroke and, finally, possible neurocognitive effects.

Both duration of HRT as well as E2 dose are important for uterine volume and BMD increase.^{301,321} To date, no studies have rigorously defined the effect of dose on BMI, height, weight, or lipids.³²⁷⁻³³¹ There is a very low risk of breast cancer in TS patients with no significant increase in those treated with standard doses of HRT.^{332,333} In women with urogenital symptoms such as vaginal dryness, vaginal estrogen is available in creams or pessaries. Vaginal E2 is not believed to carry a risk of endometrial hyperplasia based on data in older menopausal women.²⁸³

Based on these data, suggested adult doses of E2 are given in Table 8. There is very little information about the bioequivalence of preparations. Estimated daily dose equivalence from the literature (depending on assays and clinical endpoints) are 50/100 μg TD = 2 mg oral E2 = 20 μg ethinyl estradiol.²⁹⁰

As previously discussed, it is not feasible to mimic the physiological cyclic variations of the adult woman with intact ovarian function so all risks and benefits of options need to be considered.³⁰³ There are reports where up to 37% of women less than 51 years old stop their HRT prematurely.^{29,280,330,334}

Even though endocrinologists discuss E2 form, administration route and dose, the most important challenge is probably to individualize treatment in such a way that the hypogonadal woman can accept and adhere to her lifelong HRT. Therefore, a diversity of HRT possibilities is very valuable. Fear of side effects and financial constraints are among the reasons, even when evidence is given regarding poorer outcome for those without

Table 9. HRT effects on other outcomes.

Issue	Outcomes	References
<i>Lipid metabolism</i>	<ul style="list-style-type: none"> • Studies differ on whether oral E2 vs. TD E2 leads to increased total cholesterol and decreased HDL • Studies differ on impact of dose of E2 and absence of E2 treatment on lipids • Oral contraceptive pills vs. other HRT: higher total cholesterol, LDL cholesterol and triglyceride 	1,280,284,286,320,328,335-338
<i>Glucose metabolism</i>	<ul style="list-style-type: none"> • Dose and route of E2 do not affect glucose and insulin concentration and tolerance • Time of day of E2 dose may affect glucose metabolism with evening oral E2 leading to lower glucagon and insulin levels (during an OGTT), lower insulin resistance • One report of lower use of antidiabetics with E2 treatment 	1,29,284,289,320,336,339-341
<i>Liver function</i>	<ul style="list-style-type: none"> • No evidence of liver toxicity • Studies vary on effect of E2 treatment on liver function and disease 	284,342-350
<i>Bone</i>	<ul style="list-style-type: none"> • Studies vary on report of changes in BMD based on dose and route of E2 • Earlier initiation of HRT does affect BMD with higher BMD/better bone quality/greater trabecular bone score 	280,294,301,320,329,335,351-355
<i>Blood pressure</i>	<ul style="list-style-type: none"> • Oral E2 or TD E2: lowers blood pressure, although E2 may cause salt and water retention • Ethinyl estradiol containing contraceptives (unless containing an anti-mineralocorticoid progestin): raise blood pressure • Lower or higher dose of oral E2: increase of systolic and diastolic blood pressure was observed in late adolescence and early adulthood • HRT (2 mg E2, 12 weeks): higher central systolic blood pressure and indices that showed impaired endothelial function 	284,328,356-361
<i>Cardiovascular risk</i>	<ul style="list-style-type: none"> • Oral conjugated estrogens: no studies in children in view of thromboembolic and cardiovascular disease risks • Lack of association with ASI and aortic dissection 	232,362
<i>Uterine volume/puberty issues</i>	<ul style="list-style-type: none"> • Increases the uterine volume, dose and duration dependent • Ethinylestradiol: satisfactory pubertal induction and maintenance, but 20-30 µg/daily failed to induce a fully mature uterus in 50% of the girls • HRT type: no differences in uterine volume • Fixed dose of HRT (RCT) produces a satisfactory pubertal development not inferior to an individualized dose 	277,289,321,322,327,363-366
<i>Psychological aspects and brain development</i>	<ul style="list-style-type: none"> • HRT vs. non-HRT: better performance on measures of overall IQ, expressive vocabulary, and visuospatial processing but does not exclude characteristic neurocognitive profiles in some women with TS 	367-370
<i>QoL</i>	<ul style="list-style-type: none"> • Age-appropriate pubertal development and satisfaction with breast development has a positive influence on self-esteem, social adjustment 	371-376
<i>Thromboembolic risk</i>	<ul style="list-style-type: none"> • There is no sign of elevated thromboembolic risk associated with HRT in TS 	29
<i>GH-IGF1 axis</i>	<ul style="list-style-type: none"> • Ethinyl estradiol exerts dose-related suppression of IGF-I in GH-naïve patients • Studies differ on influence of E2 routes on IGF-I concentration in GH-treated subjects 	377,378
<i>Other aspects</i>	<ul style="list-style-type: none"> • TD vs oral HRT: no significant differences in protein turnover, lipolysis, osteocalcin, C-reactive protein, BMI, or waist-to-hip ratio 	336,341,379

Abbreviations: HRT, hormone (estrogen) replacement therapy; E2, estradiol; HDL, HDL-cholesterol; LDL, LDL-cholesterol; LFT, liver function tests; O, oral; oral conjugated estrogens, CEE; T-chol, total cholesterol; TD, transdermal; TG, triglyceride; TS, Turner syndrome.

treatment. The need for individualized HRT, taking full account of patient preference is crucially important and patient involvement in decisions about care are known to improve adherence. Estrogen effects on other outcomes are presented in Table 9.

Regular follow-up, about once a year, preferably in a dedicated clinic for adults with TS, is recommended. It is important to discuss compliance, patient satisfaction, side effects and the possible need for change of regimen or route of administration.

Measurement of BMD with DXA scan, ensuring adjustment of results for height and bone size, should be considered when pubertal induction has been completed. Following this, the frequency of repeat BMD assessment should be guided by the findings from the initial assessment, the patient's risk factors, and their compliance with HRT.³⁸⁰

3.9 Testosterone and oxandrolone

Viuff et al. showed that androgen concentrations are 30%-50% lower in women with TS than in controls.³⁰³ One pilot study by Zuckerman-Levin et al. has looked at testosterone replacement in adolescents/young women with TS and

confirmed that androgen replacement therapy (ART), as compared with placebo, reduced total cholesterol, triglycerides, but also HDL cholesterol. Moreover, it improved BMD, increased lean body mass, and decreased fat mass. ART improved attention, reaction time, and verbal memory, but had no effect on executive functions and spatial cognition. Their patients reported improved QoL, including general health, coping with stress, and sexual desire.³⁸¹

Oxandrolone use in TS to promote growth is well-described.^{249,250} However, its use is not considered standard of care and was reserved for very short girls. Of note, as of 2023, it is no longer available in the United States (see section on Growth in TS). Further studies of androgen use in women with TS are needed.

3.10 Practical guidelines summary

For pubertal induction in girls with TS it is important to mimic physiology as closely as possible to support linear growth and gradually induce puberty at an age and tempo within the normal range for peers. This is important for psychosocial well-

Table 10. Areas where further research is required.

Study design/epidemiology/cancer research	Related to estrogen replacement	Related to other components of HRT
QoL studies across the lifespan	Serum E2 levels during HRT need further study in relationship to: <ul style="list-style-type: none"> • Bone health • Uterine growth • Height—long-term studies from initiation of puberty through adult height • Onset of menses • Cardiovascular profile 	Frequency of progestin withdrawal and progestin regimens (agent, dose) <ul style="list-style-type: none"> • Effect on breast growth? • Effect on uterine growth? • Effect on bleeding pattern and abnormal uterine bleeding
Comparison of who uses which preparations and why	E2 dosing—rate of increase, effect on height, BMD, vaginal bleeding, uterine development and QoL <ul style="list-style-type: none"> • Should dose be? <ul style="list-style-type: none"> • Low while height still a factor but how low for how long? • High for young women • Medium for 30-40 years • Lower ~50 years 	The need and role of ART
Adherence studies	Comparison oral and TD E2 with continued GH (pubertal gain in height, uterine size/form, peak bone mass)	
Long-term outcomes in TS (endometrial cancer, cardiovascular risks, QoL)—may be different from postmenopausal studies	Comparison of oral and TD E2 effect on: <ul style="list-style-type: none"> • Bone health • Uterine growth • Height—long-term studies from initiation of puberty through adult height • Onset of menses • Cardiovascular profile 	

being, bone health, uterine growth, pregnancy outcomes, and possible neurocognitive benefits.

For girls who do not enter spontaneous puberty, as determined by elevated FSH on multiple checks between 8 and 11 years old, plan low dose E2 initiation between 11 and 12 years old. For girls with spontaneous thelarche, withhold treatment until any signs of ovarian insufficiency by FSH measurement. We recommend a starting dose of 7 mcg TD E2 or 0.25 mg oral E2, and increasing the dosing every 6-12 months. Breast stage and serum E2 concentrations can guide progression of dosing. Anticipation to reach adult dosing by year 4 of treatment with serum E2 concentrations close to 367-550 pmol L⁻¹ (100-150 pg mL⁻¹). For girls who have spontaneous puberty and then develop ovarian insufficiency, E2 dosing should be parallel to their pubertal stage. For example, a girl who has reached breast stage 3 (or mid-puberty) can start treatment at 25 mcg TD E2 or 1 mg oral E2. Once linear growth is complete, if ethinyl estradiol is preferred, we recommend dosing with 30 mcg per day.

Progesterone should be added once spontaneous bleeding occurs if it is at least 18-24 months into estrogen treatment. If bleeding occurs sooner, then progesterone can be added if endometrial stripe on ultrasound is at least 4-8 mm. If endometrium is less than 4 mm, we recommend checking serum E2 concentrations and increasing E2 dose prior to adding progesterone to allow further development of the endometrium. When available, micronized progesterone at 200 mg for 12 days per month is the preferred progestin, with dydrogesterone at 10 mg for 12 days as second choice. It is important not to underdose progesterone to prevent abnormal uterine bleeding. Patients requiring higher E2 doses may also require higher progesterone doses. We advise a sequential regimen of E2 and progesterone to allow cyclical endometrial development and avoid abnormal uterine bleeding in younger women

(Table 8). Older women may prefer a combined continuous regimen and avoid menstruation.

GH treatment can continue in any girl with continued growth potential even as estrogen treatment is initiated.

In adult women with TS, it is very important to individually adapt dosing and route options to improve adherence. Patient choice is the most important determinant of adherence. Treatment is recommended until typical menopausal age around 50-55 years. At that time assessment of value of ongoing lower E2 dosing is possible.

We do not recommend ultrasound of the uterus prior to E2 initiation as it is not a good predictor of spontaneous puberty nor changes the decision about when to start E2 treatment. We recommend ultrasound of uterus at first bleeding if there has been E2 treatment for less than 2 years or if breast development has not reached stage 3. Once adult height is reached with full E2 dosing, if the uterus is still small on ultrasound, higher E2 dosing is recommended to stimulate further uterine growth for possible future fertility options.

DXA and peripheral quantitative CT estimation of bone mass will be low until adult E2 dosing is reached. This is a good time to assess bone mass to aid in assessing adequate E2 dosing. There is little data on when women with TS reach peak bone mass, so repeat DXA and pQCT is suggested around 21 years of age. Table 10 lists areas for important future research in relation to estrogen therapy.

4. Cardiovascular health

4.1 Introduction

Individuals with TS frequently cope with a lifelong burden of congenital and acquired cardiovascular diseases, which are primarily responsible for the increased mortality of adults with TS.^{27,28} CHD occurs in approximately half of individuals with

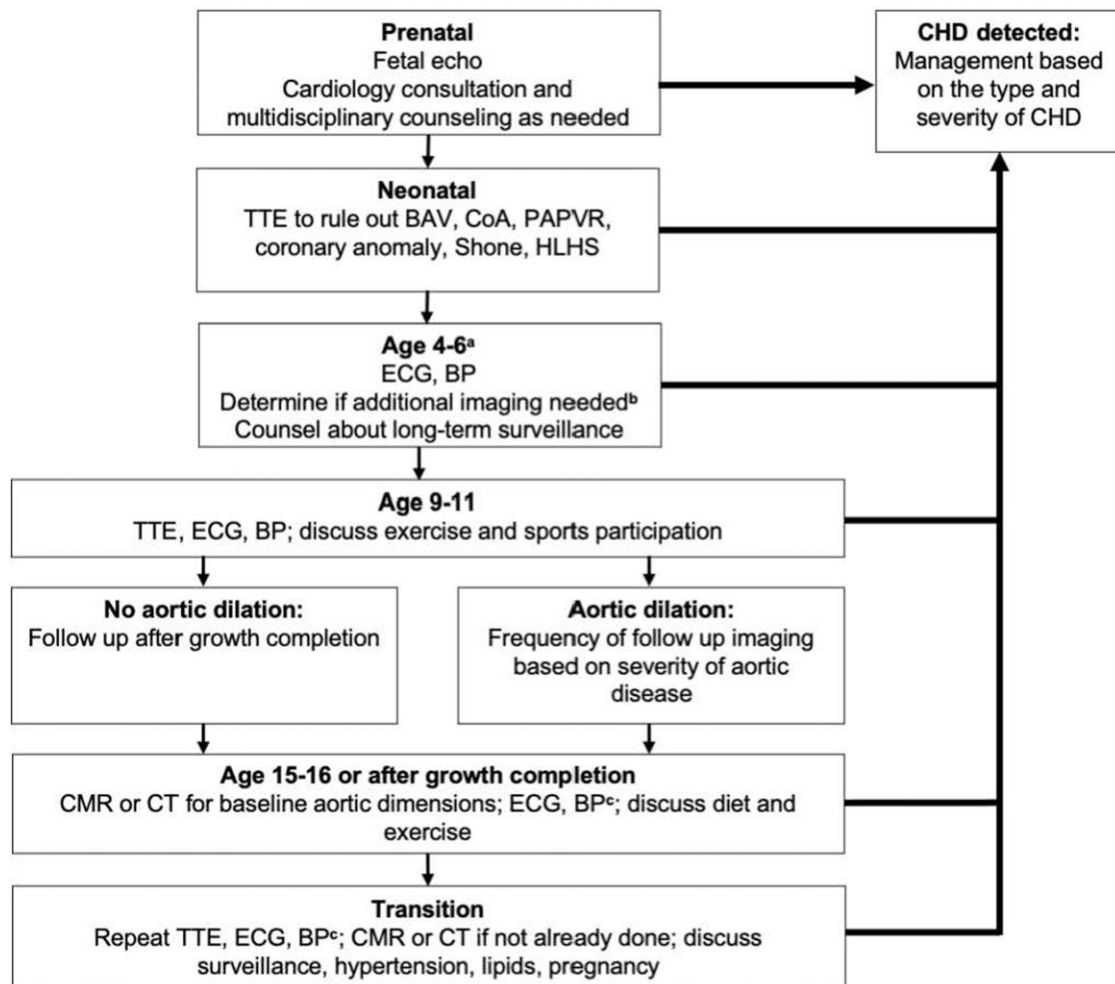


Figure 2. Suggested workflow for cardiovascular follow-up from gestation to transition. TTE, transthoracic echocardiogram; BAV, bicuspid aortic valve; CoA, aortic coarctation; PAPVR, partial anomalous pulmonary venous return; HLHS, hypoplastic left heart syndrome; ECG, electrocardiogram; BP, blood pressure; CMR, cardiovascular magnetic resonance; CT, computed tomography. (A) Consider earlier visit if clinical concern for symptoms, murmur, or other abnormal cardiovascular exam finding. If neonatal images were reviewed by a cardiologist, clinically significant congenital lesions were ruled out, and there are no signs or symptoms concerning CHD, it is reasonable to defer cardiovascular follow up until age 9-11. (B) Cardiologist may order additional imaging before or with visit if neonatal TTE inconclusive for valve morphology, coronary anatomy, or pulmonary venous anomaly. (C) Consider 24-h ambulatory blood pressure measurement (ABPM) if available.

TS, including BAV, aortic coarctation, and an arteriopathy that can lead to rare but often fatal aortic dissections. The lifetime prevalence of thoracic aortic aneurysms is approximately 25%.^{382,383} However, acquired cardiovascular conditions such as systemic hypertension, ischemic heart disease, and stroke are the major factors that reduce the lifespan.³⁸⁴ This consensus statement proposes guidance for decision-making about diagnosis, treatment, and monitoring of congenital and acquired cardiovascular diseases in TS. Clinical care guidelines for management of CHD also apply to individuals with TS with a few special considerations that are discussed.

4.2 Recommendations for cardiovascular surveillance

Early diagnosis and routine surveillance are essential for prevention and timely therapy of cardiovascular disease in TS (Figure 2). Even in the most experienced hands, prenatal or neonatal TTE may not definitively exclude BAV, anomalous pulmonary venous return, or variant aortic arch anatomy. Repeating images later in childhood and maintaining a low threshold for cardiovascular consultation may improve

diagnostic sensitivity for congenital heart lesions (Figure 3). Establishing a routine of lifelong cardiovascular care is a key issue for young people with TS.

4.3 Congenital heart disease

- **R 4.1** We recommend that if TS is highly suspected or has been confirmed prenatally, a fetal echocardiogram should be performed (⊕⊕⊕○).
- **R 4.2** We recommend that diagnosis of left-sided congenital heart disease (CHD) in a female fetus or child should prompt a genetic evaluation that includes testing for TS (⊕⊕⊕○).
- **R 4.3** We recommend that a pediatric cardiologist should be included in the multidisciplinary care team when CHD is detected prenatally in a fetus with TS to provide counseling regarding the anatomy and physiology of the specific defect, the

recommended site and mode of delivery, and postnatal cardiovascular management (⊕⊕○○).

- **R 4.4** We recommend that a newborn with prenatally diagnosed or suspected TS be examined with TTE at day 2 to 3 of life, sooner if CHD is suspected, even if the fetal echocardiogram or postnatal clinical examination was normal (⊕⊕⊕○).
- **R 4.5** In settings where postnatal TTE prior to discharge after birth are not available, we recommend clinical cardiac evaluation with 4-extremity blood pressure, pulse oximetry, palpation of femoral pulses, cardiac auscultation, and ECG prior to discharge followed by outpatient TTE within the first weeks of life (⊕⊕⊕○).
- **R 4.6** We recommend that visualization of the origin and proximal course of coronary arteries to identify potential coronary anomalies should be included in the cardiovascular assessment of all individuals with TS (⊕⊕○○).
- **R 4.7** We recommend that TTE should be performed at the time of diagnosis in all children and adults with TS, even when a fetal echocardiogram or postnatal clinical examination was normal (⊕⊕⊕○).

4.3.1 Prevalence of congenital heart lesions

Depending on the age and the imaging technique used, the prevalence of CHD in TS ranges from 40%-60%, most commonly left-sided obstructive lesions such as BAV and coarctation (Table 11).^{3,356,385-388} The prevalence is higher in individuals with 45,X karyotypes compared to individuals with X mosaicism or other X structural abnormalities.³⁸⁹⁻³⁹¹ Neck webbing and an increased anterior-posterior thoracic diameter are strong predictors of arterial and venous anomalies in TS.^{390,392,393} At least 13% of newborn girls with aortic coarctation have TS, and coarctation should be viewed as an independent marker of TS.³⁹⁴ Vascular anomalies, including partial anomalous pulmonary venous return, left superior vena cava, elongated transverse arch, and dilation of the brachiocephalic arteries, often remain undetected unless advanced imaging modalities are used.^{388,395}

Congenital coronary artery anomalies appear relatively common in TS, but their effect on mortality risk is unknown.³⁹⁶ However, there is no evidence that sudden cardiac death related to malignant anomalies such as origin from the opposite sinus is increased in TS.³⁹⁷ The cardiovascular surgeon needs to be aware of unusual coronary anatomy because it may necessitate modifications to the operative approach and can lead to adverse surgical outcomes in individuals with undetected coronary anomalies.³⁹⁸

4.3.2 Prenatal and neonatal cardiac evaluation

With advances in fetal echocardiography, prenatal detection of CHD is becoming increasingly common, allowing opportunity for parental counseling and time for planning of

perinatal management based on predicted risk of hemodynamic compromise after birth. Therefore, all fetuses diagnosed with TS or suspected to have TS should undergo a prenatal cardiac evaluation with fetal echocardiography, regardless of karyotype.³⁹⁹ If any CHD is detected prenatally, prompt evaluation by a pediatric cardiologist is recommended to determine the site and mode of delivery and postnatal management plans based on the CHD lesion detected.⁴⁰⁰ When CHD is detected in a fetus with a 45,X karyotype, the risk of cesarean section, adverse neonatal outcomes, and neonatal death is predicted to be higher than in non-TS fetuses with similar lesions.⁴⁰¹ Therefore, prenatal counseling and planning for the perinatal management of such fetuses should include a multidisciplinary team that involves, at a minimum, pediatric cardiology, neonatology, and maternal-fetal medicine.

For fetuses with known or suspected TS but normal fetal echocardiographic findings, counseling should include recognition that not all CHDs can be easily detected prenatally. Ultrasound image resolution is insufficient to distinguish small fetal cardiac structures such as the morphology of the aortic valve. In addition, there are unique features of the fetal circulation due to fetal shunts, such as patent foramen ovale and ductus arteriosus, that make prenatal detection of aortic coarctation difficult on the fetal echocardiogram. Therefore, it is not surprising that fetal echocardiographic studies detected CHD in only 13% to 16% of fetuses with TS, as compared to the 50% prevalence of CHD on postnatal images.^{401,402}

A postnatal TTE is recommended for all newborns with TS, even if the fetal echocardiogram was normal, because fetal echocardiography may not detect all CHD lesions. For TS newborns that are clinically stable with normal newborn pulse oximetry⁴⁰³ and reassuring femoral pulses on physical examination, the post-natal TTE should be planned on day 2 or 3 of life, based on the anticipated time of discharge. Postnatal development of aortic coarctation can only be completely ruled out once ductal closure is completed, which typically happens by 2 to 3 days of age. If the newborn displays any signs or symptoms concerning CHD, the TTE should be obtained sooner. Findings on the postnatal TTE should guide the timing of outpatient cardiac follow up evaluation and subsequent management. If resources are not available for postnatal echocardiography prior to discharge for a newborn that is clinically stable and with reassuring 4-extremity blood pressure, pulse oximetry, femoral pulses, cardiac auscultation, and ECG, it is reasonable to plan for TTE within four weeks of age.

4.3.3 Bicuspid aortic valve

BAV is detected in more than 25% of individuals with TS, or 50 times the rate in the general population.⁴⁰⁴ The prevalence of type 1 BAV morphology may be increased in individuals with TS.⁴⁰⁵ BAV is frequently associated with thoracic aortic dilation, coronary anomalies, coarctation, and other left-sided congenital lesions,⁴⁰⁶ which should be actively screened for if BAV is identified. Continuous surveillance is necessary for individuals with BAV to address these related issues and avert potential complications. Although BAV is a common feature of TS, isolated BAV is also common in the general population with a prevalence of 1%-2%. Therefore, the diagnosis of BAV should prompt a genetic evaluation for TS only if additional clinical features of TS are present.

- **At diagnosis, regardless of previous imaging:**
 - Diagnostic workup should include complete CV imaging with TTE and CMR or CT.
- **Individuals found to have CHD, aortic dilation, hypertension, arrhythmia, or another CV diagnosis should follow a surveillance schedule outlined by their cardiologist.**
- **Routine follow up (for individuals without a CV diagnosis):**
 - In children between age 4 – 6 years^a
 - In children between age 9 – 11 years
 - At age 15 – 16 or after growth completion
 - At transition
 - In adults at least every 5 – 10 years
- **Before beginning fertility preservation or planned pregnancy^{bc}**
- **Presentation with new symptoms:**
 - Unexplained dyspnea
 - Congestive heart failure (orthopnea, lower extremity edema)
 - Syncope
 - Palpitations
- **New concern for possible hypertension^b:**
 - Elevated clinic or home blood pressure values
- **Abnormal test results:**
 - Electrocardiogram that demonstrates left ventricular hypertrophy, bundle branch block, possible arrhythmia (QTc > 450 ms in girls (up to 16 years old) and > 460 ms in women (using Hodges formula), frequent atrial or ventricular ectopic beats) or right heart strain (new right ventricular conduction delay)
 - New diagnosis of RV dilation, coarctation, pulmonary hypertension, bicuspid aortic valve, thoracic aortic aneurysm, or evidence of shunting^b
- **New prescription of any medication that may cause cardiovascular side effects or exacerbate hypertension**

Figure 3. Indications to consider cardiology consultation. CV, cardiovascular; TTE, transthoracic echocardiogram; CMR, cardiovascular magnetic resonance; CT, computed tomography; CHD, congenital heart disease; QTc, corrected QT interval; ms, milliseconds. (A) If neonatal images were reviewed by a cardiologist, clinically significant congenital lesions were ruled out, and there are no signs or symptoms concerning CHD, it is reasonable to defer cardiovascular follow up until age 9-11. (B) In these situations, recommendations for cardiology surveillance and follow up may be more frequent and will depend on the type and severity of the lesion. (C) Before pregnancy or fertility treatments, the most recent cardiovascular imaging should not be older than 2 years and should not be overdue based on the cardiologist's last set of recommendations. CT or MRI is advised for the most thorough assessment.

4.3.4 Management of CHD in TS

Structural heart lesions such as shunts or coronary anomalies, which are prevalent in TS, can present as chest pain, dyspnea, or syncope in children or young adults. New cardiovascular symptoms in young people with TS should prompt an evaluation by a cardiologist (Figure 3).

For individuals with TS and CHD, recommendations for cardiac surveillance, medical therapies, and surgical approaches are similar to non-TS patients, as outlined in clinical care guidelines for CHD management of the fetus, child, or adult with CHD.^{400,407,408} Treatment of valve dysfunction

should be consistent with current guidelines for valvular heart disease.⁴⁰⁹ Operative management can be more challenging given the medical complexity of TS.⁴¹⁰⁻⁴¹³ Median post-operative hospital stays, reoperation rates, and mortality are increased compared to non-TS patients.⁴¹⁴⁻⁴¹⁶ Percutaneous treatment of aortic coarctation, although effective, may be associated with significant morbidity and mortality due to increased risk for aortic dissection with a percutaneous approach. These risks suggest that alternative treatment options should be carefully weighed against percutaneous strategies while considering individual risk factors.⁴¹⁷

Table 11. Prevalence of CHD in TS compared to general population.

Lesion	TS (%)	General population (%)
Overall incidence of CHD	23-50	0.8
Bicuspid aortic valve	14-40	1-2
Aortic coarctation ^a	4-15	0.34
Bovine arch ^b	6-29	13
Aberrant right subclavian artery	6-8	0.5-2.5
Persistent left superior vena cava	2-13	0.3-0.5
Partial anomalous pulmonary venous return	4-16	0.4-0.7
Hypoplastic left heart	4-5	0.0002-0.0003

^aPrevalence strongly depends on definition, eg, hemodynamic significance and grade of stenosis, including pseudo-coarctation (appearance of stenosis due to kinking of the aorta). ^bCommon origin of brachiocephalic artery and left common carotid artery from the aortic arch.

4.4 Imaging

- **R 4.8** We recommend that in the absence of significant cardiovascular disease (hypoplastic left heart syndrome, Shone's complex, aortic coarctation, bicuspid aortic valve (BAV), aortic dilation, or cardiac shunt) at the initial comprehensive screening, TTE should be performed at age 9-11 years, after growth completion or at transition to adult care, and at least every 5-10 years in adults (⊕⊕○○).
- **R 4.9** If the heart and aorta are completely visualized and are normal in an infant or child with no symptoms that could be attributable to cardiovascular disease, an initial cardiovascular magnetic resonance (CMR) scan is still recommended but can be delayed until it can be performed without general anesthesia (⊕⊕○○).
- **R 4.10** CMR should be performed, in addition to or instead of initial screening echocardiography, in all adolescents and adults newly diagnosed with TS. Imaging should ideally be completed within 12 months, with the exact interval based on initial echocardiography findings (if echocardiography completed first), presence of additional risk factors, and clinician judgement (⊕⊕○○).
- **R 4.11** Computed tomography (CT) is a reasonable alternative when CMR is not tolerated or available. Both CT and CMR scans should include electrocardiogram (ECG)-gated or ECG-triggered assessment of the thoracic aorta (⊕⊕○○).
- **R 4.12** We recommend that individuals with TS, especially with aortic dilation or BAV, should be counseled to seek prompt evaluation if they experience acute symptoms consistent with aortic dissection, such as chest, neck, shoulder, back, or flank discomfort, particularly if it is sudden in onset and severe (⊕⊕○○).

Non-invasive imaging is an essential part of cardiovascular screening and surveillance across the life span of individuals with TS,^{233,388,396,418-423} but imaging remains underutilized and not systematically applied.^{420,424} The principal non-invasive imaging modalities are TTE, CMR, and CT.⁴²⁵

TTE is valuable for the diagnosis and surveillance of CHD and aortic dilation,⁴²⁶⁻⁴²⁸ but may be limited by poor acoustic windows, especially in older children and adults. Acoustic shadowing tends to be more pronounced in TS and may significantly limit the sensitivity of TTE to detect potentially outcome-determining lesions. CMR is not constrained by anatomic factors and is thus more sensitive for extra-cardiac lesions such as partial anomalous pulmonary venous return.^{388,395,420}

CMR is also superior to TTE for the diagnosis of BAV, aortic dilation and aortic arch anomalies^{395,429-433} while also providing important data on shunt fractions and ventricular volumes that may inform clinical management.³⁸⁸ CMR is radiation-free and can be acquired without intravenous contrast medium and is, therefore, especially useful during pregnancy and in younger individuals. However, CMR is less widely available compared to TTE and requires more extensive patient cooperation. Young children will therefore need a general anesthetic to undergo CMR. CT is a reasonable alternative to CMR when CMR access is limited or if the individual cannot tolerate an awake CMR. CT provides anatomical information of comparable quality to CMR during a much more rapid acquisition. However, CT involves radiation exposure, which is increased when ECG gating is used to obtain accurate aortic measurements. Therefore, CT is less suitable for serial surveillance.

4.5 Aortic dilation and dissection

- **R 4.13** Individuals with TS require lifelong cardiovascular surveillance at a frequency that should be determined by their risk factors for aortic dissection (⊕○○○).
- **R 4.14** For children <15 years old, aortic dilation may be categorized by calculating the TS-specific Z-score (Z). For adults and adolescents >15 years old, aortic dilation may be categorized by calculating the aortic height index (AHI), the aortic size index (ASI), the TS-specific Z-score, or the general population Z-score.
- **R 4.15** For adults with TS, we recommend informed, individualized decision-making about the timing of elective aortic surgery, considering risk factors for aortic dissection, including moderate aortic dilation (AHI > 23 mm m⁻¹, ASI > 2.3 cm m⁻², or Z > 3.5) with at least one additional risk factor: BAV, aortic coarctation, hypertension, or a rapid increase in aortic diameter (>3 mm year⁻¹). Dissection risk probably increases if more than one additional risk factor is present. Severe aortic dilation (AHI > 25 mm m⁻¹, ASI > 2.5 cm m⁻², or Z > 4) as a single risk factor should prompt an evaluation for elective aortic surgery (⊕○○○).

- **R 4.16** For children with TS, the risk of aortic dissection is much lower than in adults. We recommend informed, individualized decision-making about the timing of elective aortic surgery, considering risk factors for aortic dissection including moderate aortic dilation (age <15 years: $Z > 3.5$; age ≥ 15 years: $AHI \geq 23 \text{ mm m}^{-1}$, $ASI > 2.3 \text{ cm m}^{-2}$, or $Z > 3.5$) and hypertension, aortic coarctation, BAV, or a rapid increase in aortic diameter ($>3 \text{ mm year}^{-1}$ or $>1 Z \text{ year}^{-1}$) ($\oplus\circ\circ\circ$).
- **R 4.17** We recommend annual assessment of blood pressure, preferably using ambulatory blood pressure monitoring (ABPM), and initiation of medical therapies if hypertension is confirmed, for all individuals with TS ($\oplus\oplus\circ\circ$).

The incidence of aortic dissection in TS is approximately 164 per 100 000 person-years, compared to 6 per 100 000 person-years in the general population.³⁸² Seventy percent of aortic dissections originate in the ascending aorta (Type A), and 30% of dissections originate in the descending thoracic aorta (Type B).⁴³⁴ Dissections occur at a relatively young age in TS (mean 30–35 years), like other genetically triggered aortopathies.⁴³⁵ Dilation of the aorta, brachiocephalic and carotid arteries may be present even in the absence of structural heart disease, consistent with an underlying generalized arteriopathy.^{419,436,437} It is also important to note that aortic dissections occur at smaller absolute aortic diameters in TS than in other genetically triggered aortopathies.⁴³⁴ The proximal aorta may dilate more rapidly in individuals with TS if BAV is present,⁴³⁸ but there is no evidence that overall aortic dilation rates in TS are accelerated compared to matched controls without TS.^{421,434}

Many individuals with TS are significantly smaller than age and sex matched controls in the general population. In this context, applying the current absolute diameter thresholds for aortic dilation ($>4.0 \text{ cm}$) or aneurysm ($>4.5 \text{ cm}$) to adults with TS would almost certainly lead to delayed recognition of aortic disease.⁴³⁹ To correct for this size difference, we recommend indexing the ascending aortic diameter to body size.⁴⁴⁰ The most frequently used indexing methods are the Z-score (Z, dimensionless unit indicating the number of standard deviations from the population mean), the aortic height index (AHI, aortic diameter in millimeters divided by body length in meters), and the aortic size index (ASI, aortic diameter in centimeters divided by body surface area (BSA) per square meters) (Table 12).^{232,233,441–443} It is important to note that these indexing methods only apply to the ascending aorta, and ASI or Z-scores should only be used to guide medical decisions for adults who fall within 1–2 standard deviations around the mean BSA of 1.7–1.9 m^2 for all adult women. In practice, AHI is easiest to use and in one study showed greater predictive value compared to the absolute diameter, Z-score, or ASI. This is probably due to the prevalence of obesity, which can deflate the ASI or Z-score (Table 13).^{233,234,445} There is currently insufficient evidence to recommend one indexing method over another.²³³ For surgical decision-making, it may be useful to compare more than one indexing method.

Table 12. Methods to index ascending aortic diameter to body size.

Method	Calculation	Dilation cutoff	High risk cutoff
Absolute diameter (cm)	Direct measurement	>4.0	$>4.5^a$
Aortic height index (AHI, mm/m)	Absolute diameter/Height	>20	>25
Aortic size index ^b (ASI, cm/m^2)	Absolute diameter/BSA ^c	>2.0	>2.5
Z-score ^b (Z, dimensionless)	$Z = (x - \mu)/\sigma^d$	>2.5	>4

^aConsider this absolute diameter threshold for individuals at extremes of BSA (<1.3 or $>2.4 \text{ m}^2$).⁴³⁹ ^bUse ASI or Z-score with caution at extremes of BSA (<1.3 or $>2.4 \text{ m}^2$). ^cUse Dubois or Haycock methods to calculate BSA. ^dCalculated according to Campens et al.⁴⁴⁴ or Quezada et al.²³⁴ Z-score calculators are available online or may be downloaded from Prakash et al.,⁴⁴² Supporting Information.

Table 13. Effect of increasing body weight on ascending aortic size indices for a female age 40 years and height 150 cm.

Weight (kg)	50	60	70 ^a	70 ^a
BMI (kg m^{-2})	22.2	26.7	31.1	31.1
BSA (Haycock)	1.45	1.60	1.74	1.74
BSA (Dubois)	1.43	1.55	1.65	1.65
Absolute diameter (cm)	3.3	3.3	3.3	3.7
AHI (mm m^{-1})	22	22	22	25
ASI (cm m^{-1})	2.3	2.1	2.0	2.2
Z-score	2.5	2.2	1.9	3.0

Values considered to indicate aortic dilation are bolded. ^aNote that the absolute diameters (3.3 or 3.7 cm) in the two columns with the same weight of 70 kg are not considered to be dilated according to current guidelines.

Confirmatory studies are needed to clarify which indexing method may be optimal for TS individuals.

The prevalence of hypertension, aortic coarctation, and BAV is higher in individuals with TS who developed aortic dissections. Therefore, these diagnoses are viewed as additional risk factors for aortic dissection.⁴³⁴ A rapid rate of aortic dilation ($>3 \text{ mm year}^{-1}$) may also be a risk factor for dissection, but this has not been validated in TS. Individuals with one or more of these factors may require more frequent aortic surveillance or more intensive medical therapies to prevent aortic dissection (Figures 4 and 5).

We recommend a pragmatic approach to managing individuals with aortic dilation, recognizing the absence of clinical trials in TS cohorts that might provide guidance. Therefore, medical therapy of aortic disease in TS should be based on current clinical guidelines for aortic disease.^{439,446} As in other aortopathies, cystic medial degeneration has been documented in resected aortic tissues, suggesting that a similar medical management strategy is reasonable. As hypertension is common, maintenance of normal blood pressure may reduce the risk for aortic events.^{433,441,447} Because dissections can occur at relatively normal absolute aortic diameters, it is reasonable to begin prophylactic medical therapies as soon as aortic dilation is recognized, especially if hypertension is also present.

In general, technical concepts and perioperative care are not different for patients with TS compared to other patients with thoracic aortic aneurysms.^{446,448} When considering elective aortic surgery, an individualized shared decision between the patient and provider should be undertaken in consultation with an experienced team. In two studies, $ASI > 2.5 \text{ cm m}^{-2}$, corresponding to $AHI > 25 \text{ mm m}^{-1}$ or $Z > 4$, was identified

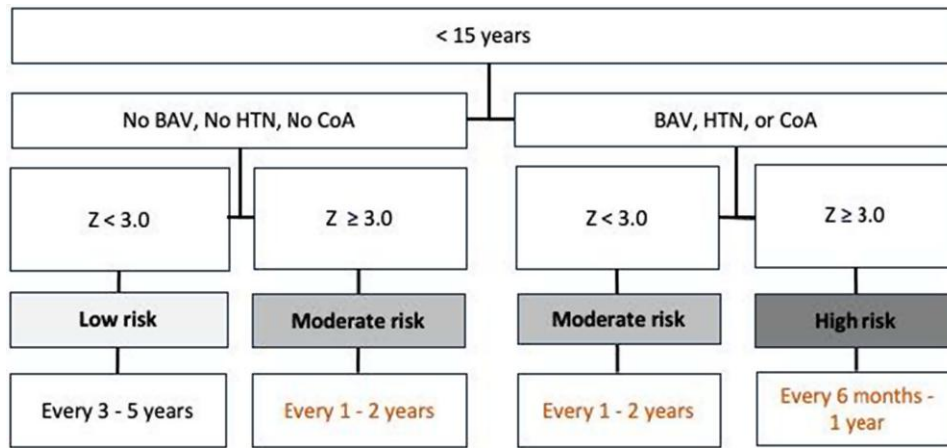


Figure 4. Suggested algorithm for the frequency of aortic surveillance of children and adolescents with TS, based on the perceived severity of aortic dilation and additional risk factors for aortic dissection. BAV, bicuspid aortic valve; HTN, hypertension; CoA, aortic coarctation; Z, Z-score. Frequency of surveillance may be affected by additional risk factors such as rapid aortic dilation. Aortic surveillance refers to measurement of aorta using TTE, cardiovascular magnetic resonance, or CT by a cardiovascular specialist.

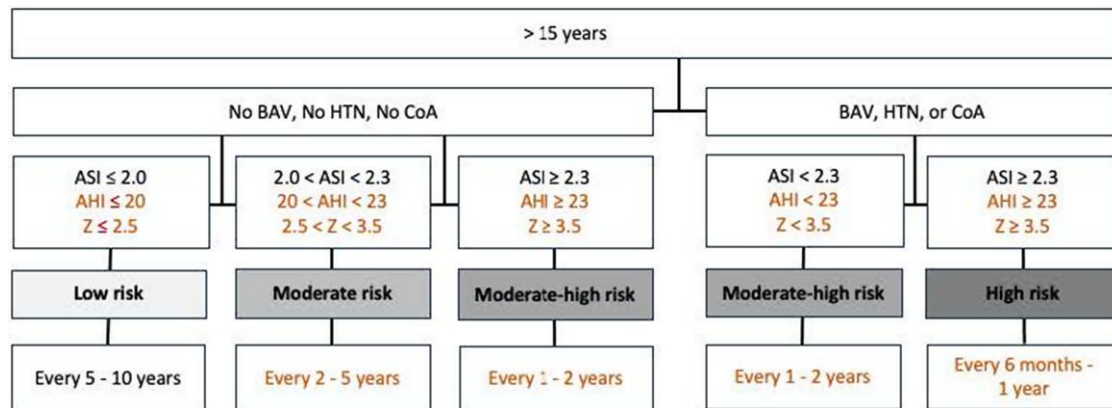


Figure 5. Suggested algorithm for the frequency of aortic surveillance of adults with TS based on the perceived severity of aortic dilation and additional risk factors for aortic dissection. BAV, bicuspid aortic valve; HTN, hypertension; CoA, aortic coarctation; ASI, aortic size index; AHI, aortic height index; Z, Z-score. Frequency of surveillance may be affected by additional risk factors such as rapid aortic dilation. If $ASI > 2.5 \text{ cm m}^{-2}$ (corresponding to $AHI > 25 \text{ mm m}^{-1}$ or $Z > 4$) or $ASI > 2.3 \text{ cm m}^{-2}$ (corresponding to $AHI > 23 \text{ mm m}^{-1}$ or $Z > 3.5$) with additional risk factors (see text), consider evaluation for elective aortic repair. Aortic surveillance refers to measurement of aorta using TTE, cardiovascular magnetic resonance, or CT by a cardiovascular specialist.

as an independent risk factor for aortic dissection in TS.^{435,449} However, other factors in addition to aortic dilation, such as a rapid increase in the absolute aortic diameter ($> 3 \text{ mm year}^{-1}$), hypertension, aortic coarctation, or BAV, may increase dissection risk and should be considered when counseling patients about an elective preventative aortic procedure.⁴³⁵

4.6 Hypertension

- **R 4.18** We recommend treatment with a beta-blocker, an angiotensin receptor blocker, or both for individuals with TS who have hypertension and have a dilated aorta (age < 15 years: $Z \geq 2.5$; age ≥ 15 years: $AHI \geq 20 \text{ mm m}^{-1}$, $ASI > 2.0 \text{ cm m}^{-2}$, or $Z > 2.5$) ($\oplus\oplus\circ\circ$).

- **R 4.19** We suggest that treatment with a beta-blocker, an angiotensin receptor blocker, or both should be considered for individuals with TS who have a dilated aorta (age < 15 years: $Z \geq 2.5$; age ≥ 15 years: $AHI \geq 20 \text{ mm m}^{-1}$, $ASI > 2.0 \text{ cm m}^{-2}$, or $Z > 2.5$), even if they are not hypertensive ($\oplus\circ\circ\circ$).
- **R 4.20** We recommend that medical treatment of hypertension for all individuals with TS who do not have a dilated aorta (age < 15 years: $Z < 2.5$; age ≥ 15 years: $AHI < 20 \text{ mm m}^{-1}$, $ASI < 2.0 \text{ cm m}^{-2}$, or $Z < 2.5$) should be based on the appropriate pediatric or adult guidelines for medical management of hypertension ($\oplus\oplus\circ\circ$).

4.6.1 Prevalence of hypertension

Hypertension is three to four times more prevalent in individuals with TS than in matched controls and does not vary significantly by karyotype.⁴⁵⁰⁻⁴⁵² The prevalence of hypertension is as high as 20%-40% in children^{441,453} and up to 60% in adults with TS.^{357,452,454-456} Systemic hypertension appears at early ages and progresses in frequency and severity throughout adulthood.^{384,450} Hypertension is more frequent in individuals with dysmorphism, coarctation, or renal anomalies but may also be idiopathic.⁴⁵⁷ Hypertension can persist after coarctation repair, even in those without residual descending aortic pressure gradients. The intrinsic shape of the aorta in individuals with TS who do not have coarctation may also contribute to the etiology of hypertension and can become more accentuated over time as the aorta elongates.⁴³³ Therefore, lifelong monitoring and follow up of hypertension is essential for individuals with TS.

4.6.2 Screening for hypertension

For everyone with TS, frequent screening to identify hypertension is recommended, beginning in childhood.^{447,458,459} Left ventricular hypertrophy and increased ventricular mass are commonly observed in TS, even in those who do not have a diagnosis of hypertension.^{460,461} This could be an end-organ effect of hypertension, altered aortic biomechanics, or loss of diurnal blood pressure variation that is masked during clinic blood pressure measurement.⁴⁵⁴ Proximal aortic stiffness is frequently increased in TS, even if the aorta is not dilated and the aortic valve is tricuspid.⁴⁶²⁻⁴⁶⁵ ABPM may be useful to confirm suspected hypertension and document impaired nocturnal dipping, which has been linked to other evidence of autonomic dysfunction in TS.^{328,466,467} Non-dipping or nocturnal hypertension is found in up to 50% of TS patients starting from a young age.⁴⁶⁸ Diagnosis of nocturnal hypertension can only be made by ABPM. We therefore advise ABPM for surveillance of hypertension for adults and for children beginning around age 10 years. Other methods to screen for hypertension, such as patient-reported home blood pressure monitoring or submaximal exercise testing, are reasonable if ABPM is not available.^{469,470} While hypertension is correlated with the presence of aortic dilation in TS, no studies have demonstrated that antihypertensive therapies slow or prevent aortic dilation.^{447,456,458} Nevertheless, the presence of hypertension is an additional argument to start medical treatment if aortic dilation is present.

4.6.3 Management of hypertension

Several guidelines for assessment of systemic hypertension in children and adolescents⁴⁷¹ or adults⁴⁷² are available, but none specifically addresses hypertension in individuals with TS. Therefore, we propose an algorithm for assessment and treatment of hypertension in TS that is derived from current guidelines (Figure 6). Hypertension in adults is defined as a mean systolic blood pressure >130 mm Hg or a mean diastolic blood pressure >80 mm Hg over at least two measurements.⁴⁷² For children, diagnosis of hypertension is dependent on normative values based on age, sex, and height that may vary between regional guidelines.^{471,473} For all individuals with TS who have hypertension, it is essential to diagnose and treat secondary causes of hypertension such as renal anomalies, obstructive uropathy, or coarctation. Both non-medical and medical treatments should be considered if hypertension is present. In all

cases, the therapeutic approach to hypertension should begin with assessment and treatment of risk factors such as obesity, dietary counseling, and encouragement of healthy lifestyle choices such as regular aerobic exercise.

If aortic disease is present (BAV, dilation, defined as $Z > 2.5$, $AHI > 20 \text{ mm m}^{-1}$, or $ASI > 2.0 \text{ cm m}^{-2}$, or aortic dissection), initial treatment targets and antihypertensive medications should be selected according to the 2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease.⁴³⁹ Medical therapy of hypertension for individuals with TS and aortic dilation should preferably include a beta-blocker, angiotensin receptor blocker (ARB), or both, which have been shown to prevent aortic dilation and aortic dissections in individuals with other aortopathy conditions.⁴³⁹ The choice between a beta blocker and ARB should be based on shared decision-making with the patient and family, taking into consideration resting heart rate, ECG abnormalities, and side effects such as fatigue. If aortic disease is absent (TAV and $Z < 2.5$, $AHI < 20 \text{ mm m}^{-1}$, or $ASI < 2.0 \text{ cm m}^{-2}$, no dissection), initial treatment targets and antihypertensive medications should be based on current guidelines for hypertension, which recommend an angiotensin converting enzyme inhibitor or ARB as first-line therapy for adults and children, depending on co-existing conditions such as diabetes.⁴⁷¹⁻⁴⁷³

4.6.4 Estrogen supplementation and hypertension

There is inconclusive evidence about the effect of estrogen supplementation on blood pressure. A recent randomized clinical trial found no difference in the rate of increase in blood pressure over 5 years in young participants with TS (23 ± 2 years) who were assigned to 2 or 4 mg of oral E2 supplementation.³²⁸ A crossover study found that arterial stiffness and central blood pressures decreased in older individuals with TS (29 ± 9 years) after they stopped taking 2 mg oral E2.³⁵⁸ Another study showed that blood pressure decreased during treatment with E2 (either oral or TD) for 6 months compared with no treatment for 4 months.³⁵⁷ There is some evidence that blood pressure may be substantially lower with TD E2 preparations compared to oral ethinyl E2, but this has not been tested specifically in TS.³⁵⁹

4.7 Coagulation and thrombosis

- **R 4.21** We do not recommend routine screening for blood clotting disorders before initiation of female sex HRT. The diagnosis, surveillance, and treatment of blood clotting disorders in TS should be based on the appropriate pediatric or adult clinical guidelines for the general population (⊕○○○).

Coagulation is generally normal when evaluated in large TS cohorts, and in general TS does not seem to be an independent risk factor for venous thrombosis.²⁹ While increased levels of procoagulant factors and reduced protein C and S were reported in some individuals with TS,^{129,474} most studies have reported normal levels of clotting factors, fibrinolytic factors, and clotting times.⁴⁵⁵ In addition, no evidence supports the concept that HRT increases risks for deep venous thrombosis.²⁹

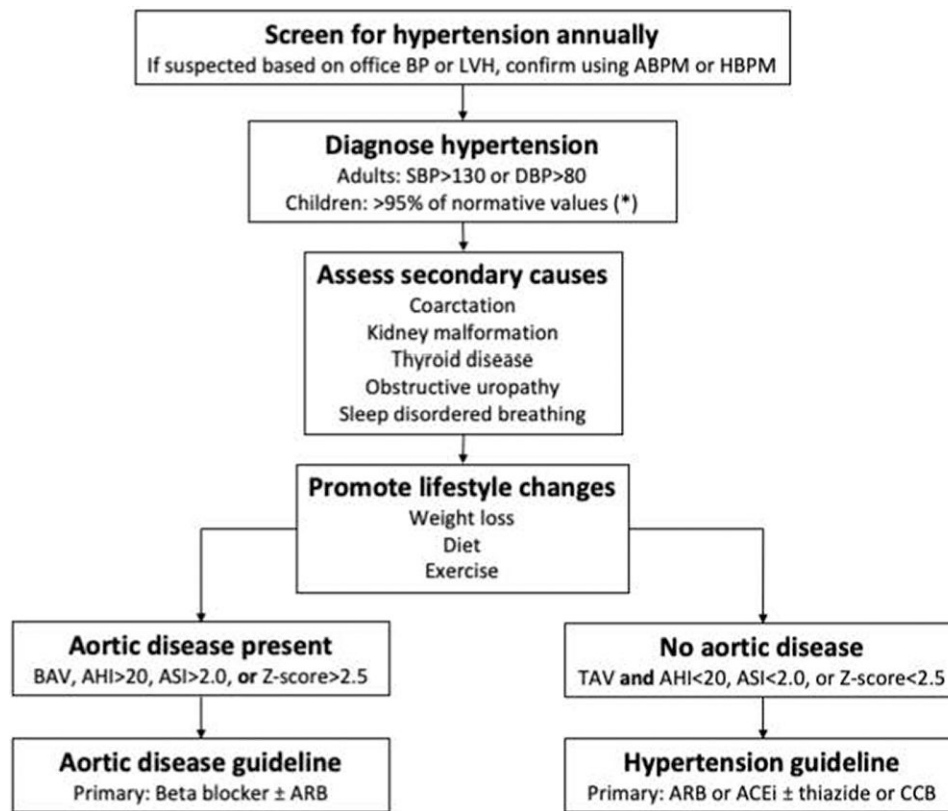


Figure 6. Algorithm for management of hypertension in TS. BP, blood pressure; LVH, evidence of left ventricular hypertrophy on ECG or echocardiogram; ABPM, ambulatory blood pressure monitoring; HBPM, home blood pressure monitoring; SBP, systolic blood pressure; DBP, diastolic blood pressure; BAV, bicuspid aortic valve; TAV, tricuspid aortic valve; AHI, aortic height index (mm m^{-1}); ASI, aortic size index (cm m^{-2}); ARB, angiotensin receptor blocker; ACEi, angiotensin converting enzyme inhibitor; CCB, dihydropyridine calcium channel blocker; Aortic disease, aortic dilation or dissection. *For children, diagnosis of hypertension is dependent on normative values based on age, sex, and height that may vary between regional guidelines.^{471,473}

Outcome data about venous thrombosis are rare in TS, and a common underlying cause of thrombotic events has not yet been identified. Because no consistent abnormalities in venous thrombosis have been described, there is no evidence-based consensus about when to assess the coagulation system in individuals with TS. However, raising awareness about thromboembolic disease can help to identify the relatively few individuals with TS who present due to coagulation issues.

While venous anomalies (anomalous pulmonary veins, left superior vena cava) are more common in TS, the question remains if malformations of the inferior vena cava or pelvic veins increase the risk for deep venous thrombosis of the lower extremities.^{395,475} Venous obstruction should be considered if an individual with TS develops unprovoked venous thrombosis.

4.8 Hyperlipidemia

- **R 4.22** We recommend that an initial lipid profile should be obtained no later than the age of initial screening recommended by country-specific guidelines or at transition and repeated every 3 years. The diagnosis and treatment of hyperlipidemia in TS should be based on the appropriate pediatric or adult clinical guidelines for the general population (⊕⊕○○).

Hypercholesterolemia is prevalent in TS and is influenced by numerous intrinsic factors, including obesity, metabolic syndrome, and type 1 or type 2 diabetes. Individuals with TS and comorbidities often exhibit higher total cholesterol, LDL cholesterol, and triglycerides compared to controls, although severe elevations are infrequently reported.^{331,476} There does not seem to be a specific dyslipidemia associated with TS.^{331,455}

Although there is evidence suggesting that estrogen treatment can affect lipid concentrations, the impact does not seem to be clinically significant. Additionally, the type or method of estrogen administration does not appear to modify cardiovascular risk.²⁹ Therefore, there is no rationale for routine assessment of lipids prior to initiation of HRT. There is no international consensus on when to begin lipid monitoring in individuals with TS. A small study showed marginally increased plasma lipids in children and adolescents with TS.⁴⁷⁷ However, the individuals in that study also had significantly higher waist circumference, impaired glucose tolerance, and higher blood pressures.⁴⁷⁷ This means that the healthy and normal weight individual with TS may not have an increased risk of dyslipidemia per se.

If hyperlipidemia is detected, it is important to investigate potential secondary causes such as hypothyroidism, familial hypercholesterolemia, or primary hypertriglyceridemia. Treatment should then align with the recommendations for the general population that feature dietary changes, weight loss, and physical activity in the initial strategy.⁴⁷⁸ Statin

exposure possibly exacerbates the risk to develop diabetes in individuals with TS, who are already at high risk for metabolic derangement.^{479,480} We acknowledge that this area requires additional research to clarify regional differences in when to assess and intervene.⁴⁷⁸

4.9 Coronary artery disease

- **R 4.23** We recommend that new onset chest pain, regardless of age, should be assessed by a cardiologist. The diagnosis, surveillance, and treatment of coronary artery disease in TS should be based on the appropriate pediatric or adult clinical guidelines for the general population (⊕⊕○○).

Ischemic heart disease is a major cause of morbidity and mortality in TS.^{27,29} Studies that rely on death certificates to determine causes of death found that the standardized mortality ratio for ischemic heart disease is elevated in TS, with most deaths due to coronary artery disease occurring after age 45.²⁷ The major risk factors for ischemic heart disease in TS are hypertension, diabetes, and the metabolic syndrome.⁴⁸¹

There is no evidence that TS predisposes to coronary artery disease independently of traditional cardiovascular risk factors, such as hypertension, type 2 diabetes, obesity, or smoking.^{482,483} Two studies reached conflicting conclusions about this issue using coronary CT.^{482,483} However, the presence of CHD may increase the likelihood of developing coronary artery disease in later life.⁴⁸⁴ In the absence of evidence for a specific cause related to TS, management of coronary artery disease should be based on the appropriate clinical guidelines.

Routine screening for coronary artery disease in asymptomatic individuals has not been beneficial and should not be considered in TS.⁴⁸⁵ However, if an adult with TS who has cardiovascular risk factors experiences chest pain, the first imperative should be to rule out coronary artery disease. With the broad use of CT angiography in different clinical settings, non-obstructive coronary plaques are likely to be observed coincidentally in individuals with TS. This could prompt a more thorough assessment of hypertension, glucose, and lipid status but should not lead to primary preventative therapy with aspirin due to the low probability of benefit and the high risk of bleeding.⁴⁸⁶

4.10 Electrocardiographic abnormalities and arrhythmias

- **R 4.24** We recommend that a resting ECG should be performed at the time of diagnosis to assess for findings consistent with CHD, an arrhythmia, or conduction abnormality. Follow up ECGs should be obtained and reviewed by a cardiologist at intervals deemed appropriate based on baseline findings, underlying CHD, and clinical course (⊕⊕⊕⊕).
- **R 4.25** We suggest, given prior concern for QTc prolongation in persons with TS, that the QTc

should be routinely calculated, ideally using Hodges formula, whenever an ECG is performed on a patient with TS. However, newer research suggests that QTc prolongation is not more prevalent in persons with TS compared to the general population when defining prolongation as QTc >450 ms in girls (up to 15 years old) and >460 ms in women and when using Hodges formula (⊕⊕○○).

- **R 4.26** We recommend that standard guidelines for the general population should apply to individuals with TS if QTc prolongation >480 ms by Hodges formula has been detected on at least two serial ECGs. In those circumstances, consultation with a cardiologist, possibly an electrophysiologist, should be completed (⊕⊕⊕○).

A higher resting heart rate has been well documented in TS cohorts and has been linked to increased resting sympathetic tone and other features of dysautonomia.^{487,488} The incidence of supraventricular arrhythmias, including atrial fibrillation, may be increased in individuals with TS compared to the general population.^{29,488,489} Other ECG abnormalities (“RSR” complexes, right axis deviation, right ventricular hypertrophy, accelerated atrioventricular conduction, and T-wave abnormalities) have also been reported at higher rates compared to the general population. However, these findings are minor in many cases and the clinical implications are not clear.^{487,490,491}

For QTc calculation, Hodges is one formula that utilizes a linear rather than an exponential term and therefore allows for less overestimation of QTc for heart rates greater than 60 bpm. Given the frequency of higher resting heart rates, calculation of the QTc interval using Hodges formula is suggested for use in individuals with TS.^{1,492} Newer research that was published after the 2016 guidelines suggests that QTc prolongation may not be more prevalent among individuals with TS compared to the general population when defining prolongation as QTc >450 ms in girls and >460 ms in women using Hodges formula. Importantly, there is no documented association between QTc prolongation in persons with TS and sudden cardiac death.^{491,493,494}

All individuals with TS should have a baseline ECG at the time of diagnosis, which can provide clues to possible structural heart or conduction abnormalities. The frequency of follow-up ECGs should be determined by baseline ECG characteristics and the clinical course (ie, discovery of CHD, development of hypertension, development of arrhythmia, new symptoms of concern, use of certain medications). For individuals with CHD, hypertension, or a history of arrhythmia, ECGs should be performed at intervals deemed appropriate by the cardiologist based on the specific diagnosis and indications. For individuals with TS who do not have existing diagnoses as above or new symptoms or medications of concern, it is reasonable to perform an ECG at each recommended imaging interval and associated visit (Figure 2).

We propose that cutoffs for QTc prolongation and thresholds for further work up, referral, activity restrictions, and medication restrictions should be consistent with existing societal guidelines and expert recommendations.^{492,495}

4.11 Exercise and activity

- **R 4.27** We recommend regular aerobic physical activities as part of a heart healthy lifestyle for all individuals with TS (⊕○○○).
- **R 4.28** We recommend that the function of the aortic valve, the presence of any other congenital heart lesions, and hypertension should be considered in determining athletic participation recommendations for the individuals with TS and aortic dilation (⊕○○○).
- **R 4.29** We suggest that for individuals with normal aortic size (age < 15 years: $Z < 2.5$; age ≥ 15 years: $AHI < 20 \text{ mm m}^{-1}$, $ASI < 2.0 \text{ cm m}^{-2}$, or $Z < 2.5$), it is reasonable to participate in all sports (⊕○○○).
- **R 4.30** We suggest that for individuals with a mild to moderately dilated aorta (age < 15 years: $Z 2.5-3.5$; age ≥ 15 years: $AHI 20-23 \text{ mm m}^{-1}$, $ASI 2.0-2.3 \text{ cm m}^{-2}$, or $Z 2.5-3.5$), participation in low and moderate static and dynamic competitive sports may be acceptable but intense weight-training should be avoided (⊕○○○).
- **R 4.31** We suggest that individuals with a moderately to severely dilated aorta (age < 15 years: $Z > 3.5$; age ≥ 15 years: $AHI > 23 \text{ mm m}^{-1}$, $ASI > 2.3 \text{ cm m}^{-2}$, or $Z > 3.5$) should be advised not to participate in any competitive sports, intense weight-training, or physical activities with risk of contact injury to the chest (⊕○○○).

In most individuals with TS, the benefits of exercise outweigh the very low risk of exercise-induced aortic dissection. Therefore, exercise should be promoted as a general component of a healthy lifestyle.

In recent surveys, a sedentary lifestyle was reported by more than half of children and adults with TS and was associated with arterial hypertension.⁴⁹⁶⁻⁴⁹⁸ There is no evidence that exercise capacity is intrinsically lower in TS.^{499,500} Given the propensity for obesity and the metabolic syndrome in TS, health care professionals should be mindful of the significant benefits of having a “heart-healthy” lifestyle in light of the low risk of aortic dissection in TS (about 40:100 000 patient-years), the rare occurrence of aortic dissection related to exercise, and growing evidence that supervised exercise is safe for individuals with thoracic aortic aneurysms or dissections.⁵⁰¹⁻⁵⁰³ While there is no published data about the effects of exercise on vascular disease in TS, aerobic exercise was shown to decrease aortic growth rates in a mouse model of Marfan syndrome and may also be protective in humans.^{504,505} Therefore, consideration of aortic dissection risk should be tempered by the importance of encouraging individualized levels of physical activity. Current recommendations include at least 150 min of weekly moderate intensity, primarily aerobic physical activities for adults and at least 60 min of daily moderate to vigorous activities for children.⁵⁰⁶

Before anyone with TS starts an exercise program, it is important to evaluate and treat any congenital or acquired cardiovascular lesions that may increase exertional risk, such as BAV, thoracic aortic dilation, hypertension, or coronary heart disease, in consultation with a cardiologist.

Provided that these risks are addressed and treated, most individuals with mild to moderate aortic dilation ($Z \leq 3.5$, $AHI \leq 23 \text{ mm m}^{-1}$, or $ASI \leq 2.3 \text{ cm m}^{-2}$) can safely engage in low to moderate intensity recreational activities. High-intensity, competitive, and contact sports or physical activities are generally prohibited for anyone with TS who has a dilated aorta ($AHI \geq 20 \text{ mm m}^{-1}$, $ASI \geq 2.0 \text{ cm m}^{-2}$ or $Z \geq 2.5$).⁵⁰⁷ Practical guidance on the type, frequency, and intensity of exercise should be based on the 2020 European Society for Cardiology guidelines on sports cardiology and exercise in patients with cardiovascular disease.⁵⁰⁸ For individuals with TS who do not have congenital or acquired cardiovascular disease, the current evidence is insufficient to make specific recommendations about competitive athletics.

4.12 Cardiovascular management during pregnancy

- **R 4.32** We recommend that cardiovascular imaging, ideally CMR or CT, should be performed at least within 2 years before planned pregnancy or assisted reproductive methods and repeated closer to pregnancy if recommended by a cardiovascular specialist (⊕⊕○○).
- **R 4.33** In the presence of aortic dilation ($AHI > 20 \text{ mm m}^{-1}$, $ASI > 2.0 \text{ cm m}^{-2}$, or $Z > 2.5$) or at least one other risk factor for dissection (BAV, aortic coarctation, hypertension, rapid aortic diameter increase), we recommend informed, individualized peripartum cardiovascular care by a multidisciplinary team that ideally should include a maternal-fetal medicine specialist and a cardiologist with expertise in managing women with TS, preferably in a center with expertise in aortic surgery and TS (⊕○○○).
- **R 4.34** In the presence of severe aortic dilation ($AHI > 25 \text{ mm m}^{-1}$, $ASI > 2.5 \text{ cm m}^{-2}$, or $Z > 4$) and especially when other risk factors for aortic dissection are present (previous aortic surgery, previous aortic dissection, or rapid aortic diameter increase ($>3 \text{ mm year}^{-1}$), BAV, hypertension, or aortic coarctation), we suggest that assisted reproductive technologies or spontaneous conception should be avoided (⊕○○○).
- **R 4.35** We recommend tight blood pressure control to a target of less than 130/80 mm Hg during the peripartum period. Antihypertensive therapies and low dose aspirin for the prevention of adverse pregnancy outcomes due to preeclampsia and related hypertensive disorders should be administered

according to current clinical practice guidelines (⊕⊕○○).

- **R 4.36** We recommend obtaining a TTE at least once during pregnancies in low-risk women ($AHI < 20 \text{ mm m}^{-1}$, $Z < 2.5$, $ASI < 2.0 \text{ cm m}^{-2}$ and no BAV, aortic coarctation, hypertension, or rapid aortic diameter increase), ideally around 20 weeks of gestation (⊕⊕○○).
- **R 4.37** In the presence of aortic dilation ($AHI > 20 \text{ mm m}^{-1}$, $ASI > 2.0 \text{ cm m}^{-2}$, or $Z > 2.5$) or at least one other risk factor (BAV, aortic coarctation, hypertension, rapid aortic diameter increase), we suggest TTE at least once every 12 weeks during pregnancy, or more frequently on an individualized basis. Consideration of an additional imaging study in the early third trimester is reasonable and is strongly encouraged if there is any concerning change noted on the second trimester TTE (⊕○○○).
- **R 4.38** We recommend that CMR (without contrast medium) should be performed during pregnancy when TTE raises suspicion of rapid aortic dilation. If aortic segments previously known to be dilated cannot be adequately visualized, or if new dilation is suspected, CMR should be used for confirmation (⊕⊕○○).
- **R 4.39** We suggest that rapid aortic diameter increase ($>3 \text{ mm}$ compared to pre-conception imaging) should lead to renewed risk assessment and discussion in an expert center with a multidisciplinary team to determine potential modifications of maternal risk factors for aortic dissection, delivery, and postpartum planning, including consideration of prophylactic aortic replacement (⊕○○○).
- **R 4.40** We recommend the mode of infant delivery should be based on the safest method to prevent aortic and obstetric complications, individual preferences, and local professional expertise. Preventive measures (epidural anesthesia, expedited second stage of labor) that reduce the risk of aortic dissection should be considered, but are especially recommended in the presence of aortic dilation ($AHI > 20 \text{ mm m}^{-1}$, $ASI > 2.0 \text{ cm m}^{-2}$, or $Z > 2.5$) or additional risk factors for aortic dissection (BAV, aortic coarctation, hypertension, rapid aortic diameter increase). Cesarean section is preferred for individuals with severe aortic dilation ($AHI > 25 \text{ mm/m}$, $ASI > 2.5 \text{ cm m}^{-2}$, or $Z > 4$) or a history of aortic dissection (⊕○○○).

- **R 4.41** We recommend postpartum cardiac imaging and cardiology consultation due to the continued risk of aortic dissection. For individuals with severe aortic dilation ($AHI > 25 \text{ mm m}^{-1}$, $ASI > 2.5 \text{ cm m}^{-2}$, or $Z > 4$) or a history of aortic dissection, the initial post-partum visit should occur 2-6 weeks after delivery with at least one additional follow up cardiology visit. For individuals with less severe aortic disease, one postpartum visit 4-6 months after delivery may be sufficient before resuming routine follow-up intervals (⊕○○○).
- **R 4.42** We recommend that individuals who can become pregnant and have left-sided obstructive lesions (subaortic stenosis, aortic valve stenosis, or coarctation) should have regular aortic imaging and cardiovascular follow up with consideration for intervention before pregnancy (⊕○○○).
- **R 4.43** We recommend that individuals with severe subaortic or aortic valve stenosis or significant valve disease and reduced cardiac function should be advised against pregnancy (⊕○○○).

4.12.1 Aortic dilation and dissection

In 2003, the first reports of serious cardiac complications and deaths of pregnant women with TS were published.⁵⁰⁹ Initial estimates of maternal deaths due to aortic dissections during pregnancy were much higher than in more recent studies, probably because pre-pregnancy cardiac evaluations were performed less frequently in older cohorts.⁵¹⁰⁻⁵¹³ There is no evidence that multiple gestations are a significant risk factor for aortic complications, although multiple pregnancies and multiple embryo transfers does lead to an increased risk of hypertension, which might contribute to dissection risk.⁵¹⁴ Cardiovascular demands of pregnancy are high due to increased cardiac output, stroke volume, heart rate, and plasma volume. The risk of aortic dissections may be increased during the peripartum period in TS.⁵¹⁵⁻⁵¹⁷ Assisted reproductive technologies were proposed to be a risk factor for aortic dilation or dissection, but recent studies did not show any difference in aortic complications.⁵¹⁰ Several studies have shown that aortic dimensions do not change significantly during pregnancy.^{511,512} In TS cases when the aorta is dilated, there are no studies that consider the advisability of elective aortic surgery before pregnancy. After proximal aortic repair, women with TS are still considered to be at high risk for aortic dissections.

4.12.2 Other cardiovascular conditions

Apart from the risk for aortic dissection, women with TS may have other cardiovascular abnormalities such as aortic valve stenosis or coarctation of the aorta that can impact the management of pregnancy and delivery. The hemodynamic consequences of stenotic BAVs, subaortic obstruction, and coarctation can be exacerbated by increased cardiac output during pregnancy. It is important to conduct a comprehensive evaluation before a patient becomes pregnant to identify

potential risks and provide guidance for pre-pregnancy valve interventions, coarctation repair, or other necessary measures. It is also important to compare the potential risks associated with interventions, such as mechanical valve replacement necessitating warfarin therapy during pregnancy, to the risks of pregnancy without intervention. Although there is limited data on TS, a Registry of Pregnancy and Cardiac Disease (ROPAC) study clearly demonstrated that women with moderate to severe aortic stenosis can complete successful pregnancies without fatalities. However, some experienced heart failure and required medical interventions.⁵¹⁸ The hemodynamic challenges during pregnancy are similar for those with subaortic stenosis.⁵¹⁹

Pregnancy is generally well tolerated by women who have undergone aortic coarctation repair.⁵²⁰ However, individuals with unrepaired coarctation or those who have undergone repair and have hypertension, residual coarctation, or aortic dilation, have an increased risk for complications, including aortic dissection.⁵²¹ Therefore, pre-pregnancy assessment and counseling should include complete aortic imaging and blood pressure control. Balloon dilation of coarctation during pregnancy should be avoided in TS due to complication risks.⁴¹⁷

Current guidelines recommend counseling against pregnancy only for symptomatic patients with severe aortic stenosis or asymptomatic patients with impaired left ventricular function or an abnormal exercise test.⁵²¹ Otherwise, pregnancy appears to be well tolerated. The guidelines for care are similar to those for women with cardiovascular disease without TS.⁵²¹

4.12.3 Hypertension during pregnancy

Women with TS are at increased risk for hypertensive disorders of pregnancy, including pre-eclampsia.⁵²²⁻⁵²⁴ Pre-eclampsia in the general pregnant population is associated with several risk factors, including a family history of pre-eclampsia, nulliparity, older age, elevated BMI, pre-existing diabetes mellitus, chronic renal disease, antiphospholipid antibodies, multiple gestations, and pre-existing hypertension.⁵²⁵ Hypertension is more common in women with TS throughout the lifespan, which may contribute to the higher incidence of hypertensive complications during pregnancy.

Medical treatment to reduce cardiovascular risks comprises anti-hypertensive medications and prophylactic medications to prevent aortic dilation. Anti-hypertensive treatment recommendations do not differ from those for pregnant women who do not have TS. There is no clear evidence for prophylactic medication during pregnancy in women with TS who have aortic dilation and no support for a specific type of anti-hypertensive medication. Beta-blockers may be considered during pregnancy for women with aortic dilation (extrapolated from data for women with Marfan syndrome) and do not cause fetal abnormalities. However, decreased fetal birth weight may be associated with peripartum use of beta-blockers and fetal growth should be monitored.^{526,527}

To prevent hypertensive disorders of pregnancy, it is recommended to start 75-81 mg aspirin daily beginning at 12 weeks of gestation until delivery. This recommendation is based on evidence that aspirin use may be beneficial to individuals who have two or more moderate risk factors for adverse pregnancy health outcomes, such as a first pregnancy, chronic hypertension, or kidney disease.⁵²⁸ While oocyte donation is not seen as a specific risk factor, it does confer a 2-3-fold risk of preeclampsia⁵²⁹ and aspirin should also be considered for TS pregnancies that result from oocyte donation.⁵³⁰

4.12.4 Delivery plan

A delivery plan should be made by a multidisciplinary team consisting of at least an obstetrician, cardiologist, and anesthesiologist with expertise in pregnancy in the context of maternal heart disease or arteriopathy. Vaginal delivery is the preferred mode of delivery in most women, based on the available literature. In ROPAC data, cesarean section was not superior to a vaginal delivery in terms of maternal outcomes, but an increase in adverse fetal events was observed.⁵²⁷ Based on expert opinion, in women with a dilated aorta, a cesarean section is reasonable, although it also leads to hemodynamic changes. Aortic dissection during pregnancy is a life-threatening complication that requires emergent cardiovascular specialist care. If the dissection happens in early pregnancy without a viable fetus, emergency aortic surgery is recommended. If the fetus is viable, it is recommended to perform a cesarean section followed by emergency aortic surgery.

GRADE question 3: what are the effects of blood pressure treatment on clinical outcomes in TS? TS is often accompanied by hypertension, which has been linked to the development of aortic dilation or dissection, which are both observed with strikingly increased frequency in TS. Some experts have advocated for stricter blood pressure control in TS individuals. Therefore, two questions were formulated:

1. At what blood pressure threshold should hypertension in TS be treated?
2. What anti-hypertensive treatment is most effective in TS?

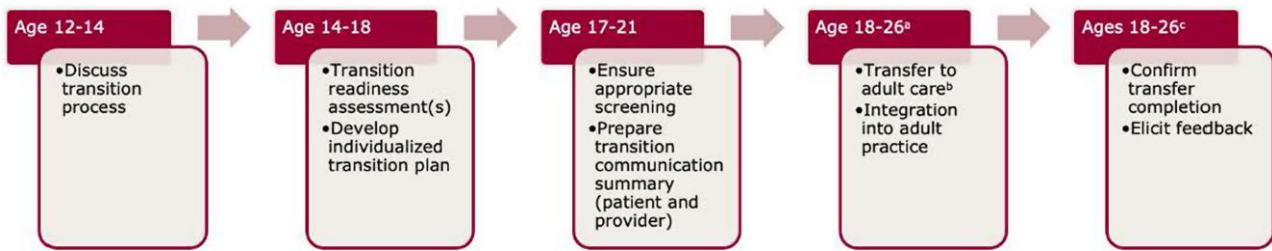
We searched for studies comparing different blood pressure targets and different blood pressure treatments. Randomized and non-randomized studies were considered; cohort studies without a control arm and case series were ineligible. Two systematic reviews of hypertension in pediatric (127 full texts) and primarily adult (63 full texts) TS case series were published in 2022.^{453,458} No comparative studies of specific anti-hypertensive treatments or blood pressure targets were identified in either review. Therefore, there is currently insufficient evidence to answer the GRADE question.

5. Transition

- **R 5.1** We recommend an intentional, defined, individualized pathway to transition from pediatric to adult care for adolescents with TS beginning in early adolescence (⊕⊕○○).

5.1 Importance of intentional and defined transition pathway

Adolescents and young adults (AYA) with chronic health care needs have high rates of complications during the crucial years of transition.⁵³¹ Structured transition in AYA with chronic health care needs is shown to be beneficial in a number of specific situations,^{532,533} though data are mixed.⁵³⁴⁻⁵³⁶ Measures of transition success have not been well-defined or applied^{531,534,537} and longitudinal studies have not been conducted.⁵³⁷ Data specific to the impact of transition process in the TS population are sparse, though one study showed



Transition considerations specific to TS:

- ^a Transition may be delayed due to cognitive differences
- ^b Paucity of specialized adult providers (quality of care may be highest with endocrine provider)
- ^c Failure of appropriate screening in adulthood is common

Figure 7. Proposed TS transition timeline (adapted from White 2018).⁵³²

lower loss to follow up in AYA with TS with organized transition.⁵³⁸

5.2 Transition pathway elements

White et al. define six core elements of health care transition (Figure 1 in⁵³²), outlining pediatric and adult contributions, with input from various members of the health care team. This guideline includes a specific focus on youth with medical complexity, and outlines responsibilities of various transition team members. The transition team may include physicians, social workers, nurses, clinic administrators, information technology staff, and home care clinicians. Applying the doctrines of this core structure allows adaptation of its principles to each setting and everyone. The process begins with an introduction of the transition plan, tracks the progress through transition, applies assessment(s) of transition readiness, defines specific steps towards transition, completion of transfer, and confirmation of transition completion/success (Figure 7). Through this process, concise and clear written clinical summaries and educational materials may be used to empower families and address gaps based on the type of clinician that is coordinating the care for a given individual with TS.^{424,451,539,540} Efforts for hospital systems and/or payors to support a care coordinator for individuals with TS are crucial to guide navigation of the various health care system and payors, and to ensure completion of referrals and visits. Transition checklists are available via various societies/organizations to ensure completion of essential elements. Future efforts could include a list of talking points and/or suggested questions for individuals with TS to bring to their new provider. Efforts should also be made to connect individuals with TS and their family to advocacy groups during healthcare transition.^{451,532} In Europe many pediatric caregivers have access to adult TS health care teams, and the European Reference Network (<https://endo-ern.eu/>) supports coordination and collaboration between health care centers also across borders.

- **R 5.2** We suggest a formal assessment of transition readiness at multiple timepoints of the individual and/or caregiver/support person to identify specific needs and barriers to successful transition (⊕○○○).

5.3 Transition readiness tools

Given the numerous challenges noted in healthcare transition for AYA with TS, tools have been developed for assessment and ongoing monitoring of transition readiness.^{451,541} Several general (non-disease specific) transition readiness tools have been created, with variable psychometric properties.⁵⁴² The Transition Readiness Assessment Questionnaire 5.0 (TRAQ) is a 20-item validated measure which is used to examine knowledge and health-related skills (eg, appointment-keeping, managing medications and daily activities, communicating with providers).⁵⁴³ Studies have shown adolescent and young adults with TS have lower TRAQ scores than those without TS.^{544,545} Another tool that has been used in clinical research but not yet validated is the TS-specific transition tool provided by the Endocrine Society (Table S8), which includes 10 questions about health, 16 about using health care, and 15 focused on social and emotional factors salient to TS.⁵⁴⁶ In addition to these assessment tools, various TS teams have described educational materials they use to facilitate healthcare transition for their TS population⁵³⁸ (Table S9).

5.4 Limitations to transition readiness tools

Despite the potential benefits of using these transition readiness assessment tools, many limitations exist. There is a paucity of research examining a broad spectrum of health outcomes, including developmental and biopsychosocial outcomes (eg, adherence, self-efficacy, QoL) based on transition readiness scores and/or use of these tools in AYA with chronic conditions.^{537,542} Most transition-related research in AYA with TS and other endocrine conditions has focused mainly on the number of follow-up appointments and/or drop-out of care.^{538,547} Further, whereas these tools have been designed to assess progress towards transition readiness over time,⁴⁵¹ longitudinal studies have not been conducted.^{537,542} Additionally, perspectives of transition readiness may differ across informants—specifically, research in TS and other conditions has shown conflicting readiness scores reported by patients versus caregivers, and it is not clear how clinicians should address these discrepancies.^{537,546} Identifying implementation strategies for these tools is also critical, as research has shown transition discussions are inconsistent (particularly regarding reproductive, lifestyle, and psychosocial factors) and that transition tools are not routinely used in TS care.⁵³⁹

5.5 Barriers to successful transition

The identification of barriers to successful transition is challenging due to a lack of consistent measures of what constitutes transition success.^{531,534} In a systematic review, the most important barriers to successful transition across chronic illness groups were in the “relationship domain” (eg, difficulties in letting go of long-standing relationships with pediatric providers), “access to adult services,” “knowledge” (regarding medication/illness), and “insurance issues”.⁵⁴⁸ There are aspects of care in individuals with TS that pose barriers to transition that are unique from other chronic conditions, such as lower visuospatial processing and self-esteem, and difficulties with executive functioning.³⁶⁷ Moreover, although 80% of all TS adolescents were 100% accurate in reporting their personal medical history in a US single center study, this accuracy was not an adequate surrogate for transition readiness.⁵⁴⁹ Transition readiness and/or success in individuals with TS seems to differ from other chronic conditions, with distinct requirements including, but not limited to, individualization of transition timing, and a longer period of caregiver support may be necessary.⁵⁵⁰

Indeed, a survey showed most women with TS 18-25 years of age still relied on their parents for both care and finances, though independence increased with age.⁵⁵⁰ Additionally, perspectives of AYA with TS and their caregivers often differ regarding readiness for independence, with TS individuals reporting a much higher readiness than their caregivers.⁵⁴⁶ While full emancipation may be delayed, a gradual shift in responsibility (eg, having the adolescent make appointments, answer questions during clinic visits, and call for medical refills) should be encouraged.⁴⁵¹ General guidelines recommend that transition begin between 12 and 14 years of age, yet developmental age is likely more relevant than chronological age in individuals with TS given the increased neurocognitive and psychosocial differences.^{424,532,533}

Systematic barriers are also important to consider and address as AYA with TS reach adulthood and need to establish an adult medical home. Gaps in care among adult women with TS are in large part attributed to the lack of specialized adult TS providers/centers.⁴²⁴ Future efforts within societies and advocacy groups that support TS care and education should seek to improve early exposure of trainees in various specialties and promote outreach/networking between societies (eg, joint conferences).

5.6 Studies related to transition

- **R 5.3** We suggest that developmentally appropriate organ systems-based assessment and counseling occurs during transition, ensuring that these elements are documented upon transfer (⊕⊕○○).
- **R 5.4** We suggest that pediatric health care teams transition individuals with TS to adult providers with expertise to manage TS comorbidities (⊕⊕○○).

Studies on the impact of transition interventions have been undertaken in a range of clinical settings, in different age groups, and with differing endpoints, limiting comparisons

across studies. There is also a lack of a unifying definition of a “successful transition.” Interventions to improve transition show variable results, and data on transition outcomes in individuals with TS is limited.

Several studies have focused on the impact of transition interventions on loss to follow up. In one study, there was no impact on the consistency of follow up after meeting the specific adult provider with whom individuals with TS would eventually establish adult care.⁵⁵¹ A separate study assessed data in French women with TS with and without organized transition. In this study, a significantly greater proportion of those without organized transition were lost to follow up. Organized transition was defined as having been referred directly from pediatric endocrinology care, while those without organized transition were individuals referred by their general practitioner, gynecologists, or self-referred.⁵³⁸ A survey study regarding priorities of adult women with TS showed that they prioritized flexibility in scheduling, followed by having one provider overseeing all aspects of care.⁵⁵⁰ One suggested transition strategy emphasized the need for multiple medical visits for AYA with TS over months to years dedicated to transition preparation within either the pediatric or adult setting, with joint visits (with both a pediatrician and adult endocrinologist), or with alternating visits.⁵⁴¹ To this point, adolescents (not only TS individuals) have reported that it takes at least four to five visits before they trust a particular doctor.⁵⁵²

The transition process is likely optimized with the inclusion of a transition coordinator as a member of the healthcare team. The tasks of the transition coordinator could include assessment of transition readiness at multiple time points to aid in identification of barriers specific to that individual, educating patients and caregivers on the transition process (including with handouts specifying the transition roadmap and providing a checklist), providing guidance regarding health care system navigation (eg, appointments, insurance, pharmacies, social security systems), and assisting with communication between pediatric and adult team, including facilitating appointments. A transition coordinator could also be responsible for compiling the document detailing specifics of care for the individual to ensure the transfer of a medical summary to the adult provider. For many adolescents with TS (as with other multidisciplinary clinics), the inclusion of a psychologist to develop individualized transition planning and assessing readiness may be valuable.⁵⁵³

Some authors have advised group sessions to prepare for transition and independence.⁵⁴¹ In France, a one-day therapeutic small-group program for AYA with TS utilizing workshops focused on various aspects of health has been developed, but the impact of this program is unclear.⁵³⁸ An ongoing study in non-TS adolescents with prospective RCT has been set up to investigate the benefits of comprehensive transfer programs, but the results are not yet available.⁵⁵⁴ No studies were found investigating the benefit of structured transition pathways specifically in TS on the rate of loss to follow-up, QoL, or other health outcome measures.

Age-appropriate, individualized screening practices are covered in other sections of this guideline. However, we suggest that the pediatric provider confirm the completeness of this screening prior to transfer (Table 14). The period of transition to adulthood is particularly important given the high rates of loss to follow up, complications, and lack of health care access and affordability in adulthood in certain parts of the world. For example, in many areas of the United States specific

services are either not available or not covered by payors for adults. This includes, but is not limited to, neuropsychological and audiologic testing, and access to occupational and speech therapies. Table 14 emphasizes selected areas that warrant particular attention around the time of transfer. Additionally, there is a paucity of specialized adult providers with experience caring for individuals with TS, and quality of care and detection of comorbidities improves with adequate adult care.^{334,424,555,556}

An accurate summary of the individual's medical history is essential to a successful transfer, and copies should be provided to the patient, their caregiver (as indicated), the primary care provider, the TS adult healthcare provider, and any relevant subspecialists. As previously mentioned, the assistance of a transition coordinator for this task would be invaluable.⁵³⁶ Often, this task falls upon the pediatric TS provider, with input from the various pediatric subspecialists.

Given that social skills are often, though not always, reported as a concern in TS, programs to foster these skills may be useful prior to transition. Wolstencroft et al.⁵⁵⁷ report on a feasibility study that adapted the Program for Education and Enrichment of Relational Skills (PEERS) to provide an intensive 8-week online course to female adolescents with TS, 17-20 years, blended with some face-to-face group meetings. Parents and adolescents typically report improvements in social skills after taking part in social skills interventions. However, expectancy bias may influence their reports as an independent evaluation of their social behavior by teachers did not agree. The biggest improvement noted was a gain in confidence. The PEERS program also has modules targeted towards career building skills. Whether this program has an impact on social and/or vocational relationships in TS remains to be determined. Social skill difficulties can also impact romantic relationships and sexual experiences. A study of first romantic and sexual experiences in the DSD Life Study⁵⁵⁸ showed that amongst all participants, those with TS showed the oldest debut age of sexual activity amongst individuals with DSD. Compared with individuals with premature ovarian insufficiency, individuals with TS showed a delay in median age at first relationship, irrespective of the age at start of estrogen treatment (below or above 14 years of age). Further, fewer women with TS had ever had sexual intercourse, and those who did were older at first intercourse. Thus, while all TS morbidities must be addressed prior to transfer, we suggest paying particular attention to guidance in sexual development and support in psychosexual wellbeing (see also Section 8).

Various healthcare transition models exist, ranging from adult and pediatric providers working within an integrated health care system, to completely separate settings/health systems and no structured hand-off process.⁵³⁸ While the availability of providers and resources often dictate transition, the type of physician consulted has been associated with adequacy of follow-up and screening. Endocrinologists are noted to complete more of the recommended testing than gynecologists or general practitioners. Notably, only 4% of adult women with TS undergo all recommended routine health care assessments.⁵⁵⁵

Much of the transition literature highlights the need to identify local adult providers with expertise in TS to optimize care in adulthood.⁵⁵⁹ However, it is important to recognize that the "optimal" healthcare transition plan is frequently not a

Table 14. Selected testing and interventions to complete prior to transfer from pediatric to adult care; for full recommendations leading up to and post-transfer, see relevant sections.

Clinical focus	Testing or intervention to be completed prior to transfer ^a
Cardiovascular health	Imaging (echocardiogram or cardiac MR), blood pressure
Neuropsychology	Full neuropsychological testing
Reproductive and HRT	Provide counseling about risk for premature ovarian insufficiency; offer fertility specialist visits, as indicated; evaluate for ovarian insufficiency in those not already progressed to premature ovarian insufficiency; ensure adequate HRT regimens for those with premature ovarian insufficiency ^b
Comorbidities	Obtain relevant screening labs (eg, liver and function, diabetes and celiac screening) and baseline DXA; clinical screening for other conditions (skeletal, sleep, ophthalmologic, otologic)

^aDepending on region, often difficult to access expert care and/or obtain payor coverage in adulthood. ^bRefer to HRT and fertility section for additional details. Abbreviations: DXA, dual X-ray absorptiometry; HRT, hormone replacement therapy.

reality. A recent national survey in the United States showed that endocrinologists and cardiologists were the most frequently visited providers among adult women with TS, yet almost one-third stated they were not seeing an endocrinologist or cardiologist, more than half were not seeing a gynecologist, and less than a quarter were seeing a psychosocial provider.⁵⁵⁰ Transitioning care to an adult TS team may not be feasible in many centers and regions due to lack of access to specialists who have knowledge and training in TS care and/or inadequate funding to support streamlined transition processes and resources.^{532,548,550,552} In this context, it has been suggested that pediatric endocrinologists should take the lead in preparing adolescents with TS for healthcare transition in collaboration with gynecologists (with a focus on estrogen therapy and reproductive health). This team provides a structured "handoff" to a team to include an adult endocrinologist and a gynecologist.^{324,560} Additional adult specialists, such as cardiologists, should be involved, and the transfer details should include a summarized cardiac assessment for the adult cardiologist. Psychosocial counseling and support are critical to optimize QoL during the healthcare transition, though studies show that few individuals with TS report following with a psychosocial provider.⁵⁵⁰ Institutional/hospital boards should aim for the minimum standard of an adult endocrinologist and cardiologist as part of healthcare teams for care of adult TS women.

5.7 Cost-benefit analysis of not providing appropriate care during adulthood

Morbidity and mortality in adults with TS are well-described, with a life-long requirement for regular medical care and surveillance. Consistent screening and detection of comorbidities is inadequate in this population, and there is a high rate of inconsistent medication administration.^{334,556} The cost-benefit analysis of improving surveillance, and therefore diagnosis, of comorbidities in individuals with TS remains to be determined.

6. Fertility

- **R 6.1** We recommend developmentally appropriate disclosure of the potential for reduced fertility in individuals with TS. We recommend disclosing that the probability to conceive is primarily associated with the presence of a 46,XX cell line and spontaneous menarche, and that there is increased risk of maternal and fetal complications in pregnancy compared to the general population (⊕⊕⊕○).
- **R 6.2** We recommend counselling by the primary care provider, pediatric endocrinologist, or gynecologist as early as possible after diagnosis of TS, as appropriate, regarding family building options such as fertility preservation, foster care, adoption, surrogacy, egg or embryo donation, or the choice to remain childless (⊕⊕○○).
- **R 6.3** We recommend offering a referral to a fertility specialist with knowledge of TS-specific care to all individuals with TS (or their parents/guardians, when developmentally appropriate), at the time of diagnosis and intermittently over time (⊕⊕○○).
- **R 6.4** We recommend offering AMH measurements to all individuals with TS from diagnosis. AMH should be monitored annually if fertility preservation is considered, along with pre- and post-test fertility counselling. Isolated AMH measurements are influenced by several factors, including age and pubertal stage, with known intra-individual variability and variation in test accuracy. The utility of AMH to predict ovarian reserve in younger age groups is uncertain (⊕○○○).

6.1 Introduction

Due to ovarian insufficiency, most individuals with TS are infertile, with spontaneous pregnancies occurring in about 10%.^{11,511,561-564} Many individuals with TS identify fertility concerns as among the most distressing aspects of living with TS, ahead of short stature, lack of sexual development during adolescence, and fear and uncertainty regarding the long-term effects of GH and HRT. Distress associated with infertility may persist even beyond typical childbearing years, representing a lifelong challenge for individuals with TS.^{77,565} A range of potentially conflicting values and beliefs may affect TS individuals' goals for fertility. For example, though many individuals with TS endorse a desire for biological children and pregnancy, concern about the negative impact of pregnancy on cardiovascular health may cause some individuals with TS to forgo fertility preservation options.^{566,567}

Infertility may also affect the psychological profile of individuals with TS, and has been associated with depressive symptoms in those with TS and premature ovarian insufficiency.⁵⁶⁸

Infertility may be a barrier to intimate relationships. Despite having normal sex drive/libido, individuals with TS are less likely to be married or in relationships as compared to women of the same age.^{371,372,569,570} The perception of being unable to participate in one of the primary functions of a long-term relationship—parenthood—may drive feelings of inadequacy among individuals with TS.⁵⁷¹

6.2 Fertility assessment, monitoring, and counseling

Patients with TS are at risk of premature ovarian insufficiency due to rapid loss of ovarian follicles. As a result, discussions of options for fertility preservation for appropriate individuals should occur with parents of affected girls at early ages. Counseling about future options for family building should be provided by physicians experienced in caring for patients with TS, and should include fertility preservation, fertility treatment, and alternative approaches to family planning, such as use of donor oocytes, adoption, fostering, and the choice not to have children.

Counseling should be revisited from time to time to optimize the chance of successful fertility preservation, when appropriate. To advance care and facilitate decision-making surrounding fertility preservation, we propose a set of critical information to guide the discussion (Table 15).

The risks and benefits of all options should be discussed thoroughly prior to pursuing fertility preservation to allow parents and patients make an informed decision.⁵⁷²

Physicians and caregivers must consider the ethical implications of fertility preservation or fertility treatment prior to initiating this care (see ethics section below).

The key predictive factors associated with the probability of spontaneous conception are a history of spontaneous menarche, and a 45,X/46,XX karyotype.^{11,511,561-563} Accurate characterization of even low-level chromosomal mosaicism by assessing two cell lines (lymphocytes and buccal cells) may help to more precisely estimate fertility potential.⁵⁷³⁻⁵⁷⁸

Findings that may be associated with an increased likelihood of identifying follicles in the ovarian cortex include (1) mosaic karyotype with a 46,XX cell line, (2) spontaneous puberty, (3) measurable AMH or (4) FSH <10 IU L⁻¹.^{263,578,579}

AMH reflects the primordial follicle pool and predicts the reproductive lifespan of women as a key biomarker of ovarian reserve.⁵⁸⁰ In individuals with TS, AMH is associated with clinical features of ovarian reserve^{270,581} and has the strongest positive correlation with the presence of follicles in ovarian cortex tissue.^{263,579,582} However, AMH concentrations can vary in the same patient due to inter-test and biological variability,^{581,583} and heterogeneity exists in available AMH assays and detection levels.⁵⁸³ Therefore, interpretation of AMH for counseling should be used with caution and in combination with other markers. Longitudinal AMH measurements on an annual basis or more frequently if indicated, provide a more accurate estimate of the ovarian reserve than individual values and may show a trend over time. AMH can be utilized to provide an assessment of individual risk of premature ovarian insufficiency regardless of karyotype or menarche status.

Following spontaneous conception, miscarriages are more frequent in individuals with TS compared with the background population: 29%-48% versus 15%.^{11,511,561,584,585} Pregnancies in individuals with TS are associated with a higher

risk of maternal and fetal complications as are pregnancies after oocyte donation in both TS and non-TS individuals.^{511,524,586} Sex chromosome abnormalities may be more common in the pregnancies of individuals with TS.^{11,587,588}

Data are inconsistent regarding the risk of birth anomalies, which are reported in 0%-24% of spontaneous TS pregnancies compared with ~3% in the background population.^{11,511,561,562,584,589} Reported anomalies include cerebral palsy, neuropsychological disorders, cleft lip and palate, coarctation of the aorta, ambiguous genitalia, hydrocephalus as well as trisomy 21.^{11,562,563} The odds of a preterm birth and small-for-gestational-age of infants born to individuals with TS compared with women in the general population are 3-fold and 5-fold greater, respectively.⁵⁹⁰ Caesarean section rates in large TS cohorts are higher (35.6%) compared with the background population (12%).^{561,589} The risk of developing preeclampsia is 6.3%-11% in TS vs. 3% in the general population.^{511,561,589}

6.3 Fertility preservation

- **R 6.5** We recommend thorough cardiac screening and appropriate counselling by a maternal-fetal medicine specialists and cardiologists with expertise in managing women with TS prior to planning a pregnancy, especially if oocyte or embryo donation is considered. (⊕⊕⊕⊕)
- **R 6.6** We recommend controlled ovarian stimulation and oocyte cryopreservation, in females with a fertility potential, as the primary fertility preservation option in post-menarche individuals of appropriate psychological maturity, in centers with sufficient expertise in managing women with TS and the availability of psychosocial support (⊕⊕⊕○).
- **R 6.7** We recommend that controlled ovarian stimulation and oocyte cryopreservation not be offered to premenarcheal children or individuals not mature enough to understand and undergo the procedure (⊕○○○).
- **R 6.8** We recommend in all TS, including minors who cannot make their own decision, that ovarian tissue cryopreservation only be offered in the context of an institutional/ethics board approved research study or with clinical ethics board approval (⊕○○○).

The current options for fertility preservation in girls with TS are cryopreservation of oocytes retrieved following ovarian stimulation with exogenous gonadotrophin analogues, and ovarian tissue cryopreservation (OTC) retrieved following a laparoscopy. Cryopreservation of oocytes is preferentially offered to TS adolescents who experienced spontaneous menarche and are psychologically mature enough to understand and undergo the procedure of ovarian hyperstimulation and oocyte retrieval. This rules out around 85% of patients, because they face primary ovarian insufficiency before that time,

leaving OTC as the only option for the majority. The success rate of pregnancy of using cryopreserved oocytes or OTC is unknown, because there is only one reported live birth after use of cryopreserved oocytes⁵⁹¹ and one recorded pregnancy after OTC in TS.⁵⁹²

6.3.1 Oocyte cryopreservation

Ovarian stimulation and oocyte cryopreservation is an established method of preserving fertility in adults, and oocyte cryopreservation is no longer considered experimental for AYA undergoing gonadotoxic therapy. However, the utility of oocyte cryopreservation in individuals with TS who have underlying ovarian insufficiency is unknown.^{578,593-595} To date, published data regarding oocyte cryopreservation in individuals with TS entails six retrospective studies and eight case reports comprising a total of 80 individuals ranging in age from 7 to 30 years.^{578,591,596-607}

Individuals with mosaic TS are more likely to have spontaneous puberty, normal gonadotropin levels, a measurable AMH, and follicles in ovarian biopsies as compared to those who have monosomy X karyotype.^{263,579,608} While these factors have been proposed as predictors of successful oocyte cryopreservation, discrepancies remain. In one retrospective study Martel et al. found that age, karyotype and FSH had no correlation with the number of vitrified oocytes,⁵⁹⁹ while in the largest retrospective study to date Nadesapillai et al. reported that the percentage of 46, XX cells, FSH, AMH and antral follicle count had a significant correlation with the cumulative number of vitrified oocytes.⁵⁷⁸ While the successful cryopreservation of mature oocytes has been reported in a greater proportion of individuals with TS with mosaic karyotypes, there are also reports of oocyte vitrification in individuals with monosomy X, including cases with a decreased AMH.^{597,598} It is important to keep in mind that those with monosomy X could still be fertile enough to undergo ovarian stimulation successfully or become pregnant spontaneously, as a wide variation is seen between karyotype in peripheral cells and ovarian cells.^{576,609,610} Therefore, oocyte vitrification may also be considered in those with monosomy X and sufficient ovarian reserve.⁵⁷⁸ TS individuals who have sufficient ovarian reserve to store oocytes are also more likely to be able to conceive spontaneously.

Recent publications describe oocyte preservation in minors; the youngest girl was 7 years old. Whether girls who are not competent to understand the physical and mental impact of the procedure should be exposed to such an intervention is debatable, especially if multiple treatment cycles are required for a higher number of oocytes.^{599,602,611} Because there are no data on the psychological impact of oocyte vitrification in prepubertal girls, mental well-being of this vulnerable group deserves special attention and responsibility from healthcare providers during counseling.⁵⁷⁸

In individuals with threats to ovarian reserve such as oncological patients and those with endometriosis, cumulative live birth rate after oocyte cryopreservation is associated with the number of vitrified oocytes.⁶¹² In general, 10 to 20 oocytes are needed for one live birth in non-TS individuals less than 35 years old.⁶¹² In individuals with TS, the number of oocytes needed for one live birth is expected to be significantly higher due to the high aneuploidy rate in ovarian cells, the increased risk of miscarriage and chromosomal abnormalities in offspring. Therefore, care should be taken in counselling

Table 15. Considerations for fertility counselling in individuals with TS.

Comprehensive review of options for family building or the choice to remain childless	Adoption/fostering, gestational carriers, oocyte or embryo donation, family without children; oocyte cryopreservation has unknown livebirth rate (one case report of successful live birth) and ovarian tissue cryopreservation remains experimental (no reported live births)
Discussion of maternal health risks associated with pregnancy	Cardiovascular risks including hypertensive disorders, aortic dissection or death Increased risk of spontaneous abortion and increased risk of operative delivery
Discussion of fetal health risks associated with pregnancy	Risk of fetal aneuploidy, preterm birth, intrauterine growth restriction
Complexity of procedures for fertility preservation	Ovarian stimulation and oocyte cryopreservation involves serial parenteral hormonal stimulation. Possible complications: deep venous thromboembolism, pelvic inflammation, pelvic/vaginal bleeding, mood disorders. Burden to girl/women: frequent blood testing, transabdominal or transvaginal ultrasound, transabdominal or transvaginal oocyte collection Ovarian tissue cryopreservation involves surgery under anaesthesia and should occur under research protocols with research ethics approved informed consent

individuals with TS and their families as the optimal number of oocytes required for a successful live birth is still unknown.⁵⁷⁸

6.3.2 Ovarian tissue cryopreservation

Although, OTC is an established procedure for women facing gonadotoxic therapy,⁶¹³ little is known about its utility in conditions when a chromosomal abnormality that is associated with underlying ovarian dysgenesis such as TS is present. The current knowledge on OTC in TS consists of four cohort studies and four case reports, involving a total of 185 TS-patients with ages varying between 3 and 22 years.^{263,579,582,614} Borgström *et al.* performed laparoscopic ovarian biopsies in 57 patients; in 15/57 girls (26%) follicles were observed. Nadesapillai *et al.* performed a unilateral ovariectomy in 93 patients; in 30/93 (32%) follicles were found.^{263,582} Both prospective cohort studies did not exclude TS patients based on karyotype, hormone concentrations or age, since predictive parameters on finding follicles had not been established by larger prospective studies. Mamsen *et al.* studied retrospectively histology sections of 15 TS patients who underwent OTC and in 9/15 patients (60%) follicles were found.⁵⁷⁹

Patients with a mosaic karyotype have the highest prevalence of follicles, respectively 67%-100%.^{263,579,582} Furthermore, in three of four case reports follicles were found in cases with a mosaic karyotype.^{600,615-617} The odds of finding follicles in patients with a structural X chromosome aberration or a 45,X/47,XXX karyotype is 23%-44% and with a 45, X karyotype 4%-11%.^{263,579,582}

Spontaneous puberty has a significant positive correlation with the presence of follicles.^{263,579,582,618} Follicles were found in 58%-86% of girls with spontaneous thelarche, 62%-86% with spontaneous menarche, and in 10% without spontaneous onset of puberty. No correlation was observed between age and follicle density in the ovarian cortex tissue.⁵⁸² Ovarian reserve declines as women ages and it could be expected that the younger the girl, the higher the odds of having follicles. The fact that this correlation could not be observed, could be explained by the small sample sizes of the study.

An FSH <10 IU L⁻¹ has a positive correlation with the presence of follicles. Follicles were present in 50%-100% of TS girls with FSH <10 IU L⁻¹ (including prepubertal girls).^{263,579,582} However, FSH <10 IU L⁻¹ in prepubertal girls should be interpreted with caution, as this hormone is physiologically low at this age.

The mean follicle density in TS ovarian tissue is considerably lower than the density of age-matched controls.^{610,619} Additionally, an aberrant follicle morphology of up to 30%-67% was observed in TS ovaries.^{579,609} This means that only a part of the already limited follicular reserve in girls with TS is likely to be functional for fertility purposes.

Long-term follow-up will be required to assess outcomes of OTC in TS. However, *in vitro* studies in mosaic girls have been encouraging. They showed that most oocytes had a normal X chromosomal content, while granulosa and ovarian stromal cells were mainly aneuploid.^{575,600,608-610} The functional potential of cryopreserved ovarian tissue of girls with mosaic karyotype was evaluated in a murine xenograft model.⁶⁰⁹ Despite the presence of a large content of aneuploid granulosa and stromal cells, primordial follicles underwent normal follicular development until antral stages. The follicle density of xenografts from ovaries of prepubertal girls with TS was significantly higher than that of pubertal girls with TS and was comparable to that of age-matched controls. This supports the theory that prepubertal girls with mosaic TS could have a more promising outcome after ovarian tissue transplantation (OTT) than pubertal girls.⁶⁰⁹

However, initial ovarian reserve in girls with TS is already limited, while the follicular loss after OTT is more than 50%, due to ischemia in *in vitro* transplanted tissue during the first days after the procedure.^{620,621} In this light, it is questionable whether the follicle density after OTT in girls with TS would be sufficient to achieve pregnancy.

Based on these findings, OTC could be an option for TS patients with favorable predictive factors, such as mosaic karyotype, spontaneous puberty, and detectable AMH and/or FSH <10 IU L⁻¹. Because data after OTC in TS are lacking, it remains an experimental procedure and should only be offered under research and clinical ethics board approval. Caution should be taken when counselling girls and their parents to avoid unrealistic expectations regarding the success rate of OTC and OTT. In the future, if options for *in vitro* maturation or rescue therapies of the initial accelerated follicular loss become available, OTC could become a more promising option for TS girls.

6.4 Non-autologous gametes (oocyte and embryo donation) and gestational carriers

Both oocyte and embryo donation, as well gestational carriers are alternatives in family planning for individuals with TS. All these treatments require a dedicated team with special

expertise in TS, fertility and cardiological management before and during pregnancy and should not be offered in centers without this complex expertise. Single embryo transfer is strongly recommended because of the higher risk of complications, particularly cardio-vascular complications during pregnancy. The maternal deaths reported in TS have been in oocyte donation pregnancies when IVF practitioners were unaware of TS implications. Pregnancy complications are more common after oocyte donation compared to autologous IVF or spontaneous pregnancies.⁵²⁴

6.5 Ethical considerations

- **R 6.9** We suggest that clinical teams employ shared decision-making when addressing fertility preservation and treatment for individuals with TS (Ungraded Good Practice Statement).

6.5.1 Beneficence

As discussed above, significant distress accompanies infertility for many individuals with TS and their parents/guardians. Individuals with TS may derive comfort from learning about fertility preservation options through consultation with knowledgeable providers and the associated sense of having explored all possible options for future fertility.^{572,622}

Early referral for fertility preservation—including for pre-adolescent or adolescent individuals with TS—might improve outcomes^{572,623} and allow time to consider goals/implications and the possibility of fertility preservation. Because timing of follicular atresia for any individual is difficult to predict, there are no standardized approaches to referral for fertility preservation among pediatric providers, beyond referring only those who have spontaneous puberty.^{281,575,614} While likely not eligible for oocyte cryopreservation, individuals without spontaneous puberty may benefit from expert counseling about the range of options for family planning, such as oocyte and embryo donation, use of gestational carrier, adoption, and the choice not to have children.

6.5.2 Nonmaleficence

For pediatric clinicians, reducing harm includes acknowledging unique barriers to utilizing fertility preservation procedures for children and adolescents. These include: the relative dearth of physicians with expertise in pediatric fertility care; the difficulty of assessing future family building goals for younger patients; and concerns about pre-adolescent/adolescent patients' ability to tolerate interventions such as ovarian stimulation or transvaginal oocyte retrieval.^{572,624,625}

Before proceeding with treatment, adult and pediatric clinicians should communicate clearly about the difficulty of anticipating success and limited data on long-term outcomes of fertility preservation for patients with TS, as well as the possible health risks and complications with fertility treatment.²⁸¹ Biochemical screening with AMH may allow physicians to set some expectations for the likelihood of successful oocyte retrieval prior to referral,⁶²⁶ avoiding “false hope” for patients and families.⁵⁶⁶ Patients interested in utilizing autologous oocytes should be counseled on the apparent increased risk of

pregnancy loss or birth defects and of X chromosome abnormalities being transmitted to the fetus.⁶²⁷

Patients should be counseled about the potential availability of prenatal genetic diagnosis and pre-implantation genetic diagnosis or screening, but that this approach may be limited by the number of oocytes received with ovarian hyperstimulation or if IVF is not successful.

Whether conceiving with autologous or donated oocytes, patients must be counseled regarding increased pregnancy-associated morbidity and mortality including cardiac risks (see section on cardiovascular issues). A realistic estimate of pregnancy-associated health risks must be balanced with individual patient goals, given significant fears about health consequences of pregnancy among patients with TS.⁵⁶⁶ This counseling may result in grief and hardship. Behavioral health support through multidisciplinary teams may help patients manage emotional hardship associated with this counseling, undergo healthy mourning in processing infertility and provide support during fertility preservation or treatment if they are pursued.

6.5.3 Autonomy

Patients who are pre-adolescents or adolescents at the time of decisions about fertility preservation may be too young to discuss future goals for family building, to understand the impact of infertility or to give informed consent for fertility preservation procedures. Nevertheless, the child's opinion—and assent—should be sought and due consideration given to her concerns. In order to ensure that patients are as informed as possible, clinicians should focus on providing developmentally appropriate information on TS and ovarian function, information about fertility preservation procedures, assessing the patient's understanding of the care and her willingness to accept it.^{572,628}

Decisions about fertility preservation for pediatric patients may fall in the zone of parental discretion, in which parents attempt to act in the best interest of the child. The physician's role is to ensure the patient's needs are considered alongside parent/guardian priorities, and effort is made to encourage communication between patients and their families.^{572,623} Clinicians should also be sensitive to socio-cultural or family norms that may inform the parents' responses to the discussion as referenced earlier (Section 3.1).

6.5.4 Justice

Issues of justice arise because both fertility counseling and preservation consume health care resources. Patients and families should be counseled on the possibility of being unable to utilize cryopreserved oocytes and/or ovarian tissue because of health concerns related to pregnancy, or lack resources for storage or fertility treatment.⁶²⁹

Fertility preservation/treatment may or may not be covered by health insurance or government-funded healthcare, which may mean that these services are prohibitively expensive to patients and families with limited financial resources. Evidence-based fertility preservation techniques should still ideally be made accessible to all patients who have a reasonable chance of benefiting from them, and decisions should be left to the family.^{572,623,628}

7. Health surveillance for comorbidities throughout the lifespan

7.1 Newborn and infant care

- **R 7.1** We recommend delivery of a fetus with known or suspected TS occur in a facility equipped to provide neonatal care (⊕○○○).
- **R 7.2** We recommend a comprehensive physical examination with particular attention to hip stability and lymphedema, echocardiography, and renal ultrasonography be obtained regardless of prenatal imaging results, ideally prior to discharge (⊕⊕○○).
- **R 7.3** We recommend monitoring pre-feeding blood glucose levels in the first 48 hours of life and ensure that the infant is euglycemic prior to discharge. We suggest heightened awareness for symptoms of hypoglycemia in the early years of life (⊕○○○).
- **R 7.4** We recommend counseling on, and monitoring for, feeding difficulties and poor weight gain in the first year of life, with collaborative evaluation and treatment by the primary care provider and/or specialists based on the concern and available resources (⊕○○○).
- **R 7.5** We recommend expectant and new parents/caregivers be offered genetic counseling, referred to specialists in TS care, and be provided resources for local support and advocacy groups (⊕○○○).

7.1.1 Neonatal morbidity and mortality

Incidental prenatal identification of TS is increasing, necessitating consideration of perinatal recommendations. Rates of prematurity (birth <37 weeks' gestation) are similar or only slightly higher than the general population (10%-19%), with extreme prematurity uncommon.^{401,630,631} However, TS may be associated with a higher infant mortality, with studies reporting 10-16 times greater mortality infants with TS compared to the general population.^{401,632} Similarly, several studies have reported 2-3-fold higher mortality in neonates with TS with hypoplastic left heart (HLH) compared to all cases of HLH, suggesting an independent risk of TS to mortality.⁶³³⁻⁶³⁵ In the absence of HLH, the 5-year survival of infants born with TS is ~95%.^{632,636} One study suggests that infants with TS were hospitalized more frequently in the first year of life than infants without TS.⁶³² Although more clarity is needed on the causes of neonatal morbidity and mortality, we suggest planning delivery of a fetus with prenatally identified TS in a facility equipped to provide appropriate care for neonates.

7.1.2 Postnatal evaluation

Although many complex congenital anomalies can be identified through prenatal imaging, several conditions may not be apparent until after birth. Therefore, evaluation of the neonate with known or suspected TS should include a comprehensive physical examination, confirmatory chromosome analysis

and echocardiogram ideally prior to discharge from hospital (see 4.9-4.10). Renal ultrasound and hearing screen should also be obtained in the neonatal period.

7.1.3 Feeding

Approximately one-third of infants with TS are born small for gestational age (SGA), though the degree of SGA is typically mild,^{630,631} but can be up to 600-1000 g lighter.⁵⁹ Inadequate weight gain is common, with estimates of up to half of all infants with TS experiencing failure to thrive.¹ High arched and narrow palate, hypotonia, poor coordination, and delay in oral-motor skills can all contribute to feeding and/or swallowing difficulties in infants with TS.⁶³⁷ While there are no TS-specific treatment recommendations, anticipatory guidance and proactive intervention are desired.⁶³⁷

7.1.4 Hypoglycemia

Recently, an association between TS and hyperinsulinemic hypoglycemia has emerged,⁶³⁸⁻⁶⁴² postulated to be due to haploinsufficiency of the gene *KDM6A*.⁶⁴¹ In approximately half of the reported cases of hyperinsulinemic hypoglycemia, low blood glucose first presented within the first 24 hours of life; however, the diagnosis was made as late as one year of age. In addition, many neonates with TS will have other risk factors for hypoglycemia including prematurity, SGA, poor feeding, and CHD. Neonates experiencing hypoglycemia may be asymptomatic or have subtle symptoms including irritability, jitteriness, lethargy, hypotonia, tachypnea, poor feeding, and apnea. Prompt recognition and treatment of neonatal hypoglycemia is critical to decrease the risk of adverse neurologic outcomes.⁶⁴³ Therefore, we recommend universal pre-feeding blood glucose monitoring during the first two days of life in all neonates with TS. If blood glucose (BG) is <2.8 mmol L⁻¹ (50 mg dL⁻¹) between 24 and 48 hours of life or BG <3.3 mmol L⁻¹ (60 mg dL⁻¹) at or after 48 h of life, evaluation and treatment of neonatal hypoglycemia should be pursued as recommended by relevant national guidelines in any infant with hypoglycemia.⁶⁴³ A high level of suspicion for hypoglycemia should be maintained in all young children with TS, particularly during periods of prolonged fasting or in settings of inadequate weight gain or poor oral coordination. Other symptoms that should raise concern for hypoglycemia include a history of episodic tremor, sweating, paresthesia, tingling, confusion, loss of consciousness, seizures, coma, and/or transient focal neurologic deficits.⁶⁴³

7.1.5 Caregiver counseling

Expectant parents are faced with many unknowns when they receive prenatal genetic counseling about TS.⁸⁴ Information and support needs before and after birth will be different. Resources including, but not limited to genetic counseling, consultation with medical specialists in TS, and TS support and advocacy contacts may help caregivers during this potentially vulnerable time.

7.2 Ophthalmologic health

- **R 7.6** We recommend a comprehensive ophthalmologic examination between 6 and 12 months of age, or at the time of diagnosis if older (⊕⊕○○).

- **R 7.7** We recommend follow-up ophthalmologic examinations if the initial examination is abnormal or if new visual or ocular concerns arise (⊕⊕○○).

Strabismus occurs in up to 25% of individuals with TS, and refractive errors such as hyperopia, myopia, and astigmatism affect ~40%.⁶⁴⁴⁻⁶⁴⁷ Congenital and acquired glaucoma and cataracts are also more prevalent in TS than the general population, with risk ratio estimates ranging from 3 to 6.⁶⁴⁷ Ptosis is noted in 2%-21%, epicanthal folds in 2%-35%, and congenital nystagmus in 2%-9%.⁶⁴⁴⁻⁶⁴⁶ Color blindness has previously been reported to be similar to the prevalence in males (8%),⁶⁴⁴ however a more recent study found color-blindness in only 1% of all individuals with TS.⁶⁴⁵ Early identification and treatment of glaucoma, cataracts, strabismus, and refractive errors are important to prevent amblyopia and vision loss. These serious eye conditions can be easily missed on routine medical or vision assessments, therefore comprehensive ophthalmologic examination is warranted.

7.3 Otologic health

- **R 7.8** We recommend otoscopy evaluation for detection of middle ear disease, including effusion and cholesteatoma, annually in childhood and with symptoms (⊕⊕○○).
- **R 7.9** We recommend newborn hearing screening be completed, and if this is normal, age-appropriate behavioral audiometric evaluation be conducted every 2-3 years in childhood and adolescence starting as soon as developmentally able (1-2 years of age), every 5 years in adults, and any time decreased hearing is suspected (⊕⊕⊕○).
- **R 7.10** We recommend annual tympanometry up to 5 years of age where clinically available (⊕⊕○○).
- **R 7.11** We recommend antibiotic treatment should be administered for acute bacterial otitis media per local treatment guidelines (as for a high-risk population) and a repeat examination should be done to ensure resolution (⊕⊕○○).
- **R 7.12** We suggest placement of tympanostomy tubes at the early stages of chronic or recurrent middle ear disease in childhood (as for a high-risk population) (⊕⊕○○).
- **R 7.13** We recommend rapid intervention with tympanostomy tube insertion or hearing aids for conductive hearing loss due to middle ear disease in childhood (⊕⊕○○).
- **R 7.14** We recommend rehabilitation with hearing aids or cochlear implantation for sensorineural hearing loss (⊕⊕○○).

- **R 7.15** We recommend counseling on, and monitoring for, balance and vestibular problems in adults with sensorineural hearing loss, and referral to appropriate specialists for vestibular testing and compensatory training if concerns are identified (⊕○○○).

Hearing loss affects 36%-84% of individuals with TS and negatively affects QoL and well-being.^{261,648,649} TS is associated with both conductive and sensorineural hearing loss.^{650,651} While adults can often self-identify a decline in hearing ability, 75% of children with TS identified to have hearing loss reported no concerns prior to screening.⁶⁵² Craniofacial abnormalities, history of middle ear disease, aortic anomalies, metabolic syndrome, and age have all been associated with hearing loss severity and progression in TS.^{647,650,653} Karyotypes 45,X, 45,X/46,iso(X), and ring X appear to be at the highest risk, however the incidence rate for ear and hearing diagnoses is 35-fold higher in all TS karyotypes combined compared to the general population.^{630,647}

Because of the high risk of hearing loss, universal behavioral audiometric evaluation (eg, visual reinforcement audiometry, play conditioned audiometry, pure tone audiometry) should be performed throughout the lifespan, although low-risk adults with normal hearing evaluations and no hearing concerns may not require ongoing screening.

The pathophysiology of ear disease in TS is multifactorial. The *SHOX* gene is involved in the maturation of the pharyngeal arches into external ear, middle ear, and pharyngeal structures.⁶⁵⁴ The external ear malformations observed in 20%-62% of individuals with TS, including low-set ears, cupped auricles or narrowing of the external ear canal can largely be explained by *SHOX* haploinsufficiency.⁶⁴⁸ Additionally, abnormal craniofacial development in TS leads to a less pronounced slope of the Eustachian tube, and muscular hypotonia impacts function of the soft palate and Eustachian tube opening. This negatively affects the drainage of the middle ear and facilitates intrusion of microorganisms from the nasopharynx, resulting in a higher risk of middle ear effusions and infections.⁶⁵⁵ In addition to these anatomical differences, reduced expression of the *UTX* gene is associated with impairment of the T-cell mediated immune response and chronic viral infections.⁶⁵⁶⁻⁶⁵⁸ Finally, estrogen deficiency may contribute to sensorineural hearing loss as supported by studies of inner ear pathology in estrogen receptor beta knock-out mice,⁶⁵⁹ although evidence in humans is lacking. Neither estrogen nor GH therapy has been associated with ear disease or hearing loss in TS.^{647,652,660}

From early childhood through adolescence, persistent middle ear fluid and recurrent acute otitis media are common (24%-48%) in TS.⁶⁴⁸ Recurrent otitis media in early childhood has been shown to be a strong predictor of future middle ear pathologies, including tympanic membrane perforations and scarring, retractions, and cholesteatoma.⁶⁵⁵ Furthermore, middle ear fluid is often accompanied with conductive hearing loss that is not clinically recognized, particularly in infants and young children.⁶⁵² Even mild to moderate hearing loss can negatively affect language development as well as cognition, behavior, and QoL in at-risk children.⁶⁶¹ Therefore, prompt identification and treatment of persistent middle ear fluid and

recurrent acute otitis media in children with TS is needed. Otoscopy and tympanometry can identify middle ear disease with or without associated hearing loss. While not studied in TS specifically, pneumococcal vaccination, tympanostomy tubes and/or hearing aids may have to be considered at younger ages than in the general population, with the goal of normalizing hearing and preventing middle ear disease complications.

Sensorineural hearing loss affects around one third of all individuals with TS and can occur even in the absence of preexisting middle ear pathology.⁶⁵¹ The prevalence of sensorineural hearing loss in TS increases with age, however children can also be affected. A mid-frequency dip is an early sign, followed by early onset presbycusis-like high frequency loss. This combination has a notable effect on hearing speech, therefore hearing aids are often beneficial. Progression to severe hearing loss is less common but does occur, in which case rehabilitation with cochlear implantation may be necessary. Sensorineural hearing loss is also known to be accompanied by decreased vestibular functioning, impacting balance, and increasing the risk for falls. Indeed, individuals with TS have been found to have poorer balance and fine motor skills related to hearing ability.⁶⁶² Vestibular function testing should be considered in individuals with TS and significant sensorineural hearing loss, particularly if also accompanied by low BMD due to the higher risk of fractures.

7.4 Dental and orthodontic health

- **R 7.16** We recommend at least annual dental care from first tooth eruption throughout the lifespan, with particular attention to periodontal health (⊕⊕⊕○).
- **R 7.17** We suggest orthodontic evaluation after permanent tooth eruption for initial consultation and anticipatory management (⊕○○○).
- **R 7.18** We suggest screening for obstructive sleep-disordered breathing through history and/or validated instruments throughout the lifespan (⊕○○○).

Dental and periodontal problems in TS include reduced tooth crown height (predominant finding), alteration in tooth morphology and root size, bifurcated and supernumerary roots, increased root resorption, increased tooth mobility, early tooth loss, smaller primary and permanent teeth, thin hypoplastic enamel, abnormal dentin, variation in eruption patterns and periodontal disease.⁶⁶³⁻⁶⁶⁵ Dental maturity is often advanced because of shorter length of the roots and earlier root formation. Amelogenin, the gene encoding human enamel protein located on Xp22, is expressed on both sex chromosomes, explaining the thinner and hypoplastic enamel observed in TS. While caries may be less prevalent, periodontal disease such as gingivitis appears to be more common.⁶⁶⁴

Craniofacial anomalies are common in TS. Underdevelopment of several facial structures, an increased cranial base angle, a small and narrow mandible, maxillary hypoplasia and retrusion, high-arched and narrowed palate, micrognathia, malocclusion, bilateral crossbite and ectopic tooth eruption have all been described.^{666,667} GH treatment

has been shown to have a positive impact on craniofacial dimensions; however it does not correct the proportional and positional anomalies in TS.⁶⁶⁸ Dental extractions, palatal expanders and orthodontia are often indicated. In addition to contributing to feeding problems in infancy, these anatomic differences can result in a smaller pharyngeal airway space, predisposing individuals with TS to upper airway resistance, sleep disordered breathing, and obstructive sleep apnea.⁶⁶⁹ Observational studies suggest higher rates of sleep disorders in TS even in very young children.^{414,647,670} While there is insufficient evidence to recommend formal polysomnography for all individuals with TS, inquiry for symptoms and/or use of validated questionnaires to screen for sleep disorders is suggested.⁶⁷¹ Individuals with symptoms of obstructive sleep disorders should undergo polysomnography and be treated aggressively if diagnosed. It is also worth noting that poor growth, neurodevelopmental delays, and behavioral disorders are associated with untreated obstructive sleep apnea.⁶⁷²

7.5 Skin, nails, and lymphedema

- **R 7.19** We recommend annual skin assessment to identify compromising lymphedema, dermatitis, infections, autoimmune skin conditions, and skin neoplasms, with appropriate evaluation and treatment by a dermatologist if indicated (⊕○○○).
- **R 7.20** We suggest use of compression garments, lymphatic massage, and referral to specialists in lymphedema care for any compromising lymphedema (⊕○○○).

Clinically apparent lymphedema occurs in 12%-27% of girls and women with TS.^{16,88,673} However, lympho-scintigraphy studies have demonstrated abnormal lymphatic valve and vessel development even in individuals without lymphedema on physical examination.⁶⁷⁴ Clinical lymphedema is often present at birth, frequently resolves or at least improves by age 2 years, and may have a relapsing and remitting course throughout life.⁶⁷⁵ Lymphedema is reported more often in association with a 45,X karyotype compared to other karyotypes.^{673,676}

Lymphedema may be managed supportively using techniques that encourage lymphatic drainage including compression garments and lymphatic massage. Though treatment typically leads to only temporary improvement, it may be useful in preventing further complications such as skin breakdown, ulceration, and infection. Referral to lymphatic specialists such as physical therapists, occupational therapists, and lymphatic massage therapists can be useful for patients with persistent lymphedema. Podiatrists can treat ingrown toenails and assist patients with selecting appropriate footwear. Currently, there are no recommended surgical or pharmaceutical therapies for treatment of lymphedema in the context of TS.

Fetal lymphedema may present as cystic hygroma and hydrops fetalis; both conditions conferring an increased risk for spontaneous fetal demise. Central lymphedema may contribute to the development of congenital heart anomalies in TS as well as webbed neck (pterygium colli).³⁹³ Webbed neck has been reported in 18%-25% of individuals with

TS,^{16,677} and patients with webbed neck have 3.3 (1.5-7.4) times the odds of coarctation of the aorta or BAV compared to those without webbed neck.³⁹³ While surgery may be done to correct webbed neck, there are no data to suggest superiority of one technique over another.⁶⁷⁸ Potential complications of surgical corrections that have been reported include hypertrophy of the surgical scar (keloid formation)^{678,679} and recurrence of the webbed neck.⁶⁷⁸ Meanwhile, peripheral lymphedema is thought to contribute to development of nail anomalies such as deeply set, narrow, and hyperconvex nails, affecting 19%-73% of individuals with TS.^{673,680,681} Complications can include ingrown toenails and skin infections (IRR 23.7).⁶⁴⁷

Common dermatologic conditions in TS include seborrheic dermatitis, atopic dermatitis, allergic contact dermatitis, and psoriasis.⁶⁴⁷ A specific mechanism underlying the immune dysfunction in TS leading to these skin conditions has not been elucidated. Other dermatological problems more often noted in girls and women with TS include keloid scarring, vitiligo, alopecia areata, and lichen sclerosis, though additional data are needed to determine the association between these conditions and TS.

The 45,X karyotype is associated with increased risk for benign skin neoplasms [HR 2.03 (1.42-2.9)] and non-melanomatous skin cancer [HR 5.38 (2.63-10.98)].³³² Large cohort studies disagree on whether there is an increased risk for melanoma.^{332,682}

7.6 Renal manifestations

- **R 7.21** We recommend a renal ultrasound at time of diagnosis to identify congenital anomalies of the kidney and urinary tract (⊕⊕⊕⊕).
- **R 7.22** We recommend performing additional laboratory testing or repeat imaging if there are new renal or urinary concerns, such as urinary tract infections and hypertension. Annual urinalysis for proteinuria is indicated in all individuals with renal agenesis, bilateral hypoplasia, or horseshoe kidney (⊕⊕⊕⊕).

Congenital anomalies of the kidney and urinary tract are common in TS, with highly variable reported occurrence rates ranging between 18% and 60%.⁶⁸³⁻⁶⁸⁶ Horseshoe kidney and duplicated collecting system are the most common findings in TS, each occurring at a frequency of 15%-20%. Other associated conditions include malrotation or positional rotation of the kidneys (5%), single kidney (<5%), and multi-cystic kidneys (<5%). Congenital anomalies of the kidney and urinary tract have been ascribed to a variety of genetic and environmental elements present at the time of renal development *in utero* that disrupt the fetal renal migration pattern, including possible lymphatic factors.⁶⁸⁷

Structural renal anomalies may occasionally predispose to urinary tract infections or impaired renal function.⁶⁸⁸ In the general population, around half of individuals with congenital anomalies of the kidney and urinary tract develop chronic renal insufficiency, a precursor to end-stage kidney disease.⁶⁸⁹ In contrast, despite a wide range of abnormal renal morphology,

long-term kidney function remains normal in most youth and young adults with TS,^{17,27,690} although there are few longitudinal studies. One pediatric study of 122 children with TS up to age 18 years showed normal estimated glomerular filtration rate (eGFR) over time, though there was a small decline in four girls.⁶⁹¹ Another study reported no change in successive eGFR measurements over time in girls with or without renal anomalies.⁶⁸⁶ Notably, creatinine may not fully reflect renal function in TS because muscle mass may be decreased due to overall smaller body size. There is a paucity of data on kidney function in older adults with TS.

Renal ultrasound is useful to identify anatomical abnormalities; however, abnormalities may still be missed if not done by experienced technicians. Ultrasound yields low sensitivity for identifying duplex kidneys and axis/rotational differences, whereas bowel gas may obscure horseshoe kidney.⁶⁹² Additional testing, eg, measurement of serum creatinine and urine microalbumin, and/or further imaging, may be indicated if there are new renal or urinary concerns, such as urinary tract infections and hypertension. Yearly urinalysis for proteinuria is indicated in all individuals with renal agenesis or bilateral hypoplasia, or horseshoe kidney beginning at the time of diagnosis of the structural abnormality. Referral to a nephrologist is recommended in case of recurrent urinary tract infections, proteinuria and difficult to control hypertension in the setting of any structural kidney anomaly. Referral to a urologist is recommended if there is hydronephrosis or urinary tract infections in the setting of collecting-system anomalies.

7.6 Cardiometabolic disorders

- **R 7.23** We recommend promotion of healthy lifestyles including exercise to address modifiable risk factors of cardiovascular disease (⊕⊕⊕⊕).
- **R 7.24** We recommend screening for diabetes with measurement of hemoglobin A1c or fasting glucose every 1-2 years starting at age 10-12 years or sooner with symptoms of diabetes (⊕⊕⊕⊕).
- **R 7.25** We recommend assessment of diabetes autoantibodies at diagnosis of diabetes in women with TS to determine the type of diabetes as it is not easy to differentiate type 1 and type 2 diabetes in this population (⊕⊕⊕⊕).

7.6.1 Overweight/obesity

Individuals with TS have a prevalence of overweight/obesity as high as 48% with some variation due to small samples sizes, age, definitions, and local prevalence of overweight/obesity.^{450,693-697} Overweight/obesity increases from childhood to adulthood, with a cumulative incidence of 8%-60% from age 10 to 30 years.⁶³⁰ Factors related to the increase in overweight/obesity have not been well elucidated, though fetal programming and small for gestational age (SGA) have been proposed as contributing factors.⁶⁹⁸ Resting energy expenditure (REE) does not seem to explain the difference as resting energy expenditure per fat-free mass is actually higher in girls with TS,⁶⁹⁹ and a study in adults found higher body fat, lower leptin concentrations, and no difference in resting energy expenditure per fat-free mass compared to controls.⁷⁰⁰

Both visceral and total fat mass are elevated in adults with TS, while lean body mass and skeletal muscle mass are decreased.⁷⁰¹ Youth with TS have higher waist circumference and visceral adiposity.⁴⁷⁷ Periaortic, epicardial, and perihepatic fat thickness are positively correlated with cardiometabolic abnormalities in youth with TS.^{694,702}

7.6.2 Dyslipidemia

A quarter of children and half of young adults with TS have dyslipidemia^{450,696,697} and hyperlipidemia is present in about 30% of adults and is closely linked with BMI.³³¹ Age, BMI, and waist-to-height ratio correlate with adverse lipid profiles but account for only a minority of the variability.^{693,696} This leads to the question of how TS itself impacts lipid metabolism and what other variables contribute to this pathology. To date, there are no data directly linking cholesterol profiles to morbidity or mortality in TS, and there are no studies evaluating treatment of dyslipidemia in TS. Therefore, lipid profiles remain a biomarker of uncertain significance in this population.

7.6.3 Diabetes mellitus

Diabetes mellitus is common in TS, with studies reporting a 25%-70% lifetime prevalence.⁷⁰³⁻⁷⁰⁵ Individuals with TS are at an increased risk for both type 1 and type 2 diabetes.^{29,222,227,357,384,706} Although the majority of diabetes in adult women is attributed to type 2 diabetes,³⁸⁴ there is accumulating data for a TS-specific type of diabetes.^{384,707} Several studies support that diabetes occurs at an earlier age^{384,708} and is less likely to involve the usual risk factors (BMI, body composition, and family history) in TS compared to the general population.⁷⁰⁴ Furthermore, multiple studies demonstrate impaired beta cell function as well as reduced insulin sensitivity are involved in the development of diabetes in TS,^{227,229,384,705,707,708} while one study found glucose intolerance despite apparently normal beta cell function.⁷⁰⁹ Genes on Xp related to beta-cell function and insulin signal transduction affect overall glucose metabolism and likely contribute to the risk of diabetes in TS, as illustrated by studies showing individuals with a 45,X karyotype or deletions of Xp to have a much higher incidence of diabetes compared to individuals with deletions isolated to Xq (17%-23% vs 9%).^{630,703}

Several studies have demonstrated that fasting glucose and hemoglobin A1c can be normal even in the setting of impaired glucose tolerance in individuals with TS.^{704,708} Therefore, some authors suggest that oral glucose tolerance testing (OGTT) may be a better screening test for diabetes in TS. However, given the higher burden of OGTT, more evidence is needed. There are no TS-specific intervention studies to inform the best treatment modalities for diabetes (insulin, GLP-1 agonist, oral agents, etc.).

7.6.4 Predictors and modifiers of cardiometabolic risk

Some studies have found an association of metabolic abnormalities with monosomy X, ring X, isochromosome Xq, and Xp deletion, however findings are inconsistent and require more data before clinical interpretation.^{450,630,697,703}

Despite the willingness of women and parents of individuals with TS to participate in research related to eating and/or nutrition,⁷¹⁰ there is a paucity of research in this area. The available literature shows that girls and women with TS do not

meet current general recommendations for physical activity,^{357,455,496-498} which is concerning because less physical activity has been associated with excess weight gain and hypertension in adults with TS. A mixed methods study in adolescents found individuals with TS may have unique factors, such as psychosocial complications, impacting physical activity engagement that warrant tailored approaches to achieve best outcomes.⁴⁹⁷ Another study found only 37% of TS adults had received nutrition counseling and only one fifth of these were adherent to the recommended Mediterranean diet which is believed to support cardiometabolic health.⁴⁹⁸ There is no information available on use of pharmacotherapy for the treatment of obesity in TS.

The effect of GH on cardiometabolic health is contradictory, though leans toward benefit.^{229,384} BMI increases during the time that girls with TS are on GH therapy,³⁷⁹ although body composition in adults who had been treated with GH was not different from those who did not receive GH.⁷¹¹ GH increases insulin resistance; however, estrogen replacement appears to reverse this⁷¹² and the insulin resistance reverses after completion of GH therapy. GH favorably affects the lipid profile by lowering total cholesterol and LDL and raising HDL. There is also evidence that GH is not associated with an increased risk of diabetes in TS^{229,384} and better heart health⁷¹³ in TS.

7.7 Liver disease

- **R 7.26** We recommend measuring liver enzymes (alanine aminotransferase (ALT) at minimum) in childhood and every 1-2 years starting at the age of 10 and continuing throughout the lifespan. Aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and alkaline Phosphatase (ALP) should be added in adults (⊕⊕⊕⊕).
- **R 7.27** We suggest that if liver enzymes are elevated at least twice the upper limit of the normal, re-assessment is recommended as fluctuation is common. Persistent liver function abnormalities (LFA) warrant further investigation including a liver ultrasound and referral to a gastroenterologist (⊕⊕⊕⊕).
- **R 7.28** We suggest that in adults with LFA, the FIB-4 score and/or liver elastography is useful for evaluating the severity of liver damage (⊕⊕⊕⊕).
- **R 7.29** We recommend that HRT should be continued in the presence of LFA (⊕⊕⊕⊕).

LFA, defined as increased liver enzymes are present in 40%-80% of patients with TS, with more recent studies on the high end of that estimate.^{342-344,714,715} Fluctuations of LFA are frequent in TS. Risk factors for LFA are age, obesity, insulin resistance, and Xq isochromosome, however even young children with TS without risk factors have a higher prevalence of LFA.^{342-344,714,715} In the presence of LFA, the

risk of cirrhosis among TS is six times higher than in the general population.^{344,716} Similarly, a British study showed a 3-fold increased risk of liver disease-associated death in patients with TS.²⁷ Therefore, assessment for LFA in TS is important.

The pathophysiological mechanisms underlying LFA in TS are poorly understood. Three main types of hepatic damage are described in TS: steatohepatitis, vascular damage mostly observed in regenerative nodular hyperplasia (RNH), and autoimmune disease.³⁴⁵ Metabolic-associated fatty liver disease (MAFLD), is the most common finding in patients with TS.⁷¹⁷ In the presence of LFA (at least twice the upper limit of normal or persistent), alcohol abuse and medications with potential liver toxicity should be sought. Measuring ferritin and viral hepatitis B, C, and E serological status are useful to rule out hemochromatosis and infectious hepatitis, respectively. Screening for the presence of antinuclear, anti-smooth muscle, anti-liver cytosol antigen type 1 (LC1) and anti-microsome type 1 (LKM1) and anti-mitochondrial autoantibodies should be performed if the initial evaluation is negative or if the patient has other autoimmune conditions. Liver ultrasound plays a crucial role in the presence of LFA to exclude focal hepatic lesion(s), bile duct dilatation (obstructive cholestasis), or signs of portal hypertension. However, it should be noted that ultrasound does not reliably detect lower-level steatosis (<20%) and does not reliably detect steatosis in individuals with a BMI higher than 40 kg m⁻². Individuals with TS should be referred to a hepatologist when LFA persist to determine if a liver biopsy is indicated.

Simple non-invasive methods are available to assess the severity of liver damage in the presence of persistent LFA. One of the most sensitive surrogate markers of liver fibrosis in adult patients with chronic hepatitis is the FIB-4 score. It is based on a formula combining age, biological markers including AST and ALT, as well as the platelet count: $(\text{age} \times \text{AST}) / (\text{platelet count} \times \sqrt{[\text{ALT}]})$.⁷¹⁸ A FIB-4 score below 1.45 indicates a low risk of fibrosis and a score above 3.25 is in favor of advanced liver fibrosis. Recent studies suggest that FIB-4 scores are lower than expected in patients with TS,^{714,715} possibly reflecting that liver diseases are mild in most cases. Vibration-controlled transient elastography (FibroScan) measures liver stiffness as a surrogate marker of liver fibrosis and is another non-invasive tool now widely available in routine clinical practice. However, its predictive value for liver diseases has not yet been tested in large cohorts of patients with TS. Acknowledging the utility of noninvasive markers has not been fully evaluated in TS, we recommend calculating the FIB-4 score in adults and considering elastography when LFA are present.

Several studies have shown that HRT is not deleterious to liver function in patients with TS and there may even be benefit.³⁴⁴ The deleterious role of hypogonadism on LFA has been emphasized in two review articles.^{326,719} A recent study has shown that there is no difference in the prevalence of LFA between women with TS who have endogenous ovarian function compared to those receiving HRT.⁷¹⁵ Therefore, HRT should be initiated or continued in the presence of LFA. Close monitoring is required for patients with histologically proven liver vascular disease (RHN) or hepatic adenoma.⁷²⁰

Management of LFA largely depends on the etiology. Addressing steatohepatitis should initially include lifestyle interventions, such as avoiding alcohol, reducing weight, and increasing exercise.^{721,722} No intervention studies targeting LFA in TS have been published.

7.8 Celiac disease

- **R 7.30** We recommend screening for celiac disease by measuring tissue transglutaminase antibodies (TTG IgA with total IgA) in asymptomatic individuals starting at age 2 years, and subsequently every 2-5 years (⊕⊕○○).
- **R 7.31** We recommend screening for celiac disease if there are gastrointestinal symptoms, poor growth, weight loss, osteoporosis, skin changes, anemia and/or other symptoms present at any age (⊕⊕○○).

The incidence of coeliac disease is increased in TS compared to the background female population consistent with other autoimmune diseases,³⁴⁴ although the mechanism remains speculative. A single report demonstrated an increased incidence of the possible high-risk polymorphism *MYO9B* in individuals with TS.⁷²³ A recent metanalysis found approximately 1 in 22 individuals with TS have coeliac disease,⁷²⁴ with minimal difference if serology (3.4%) or biopsy (4.8%) is used for diagnosis. The prevalence of coeliac disease increases with age^{725,726} and is highest in 45,X, 45,X/iso q or ring chromosome karyotypes where up to 7.5% have positive coeliac antibodies.^{26,630} Coeliac disease may present with weight loss, poor growth, abdominal pain, diarrhea, anemia, and cutaneous stigmata, however symptoms can be very subtle and but no definitive associations have been shown in TS per se. Tissue transglutaminase IgA is 98% sensitive and specific for coeliac disease, however intestinal biopsy is recommended to confirm the diagnosis.⁷²⁷ While HLA DQ2 and DQ8 are found in most patients with coeliac disease, routine HLA testing is not currently recommended in TS, although it may be helpful if the diagnosis is uncertain.

7.9 Anemia, inflammatory bowel disease, and intestinal bleeding

- **R 7.32** We suggest measurement of complete blood count to evaluate for anemia every 1-2 years in adolescents and adults (⊕⊕○○).

Emerging data indicate an increased risk of iron-deficiency anemia among TS populations.³⁴⁴ Anemia may be related to a variety of risk factors and mechanisms including autoimmune conditions, gastrointestinal bleeding, coagulopathy, or anti-coagulation medications.

Inflammatory bowel disease (IBD) is more common among individuals with TS than the general population. A 2023 meta-analysis found an increased expressivity of IBD in TS of 1.86% (95% CI 1.48%-2.34%),⁷²⁸ congruent with the findings in a previous systematic review reporting a prevalence range between 0.67% and 4%.⁷²⁹ Unlike previous studies reporting higher rates of IBD among patients with isochromosome Xq karyotype,^{730,731} a systematic review of 25 cases in the literature found equal distribution between monosomy and structurally abnormal X chromosomes.⁷²⁹ IBD in TS

may also present at a younger age (mean 17.8 ± 2.3 years, range 3-41 years),⁷²⁸ be more severe,⁷²⁹ and/or have unique treatment complications,⁷³² although there is likely reporting bias.

A study from the national Danish registry that compared 1156 Turner women with age-matched controls identified increase incidence rate ratio (IRR) of gastrointestinal hemorrhage 3.4 (95% CI 1.8-6.2), anemia 3.2 (95% CI 2.0-5.0), and coagulation disorders 2.9 (95% CI 1.1-7.1). Interestingly anemia and gastrointestinal bleeding were not associated with IBD or celiac disease.³⁴⁴ Telangiectasias and dilated veins of the small bowel are reported as additional causes of GI bleeding among patients with TS,⁷³³ and in one case-report, bleeding from a vascular malformation in the gastrointestinal tract and resultant microcytic anemia improved with initiation of EST.⁷³⁴

7.10 Bone health

- **R 7.33** We recommend that all individuals should be counseled on healthy lifestyle measures including dietary intake of calcium and vitamin D, weight-bearing activity, and the role of estrogen replacement for bone health (⊕⊕○○).
- **R 7.34** We recommend routine screening for vitamin D deficiency using a serum 25 (OH) vitamin D level concentration between 9 and 11 years of age and every 2-3 years ongoing and treating with inactive vitamin D supplement as necessary (⊕⊕○○).
- **R 7.35** We recommend obtaining a dual energy X-ray absorptiometry (DXA) scan after completion of growth but prior to 21 years of age and every 5-10 years throughout adulthood (⊕⊕○○).
- **R 7.36** We recommend using serial DXA scans to monitor BMD in high-risk women (fractures, inadequate hormone replacement, celiac disease and other comorbidities) and once reaching menopause or discontinuing estrogen therapy (simulating menopause) (⊕⊕○○).

It is estimated that 23.8% of adults with TS have osteoporosis³⁸⁴ and a 25% increase in fracture rate exists.^{735,736} Although karyotype per se⁷³⁷ is not predictive of BMD, the “dose effect” of the *SHOX* gene is associated with thinning of cortical bone and increased bone geometry at the distal radius.^{351,738,739}

Studies on the effect of GH on BMD have not shown a consistent effect in girls with TS.^{203,740} Evidence for positive effects of estrogens in bone health is multifold: (1) spontaneous puberty is protective for BMD in TS,^{352,384,741} BMD improves with estrogen supplementation.^{301,735,736,742-744} Later start of HRT is associated with lower BMD,^{326,327,352,353} and trabecular BMD is not affected in TS during prepubertal ages with an age-dependent decrease in BMD in peripubertal children in absence of spontaneous or medically induced initiation of puberty.³⁵¹ Trabecular bone is abnormal in TS and in other causes of premature ovarian insufficiency but improves with

estrogen therapy.³⁵⁴ Current expert opinion⁷⁴⁵ suggests to start estrogen replacement at age 11-12 years (if FSH is elevated), gradually increase the dose to adult levels over several years, and to continue the treatment until the average age of menopause (mean age 51-53 years).

The risk of vitamin D deficiency in individuals with TS should parallel that in the general population with additional concern for those with other comorbidities affecting vitamin D status. Regional guidelines for both vitamin D intake as well as dietary calcium intake should be followed. The NHANES vitamin D study⁷⁴⁶ showed peak deficiency between ages 12 and 39 years in the general population. Autoimmune comorbidities add additional risk for low BMD, including celiac disease,⁷⁴⁷ inflammatory bowel disease,⁷⁴⁸ and type 1 diabetes mellitus.⁷⁴⁹ In addition, there are direct actions of thyroid hormone and thyrotropin (TSH) on bone such that both hyper- and hypothyroidism can decrease BMD but should recover in the euthyroid state.⁷⁵⁰

Studies report decreased BMD in TS by DXA (g cm^{-2}), but interpretation is confounded by the effect of short stature in this population. Research tools such as volumetric quantitative computed tomography (qCT) (g cm^{-3}), can accommodate for short stature and delineate differences in cortical versus trabecular BMD as well as characterize bone geometry and microarchitecture in TS.^{751,752} However, DXA is widely accessible in clinical practice with low irradiation exposure. Consequently, attempts to adjust for height include BMD_{HAZ} height-for-age Z-score^{753,754} (<https://zscore.research.chop.edu/calcpedbonedens.php>) and bone mineral apparent density (BMAD) adjustment⁷⁵⁵ (<https://courses.washington.edu/bonephys/opBMAD.html>). These calculations are only available <21 years of age, therefore obtaining DXA prior to age 18-21 years is a helpful baseline from which to trend spine BMD over time.

Fracture risk in TS appears most related to timing of estrogen treatment and/or compliance.^{326,327,351-353} The most common site is the forearm,⁷⁵⁶ with peak incidence at childhood and then above 45 years.⁷⁵² Fracture rate is increased in those with a hearing deficit.^{757,758} Fracture risk assessment in the general population relies on DXA-derived fracture risk assessment tool (FRAX) using BMD T-score to estimate risk of osteoporosis-related fracture over age 10 years. Due to lack of height adjustment in T-score calculation, we do not recommend FRAX in women with TS due to risk of over-estimation of fracture risk and potential for inappropriate initiation of treatment. Back pain and worsening spine DXA may prompt assessment for vertebral compressions fractures.^{759,760}

7.11 Skeletal anomalies

- **R 7.37** We recommend physical examination to identify scoliosis at diagnosis and then at least annually until skeletal maturation (⊕○○○).
- **R 7.38** We suggest screening for orthopedic anomalies (such as scoliosis, genu valgum, Madelung deformity) which in severe cases, may lead to pain and improve with intervention (⊕○○○).

A high percentage of individuals with TS have skeletal anomalies, though the true prevalence is difficult to assess given that

most studies are small, retrospective, completed at various stages of life, have poor definitions of anomalies and poorly documented inter- and intra-reliability (Table 16). SHOX is expressed in the developing bone with the strongest expression in the middle of the limb (eg, elbow and knee) and may account for the skeletal phenotype associated with TS including disproportionate growth, genu valgum, cubitus valgus, and Madelung deformity.^{761,769} SHOX is also expressed in vertebral bodies, possibly playing a role in development of kyphosis and scoliosis.⁷⁷⁰

We recommend that girls and women with TS be evaluated by an orthopedist if there is back, wrist, elbow, knee, or ankle/foot pain. Idiopathic scoliosis is the most common form of scoliosis noted in individuals with TS though congenital scoliosis, thought to be due to abnormalities of vertebral bodies, also occurs.^{215,761} Research is varied on whether GH therapy leads directly or indirectly to progression of scoliosis with new data suggesting there is no clinically significant progression.^{215,771} As intervention for scoliosis has shown to decrease progression of the curve, we recommend screening for scoliosis through full skeletal maturation. Newborns and infants should be examined for developmental dysplasia of the hip and screened with imaging per guidelines in the setting of breech delivery, family history of dysplasia and abnormal examination.⁷⁶¹ Slipped capital femoral epiphyses is rare but can appear in girls with TS while on GH therapy. Concern for slipped capital femoral epiphyses should lead to recommendations for non-weight bearing and urgent orthopedic referral. A recent review outlines common skeletal abnormalities in TS along with guidance on referral and treatment.⁷⁶¹

7.12 Neoplasia

- **R 7.39** While there is no indication for general cancer surveillance in TS, we recommend adhering to population screening guidelines (⊕⊕⊕⊕).
- **R 7.40** We recommend individualized decision-making about gonadectomy/salpingo-oophorectomy in girls and women with TS and Y chromosome material identified on standard karyotyping or FISH analysis. This also includes a discussion of the timing of the procedure weighing risk of gonadoblastoma/dysgerminoma against the potential benefit of gonadal function and fertility (⊕⊕○○).

Large population- and registry-based studies have shown that the overall risk of cancer is either not increased in TS [Denmark: hazard ratio 1.04 (95% CI 0.80-1.36)³³²; Great-Britain: standard incidence ratio 0.9 (95% CI 0.7-1.2)²⁵] or only slightly increased [Sweden: standardized incidence ratio 1.34 (95% CI 1.04-1.69)⁶⁸² and Korea: hazard ratio 1.82 (95% CI 1.01-3.27)⁷⁷²]. Increased risk for melanoma and central nervous system tumors (meningioma and astrocytoma) were identified in two of the three series, while an increased risk for thyroid, colon, rectal, and tongue cancer was

Table 16. Skeletal findings in females with Turner syndrome.

Skeletal findings	Prevalence (%)
Increased sitting/height index	24-97
Scoliosis	3-59
Kyphosis	75
Short neck (webbed)	36-87
Short sternum—shield chest	14-100
Pectus excavatum	13-20
Cubitus valgus	21-79
Madelung deformity	0-7
Short fourth and/or fifth metacarpal	10-75
Developmental dysplasia of the hip	1-20
Genu valgum	35-68
Prominent, misplaced tibial tuberosities	46
Hypertrophic medial femoral condyle	54
Hyperextension of the great toe	78
Foot arch abnormalities	62

Sources:^{16,99,390,457,681,761-768}

reported in only a single study. There is a lack of consistent prospective data and likely ascertainment bias in smaller studies; thus, no routine screening protocol is currently recommended beyond awareness of possible incidental abnormalities which should be investigated and managed as appropriate.

There is no current unifying pathogenesis to explain any increased risk of specific tumors in TS. Importantly, no relationship has been found between increased risk of development of neoplasms and HRT or GH treatment, including, for the latter, in multiple large post-marketing GH registries. Finally, a *decreased* risk of breast cancer has been reported in TS patients which may be due to lower lifetime estrogen exposure.^{332,333}

Gonadoblastoma with or without malignant transformation is associated with the presence of Y-chromosomal material. An increased prevalence of germ cell tumors such as gonadoblastoma and dysgerminoma among individuals with TS with Y chromosome material has been reported. However, there is a significant variation in the rates of gonadoblastoma, ranging from 0% to 100% in the different studies (for review see⁷⁷³). An entire Y-chromosome is suggested as bringing a higher risk.⁷⁷³ The risk of malignant transformation has been reported to be rather low (1%-22%); it usually occurs after the second decade and metastasis is rare,⁷⁷³⁻⁷⁷⁵ resulting in a relatively good prognosis. However, no reliable clinical markers or imaging for follow-up exist^{774,775} and some patients may be at risk to loss of follow-up. Spontaneous puberty, menarche, and pregnancies have been reported in TS individuals with 45,X and Y chromosome material, but information regarding residual ovarian function after puberty and fertility potential is still limited.⁷⁷³⁻⁷⁷⁵ Early gonadectomy includes a surgical intervention prior to an age in which patient participation is possible and can therefore affect bodily autonomy. Thus, based on the current data, we recommend individualized decision-making about gonadectomy/salpingo-oophorectomy in TS girls and women with Y chromosome material identified on standard karyotyping or FISH analysis. This also includes a discussion of the timing of the procedure weighing risk of gonadoblastoma/dysgerminoma against the benefit of gonadal function and potential fertility.

7.13 Autoimmunity

- **R 7.41** We recommend screening for hypothyroidism with measurement of TSH every 1-2 years starting at 2 years of age and continuing through adulthood, and with new symptoms. If TSH is elevated, we suggest testing for anti-thyroid antibodies (⊕⊕○○).
- **R 7.42** We recommend counseling on and screening for symptoms of other autoimmune conditions, such as vitamin B12 deficiency, celiac disease, psoriasis, vitiligo and inflammatory bowel diseases (⊕○○○).

Women with TS are at increased risk of autoimmunity with a 61% lifetime prevalence and positive association with age.^{384,630,726,776,777} Hashimoto's thyroiditis is the most prevalent autoimmune disease in TS^{17,384,450,726,778,779} followed by celiac disease (4%-7%) and vitamin B12 deficiency (5%-12%). Yet many other autoimmune disorders have been reported including, though not limited to, type 1 diabetes, Addison's disease, Grave's disease, psoriasis, vitiligo, alopecia, lichen sclerosis, inflammatory bowel disease, gastritis, primary biliary cirrhosis, rheumatoid arthritis, ankylosing spondylitis, and idiopathic thrombocytopenic purpura. A recent study demonstrates increased incidence of vitamin B12 deficiency independent of malabsorption and associated with hypothyroidism in TS.⁷²⁶

The reason for increased autoimmunity is multi-factorial. A lower ratio of CD4+/CD8+ lymphocytes and/or excess pro-inflammatory cytokines and decreased anti-inflammatory cytokines have been reported.⁷⁸⁰ However, they do not consistently relate to clinical findings of autoimmunity. Given that estrogen and androgens are involved with immune regulation, hormonal deficiencies due to primary ovarian insufficiency are potential contributors to immune dysregulation in TS.⁷⁸¹ In addition, genetic causes have been described, such as absence of Xp (ie, 45,X and 46, X,i(Xq)).^{630,778,782,783} Research exploring the association of parental origin of the "X" in TS with increased autoimmunity remains unclear.^{111,784,785} Haploinsufficiency of X-linked genes or varied X inactivation may also be associated with autoimmunity in TS through differential expression of genes on the X chromosome. They include AR1, CD99, DSF2RA, IL3RA, AP1S2, TLR7, CD40L, FOXP3, XIC, KDM6A, and MECP2.^{106,111,114,781} The high-risk polymorphisms known to be associated with thyroid autoimmunity (*PTPN22* and *ZFAT*) in the general population have not consistently been found in TS though the high-risk polymorphism for celiac (*MYO9B*) is more common in TS.⁷²³ Differentiated methylation patterns have been found in TS including hypomethylation of *KDM6A* which is implicated in immune regulation.^{103,106}

Screening with TSH, with or without free T4 is recommended every 1-2 years. It can be done more frequently if clinically indicated (ie, constipation or growth failure more extensive than expected). Screening with thyroid antibodies is not recommended as treatment will not be altered and no prevention of hypothyroidism is available. Treatment of autoimmune disorders is the same as that for the general population and should follow local guidelines.

See Section 7.8 for more information on coeliac disease and other GI and hepatic autoimmune disorders, Section 7.9 for more information and Section 7.6 for type 1 diabetes.

7.14 The TS clinic

Clinical care in TS is complex and chronic. As evident herein, individuals with TS may need specialty care from a dozen or more different providers. Managing this care can be challenging for anyone, with added burdens for individuals with limited health literacy, access to care, and financial resources. The authors recognize that system- and patient-level factors will affect implementation of these proposed clinical practice guidelines. Furthermore, the phenotypic heterogeneity of TS and limited high-quality research demands individualization of care. In this section, we outline considerations to improve TS clinical care delivery and outcomes. In Table 17 we present our suggestion for planned outpatient follow-up of TS.

Primary care providers (pediatricians, family practitioners, internists, generalists) are an essential part of the healthcare team, in collaboration with specialists, to deliver comprehensive and evidence-based care for individuals with TS. In a web-based survey on healthcare priorities of 543 adults with TS and 795 parents of a child with TS, respondents ranked having one provider who oversees all components of their healthcare needs as very important.⁵⁵⁰ Unfortunately, only 15%-30% felt their primary care provider was very knowledgeable about TS. Given the prevalence of TS, the average primary care provider will only have one patient with TS—therefore lack of knowledge and experience is expected. TS specialists should partner with primary care providers for their mutual patients. Creative approaches to support and educate primary care providers caring for individuals with TS, such as rare disease networks like the European Reference Network on Rare Endocrine Conditions (EndoERN) and the Endo-ERN registry "EuRRECA" (www.eurreb.eu),⁷⁸⁶ Project ECHO (Extension for Community Healthcare Outcomes)⁷⁸⁷ and local care protocols disseminated throughout a region,⁷⁸⁸ may prove valuable in TS. Finally, advocacy groups can maintain lists of primary care providers with experience caring for individuals with TS that patients could reference.

Multidisciplinary clinics (MDC) are common for specific conditions necessitating care among many specialists.^{789,790} The last iteration of the TS clinical practice guidelines recommended individuals receive care within an integrated MDC. However, there is not a strict definition of what an MDC is, and there are minimal data supporting improved clinical outcomes with MDC care in TS to date. Small studies have reported patient satisfaction with MDC care, and retrospective studies have suggested better identification of comorbidities.^{334,556} At minimum, a TS MDC presumably involves providers who are knowledgeable in TS, and this may alone have measurable benefits given the knowledge gap of providers on TS care reported in several studies.^{424,791} Given the patient-identified importance of a "ringleader" in the healthcare priority survey,⁵⁵⁰ TS MDCs should strive to have a coordinator to integrate care recommendations and facilitate communication between the patient/family, primary care provider, and MDC team. The TS Global Alliance has developed a tiered system of designations for TS MDCs available on their website, although at present this is predominantly for pediatric clinics in the United States.

Table 17. Surveillance across the lifespan.

	Infancy	Childhood (~2-9 y)	Peri-Puberty (~9-11 y)	Adolescence (~12-17 y)	Young adulthood (~18-21 y)	Adulthood	Reference Section	
Minimum Visit Frequency¹	every 3m	every 6m		every 12m		every 2y		
History								
Feeding concerns and/or hypoglycemia symptoms	every visit						7.1-4	
Sleep concerns; sleep disordered breathing	every visit			every 3-5y or other risk factors			7.4	
Lymphadema and skin concerns				annually			7.5	
Musculoskeletal (pain, fractures)				annually			7.10, 7.11	
Ear infections; Hearing concerns				annually			7.3	
Symptoms of autoimmune disease		<i>if high risk²</i>		annually			7.8, 7.9, 7.13	
Lifestyle (diet and physical activity)				annually			7.6, 7.10	
Developmental and/or academic concerns	every 3m			annually (also see Table 18)			8.2, 8.3	
Psychosocial concerns				annually (also see Table 18)			8.2, 8.3	
Physical Examination								
Weight, height, and weight-for-length or BMI	every 3m	every 6m		every 6-12m		annually	2.1, 7.6	
Blood pressure				annually			4.6	
Complete cardiovascular exam ³	neonatal	<i>if clinically indicated</i>	x1	<i>if clinically indicated</i>	x1	every 5-10y	4.2	
Ophthalmology exam	6-12m	<i>as needed if not done in infancy, new concerns, or follow up of abnormalities</i>						7.2
Otology		annually and with symptoms		<i>if clinically indicated</i>			7.3	
Hip stability	<6m						7.11	
Back (scoliosis)		annually until linear growth complete						7.11
Dental exam and care		every 6-12m						7.4
Orthodontic exam		after primary tooth loss		<i>if clinically indicated</i>			7.4	
Breast exam		<i>if clinically indicated</i>		every 6-12m for pubertal staging		<i>per local recommendations</i>	3.7, 3.10, 7.12	
Laboratory								
Pre-feed blood glucose	First 48 hrs	<i>if clinically indicated</i>					7.1	
Anti-Mullerian Hormone (AMH)		<i>consider annually</i>		offer annually if POI not already established			3.2, 6.2, 6.3	
Follicle Stimulating Hormone (FSH)	4-12 weeks ⁴		annually	<i>if clinically indicated</i>			3.2, 3.7, 3.10	
Estradiol (E2)	4-12 weeks ⁴			<i>to assist with HRT</i>	<i>every 5y to eval HRT dose; if clinically indicated</i>		3.2-4, 3.7-8, 3.10	
Thyroid Stimulating Hormone (TSH)				every 1-2y and with new symptoms			7.13	
Tissue Transglutaminase (TTG) IgA + Total IgA				every 2-5y and with new symptoms			7.8	
Liver enzymes (ALT +/- AST, GGT, Alk Phos)		x1	x1	every 1-2y			7.7	
HbA1c and/or fasting glucose		<i>if clinically indicated</i>	x1	every 1-2y and with new symptoms			7.6	
Complete Blood Count (CBC)		<i>if clinically indicated</i>	x1	every 1-2y			7.9	
25-hydroxyvitamin D ⁵		<i>if clinically indicated</i>	x1	every 2-3y			7.10	
Lipid profile (total cholesterol, triglycerides, HDL)				<i>per local recommendations</i>	x1	every 3y	4.8	
Insulin-like Growth Factor 1 (IGF-1)		<i>annually if on growth hormone</i>						2.2
Urine analysis	<i>if renal anomaly is present</i>			Annually if clinically indicated		Annually if clinically indicated	7.6	
Diagnostics								
Renal ultrasound		At diagnosis; repeat if new diagnosis of hypertension or recurrent urinary tract infections						7.6

Electrocardiogram (ECG)	x1		x1	<i>if clinically indicated</i>	x1	every 5-10y	4.1, 4.10
Echocardiogram	2-3 days of age	<i>if clinically indicated</i>	x1	<i>if clinically indicated</i>	x1	every 5-10y	4.4
Cardiac magnetic resonance (CMR)	<i>if clinically indicated</i>			x1 after growth complete	<i>before planned pregnancy; if clinically indicated</i>		4.4
Tympanometry	annually until 5y		<i>if clinically indicated</i>				7.3
Behavioral Audiogram	every 2-3y and if concerns for hearing				every 5y and with symptoms of hearing loss		7.3
Uterine ultrasound				<i>to assist with HRT</i>	<i>if clinically indicated (abnormal uterine bleeding, etc)</i>		3.7
DXA: spine and hip					x1 ⁶	every 5-10y	7.10
Comprehensive neuropsychological assessment	x1 at 5-11y of age (<i>see also Table 18</i>)		x1				8.3
Psychosocial screening / evaluations	<i>see Table 18</i>						8.2
Counseling							
Healthy lifestyle (diet, physical activity)	annually						7.6, 7.10
Genetic Counseling	with caregivers at diagnosis and as needed			with patient and as needed	if new diagnosis; pre-conception planning; and as needed		1.2, 1.3, 7.1
Transition Planning				Start transition ~12-15 y	Cont. transition + transfer		5.2-5
Fertility Counseling	at diagnosis with family; as developmentally appropriate (patient)			with patient and as-needed	<i>if clinically indicated</i>		6.2
Sexual health and sexual well-being				intermittently			8.3
Contraception / Preconception Counseling				<i>if clinically indicated</i>	<i>prior to pregnancy</i>		3.4, 6.2
<p>This table represents routine follow up of persons with Turner syndrome (TS) who do not have identified pathology including but not limited to congenital heart disease, structural renal anomalies, hearing loss, hypertension, autoimmune disease, etc. If any of these pathologies are identified, the relevant clinical guidelines should be followed. White boxes are universal recommendations in TS; lightly shaded boxes may be recommended in specific circumstances; dark shaded boxes are generally not recommended. "If clinically indicated" means that if there are indications other than a TS diagnosis alone, such as other risk factors or symptoms. ¹Visits do not necessarily need to occur with a specific specialist, but clinicians should be familiar with TS care and competent to conduct the recommended evaluations. ²Examples of high risk includes presence of one or more autoimmune conditions, strong family history of autoimmunity, isochromosome, etc. ³Complete cardiovascular exam includes auscultation, femoral pulses, four extremity blood pressure, pulse oximetry. ⁴Obtaining labs during the mini-puberty period of infancy offer an opportunity to evaluate ovarian function at a time when the hypothalamic-pituitary-gonadal axis is active, however clinical significance has not yet been shown. ⁵Alternatively, universal vitamin D supplementation may be advised rather than laboratory assessment; ⁶Calculate height-adjusted z-score; obtain baseline T-score. hrs = hours. m = months. y = years. ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index. DXA = dual x-ray absorptiometry. GGT = gamma-glutamyl transferase. HbA1c = hemoglobin A1c. HDL = high density lipoprotein. HRT = hormone replacement therapy. POI = premature ovarian insufficiency.</p>							

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Telemedicine may improve access and quality of care for individuals with TS, especially for those living in areas that are resource limited. In the healthcare priority survey, only ~5% of adults with TS stated they would be willing to travel >3 h for TS care,⁵⁵⁰ but there are many individuals who live more than 3 h away from TS experts. In addition, flexibility for appointments was their top priority. While there are minimal data on telemedicine in TS specifically, this has been studied in other chronic multisystemic conditions such as type 1 diabetes and cystic fibrosis.^{792,793} There is ample evidence that telemedicine can reduce barriers from social determinants of health.^{794,795} Telemedicine may also have unique benefits to the TS population, such as accommodations for those with hearing impairment. However, telemedicine does have important limitations, including incomplete physical examination, additional visit for laboratory or radiological studies, and legal or financial considerations in some healthcare systems.

TS support and advocacy organizations serve an important role in clinical care outcomes, and TS clinicians should identify and partner with such organizations. TS advocacy groups have taken a lead in providing peer networking forums for patients and families. Studies have demonstrated the effectiveness of peer support to enhance behavioral and social well-being for

patients with chronic conditions.⁷⁹⁶ Peer support provides opportunities for fostering social interactions, shared experiences, and local resources, all of which may foster adherence to clinical care and recommendations. Advocacy organizations are an important avenue for patient education. Following the publication of the previous clinical practice guidelines, a family-friendly version was developed and disseminated by advocacy organizations with far-reaching effects. Finally, TS organizations can advocate for policies and system change aimed at improving clinical care access and delivery for the TS community on local, regional, and national levels.

- **R 7.43** We recommend the clinical care recommendations herein be implemented on an individual basis with consideration of both patient- and system-level factors (Good Practice Statement).
- **R 7.44** We recommend all individuals with TS receive care from specialists with expertise in genetics (and/or genetic counseling), cardiology, endocrinology, reproductive medicine, audiology/otolaryngology,

Table 18. Neurocognitive and neuropsychological surveillance across the lifespan.

Developmental stage	At time of TS diagnosis	Prenatal	Infancy (0-12 months)	Early childhood (1-4)	Middle childhood (5-11)	Adolescence (13-18)	Young adulthood (19-25)	Middle adulthood	Older adulthood
Age									
Parent Education/counseling/anticipatory Guidance	○	○				●			
Parental depression screening	○	○	●						
Motor milestones and developmental Surveillance			q 3 months	Annually					
Developmental surveillance/screening	○	●	●	●	Every 3 years Annually	Every 3 years Annually	Every 3 years		
Hearing screening ^a	○								
Social cognition/autism spectrum disorder Screening	○			●					
Learning/education screening	○				Annually	Annually	Annually	Annually	Annually
Attention/ADHD/executive Function/processing speed screening	○				Annually	Annually	Annually	Annually	Annually
Anxiety/mood screening	○				Annually	Annually	Annually	Annually	Annually
Vocational Screening/guidance	○								
Self-advocacy/transition readiness	○								
Social determinants of health	○	●	●	●	●	●	●	●	●
Psychosexual/reproductive counseling	○								
Comprehensive Neuropsychological Battery ^b					●	●	●	●	●

Abbreviation: q, every. ^aEvery 3 years for TS; increase frequency w/recurrent otitis media. ^bIf clinically indicated (refer to Figure 8 Neuropsychological Evaluation Triage Flowsheet). ○ = Recommendations specific to TS. ● = Recommendations consistent with larger AAP screening guidelines (additional information here: <https://www.aap.org/periodicityschedule>).

ophthalmology, neurodevelopment, and mental health. Additional subspecialists should be involved as needed, such as dermatology, gastroenterology, nephrology, orthopedics, podiatry, nutrition, and speech/occupational/physical therapy (⊕⊕⊕○).

- **R 7.45** We recommend that girls and women with TS attend specialist interdisciplinary or multidisciplinary clinics for health surveillance in addition to their primary care provider (⊕⊕○○).
- **R 7.46** We suggest that the TS care team provide resources for additional education, self-advocacy, and connecting with other affected individuals such as through TS support and advocacy organizations (⊕⊕○○).
- **R 7.47** We suggest telehealth may supplement medical and/or psychosocial care if it is available and improves access to TS specialists (⊕○○○).

7.14.1. TS research considerations

Although many advancements in TS care are being made, the collective effort to collate evidence to inform these clinical practice recommendations also highlighted many knowledge gaps that need to be filled. The clinical landscape is constantly evolving, as illustrated by the adoption of non-invasive prenatal screening (NIPS) in many countries that identifies TS not only prenatally but also in pregnant women, generating new clinical conundrums.³⁹⁹ Unfortunately, TS research faces similar challenges like many other rare disorders, including limited sample sizes, public awareness, and funding. Most of the recommendations included within are based on single-center studies conducted in affluent countries and encumbered by multiple biases. Overcoming these barriers requires innovation and collaboration. International collaboration efforts are underway, including the European Reference Network on Rare Endocrine Conditions (Endo-ERN)⁷⁸⁶ and more specifically to TS, the international registry for TS (iTTS) (<https://sdmregistries.org/>). A national TS registry has been established within the United States as well with multi-stakeholder commitment.⁷⁹⁷ These emerging resources will be important in studies best served with larger sample sizes and international generalizability. However, as both ancestral and sociodemographic factors influence the phenotypic variability in TS, more diverse populations will need to be included. Using and even combining secondary datasets may be another way to achieve larger, more diverse TS samples, but will need to establish computable phenotypes and common data elements appropriate for this population.⁷⁹⁸

Personalized medicine presents a valuable opportunity for the TS community. Through incorporation of genetics, biomarkers, and environmental factors we can and should be able to risk stratify individuals with TS to provide individualized care rather than a global approach. Given the many TS karyotypes and the wide phenotypic heterogeneity, many studies have sought to risk stratify by karyotype; however most are far underpowered to do so. In addition, while some studies have concluded there are few undiagnosed cases of TS,⁷⁹⁹ we are still unsure of how prevalent 45,X mosaicism is and what (if any) clinical manifestations low-level

mosaicism poses. Population-based genomic biobanks may elucidate novel observations for individuals with TS⁸⁰⁰; however selection bias toward healthy participants, lack of deep phenotyping, and age-related X chromosome loss in peripheral blood present challenges in these studies as well.⁸⁰¹

Finally, integration of basic science into TS research is critical. Animal and cellular models of TS can further our understanding of pathophysiology, individual variability, and potential intervention targets. Ideally, clinical questions will inform basic science, followed by incorporation of basic science results through the translational research spectrum into clinical care. Integrated team science is particularly relevant for rare, multisystemic, lifelong conditions like TS in which a single perspective may neglect crucial details. Collaborative science along with innovation should be priorities for the TS research community.

8. Neurocognition, mental health, and well-being

8.1 Introduction

Research on neurocognition and behavior in TS now spans decades of findings consistently demonstrating a correlated phenotype, which may often impact adaptive functioning and quality of life (QoL). Genetic variations, including sex chromosome aneuploidies, are not entirely deterministic of a particular neurocognitive phenotype, ie, individuals with the same karyotype may demonstrate significant interindividual variability in the expression of associated phenotypes. Nevertheless, the volume of evidence from studies in TS provides important insights into which neurocognitive features are linked to loss of an X chromosome. Accordingly, this knowledge has the potential to inform clinical management of neurocognitive function and behavior in individuals with TS and is typically a combination of anticipatory guidance, diligent screening/detection, and early intervention when symptoms arise, to mitigate potential impacts on an individual's overall functioning.

To summarize prior literature, the overall neurocognitive profile associated with TS spans multiple stages of development, and affected domains can include attention, working memory, executive function/cognitive control, perceptual-motor and visual-spatial skills, visual memory, language, motor function, social cognition, and academic achievement. Approximately 90% of individuals with TS have overall intellectual abilities within the average range; however, significant discrepancies across domains have been documented with relative strengths in verbal reasoning compared to weaknesses in visual-spatial reasoning abilities.¹ Further, certain karyotypes, such as having a ring X chromosome, have reportedly been associated with more pronounced cognitive impairments and heightened risk of psychoeducational problems,^{802,803} though there is conflicting evidence in this domain.^{804,805}

Psychological and functional areas can also be affected, including social withdrawal, social-emotional well-being, anxiety, initiation and maintenance of peer relationships, and development of self-concept. Many of these underlying neurocognitive and behavioral domains map onto diagnostic criteria for common clinical conditions, including Attention-Deficit/Hyperactivity Disorder (ADHD), developmental coordination disorder, social (pragmatic) communication disorder, autism spectrum disorder, anxiety disorder, and specific learning disorder. Since the publication of the last

clinical practice guidelines,¹ there have been significant advances in our understanding of underlying mechanisms driving neurocognitive features in TS. These are centered around innovative findings in genetics and neuroimaging. Firstly, insights into the genetic link between abnormal X chromosome number, spanning monosomy, mosaicism, and more complex karyotypes in TS, have slowly progressed towards clearer delineation of mechanisms linking this genotype to known phenotypes,⁸⁰⁶ as well as identification of candidate genes differentially expressed in TS, potentially driving the neurobehavioral phenotype.^{103,105,107,807}

Research findings serve as important guideposts informing effective clinical management of individuals with TS as outlined in the first half of this section. The latter section summarizes recommended standards of care in clinical management of neurocognitive and behavioral features in TS. To better contextualize appropriate screening and intervention in clinical management most relevant to current understanding of each developmental stage, the present version of TS clinical guidelines in neurocognition and behavior have been structured within a developmental framework, spanning prenatal periods to adult life.

8.2 Developmental framework for neurocognition and behavior in TS

8.2.1 Prenatal period

It is currently unclear how the partial or complete loss of the second sex chromosome influences prenatal neurodevelopmental processes. A study of 117 midgestational fetuses with phenotypic TS reported no malformations of the CNS and brain weight was similar to controls of the same gestational age.⁸⁰⁸ A better understanding of fetal brain development in TS could be achieved through the application of advanced techniques for fetal MRI.⁸⁰⁹ In the future, these technologies may provide insight into a child's anticipated psychosocial and educational needs, allowing earlier interventions. Another gap in research relates to the placenta and its potential role in neurodevelopment. Because the placenta is derived from fetal cells, with a contribution from the lining of the mother's uterus, the placenta in TS is genetically different from a 46,XX or 46,XY placenta. Given this organ's key role in maternal-fetal processes, future research is needed to examine altered placental function as a potentially modifiable factor that could influence brain development in TS.

Clinical counseling, based on a prenatal diagnosis, should include psychoeducation that intelligence is typically within the normal ranges and educational achievement is like peers without TS. Expecting parents should also be informed about specific cognitive challenges and strengths that might occur in their child. Clinicians should be aware of how medical conditions associated with TS might influence prenatal brain development, such as prematurity and CHD.^{809,810} While no TS-specific neuroprotective strategies currently exist, parents and clinicians should be encouraged to implement strategies for supporting healthy brain development during pregnancy in general including appropriate nutrition, mental health support for parents, and attention to social drivers of health.

8.2.2 Infancy/preschool (0-4 years)

While early reports suggested delayed development in a variety of areas, recent studies indicate that infants and toddlers with TS demonstrate similar developmental profiles compared with children without TS, with the potential exception of motor skills. These early investigations included a study in

which parents reported late development of motor activity, fine motor control, speech, and language, as well as a very high rate of feeding problems, for which they desired greater support and advice.⁶³⁷ Feeding problems appeared to stem from both oral-motor dysfunction and dysmorphic features— notably high-arched palates.⁸¹¹ Delayed language development was reported by 15 of 122 individuals in a retrospective cohort study,⁸¹² which could be a consequence of increased rates of middle-ear disease and otitis media.

More recent reports improve on the earlier literature by using a prospective cohort design with both clinic-based assessments and well-standardized caregiver-report measures. Pretzel et al. found that standardized measures of cognitive abilities, temperament, and adaptive function were largely within the average range for 12-month-old girls with TS⁸¹³ and only the gross motor scale differed significantly between girls with TS and typical male and female individuals after controlling for key covariates. Motor skills also fell in the bottom quartile on a caregiver rating form of adaptive skills (Vineland Adaptive Behavior Scales-II), confirming this is an area where infants and toddlers with TS may benefit from early screening and additional support. Finally, caregivers reported that girls with TS were more cautious in approaching new people and situations, which could contribute to social challenges sometimes observed in older children and adults with TS. Because individuals with TS are more likely than those without TS to meet diagnostic criteria for autism spectrum disorder (ASD), screening for ASD during routine well-child checkups is important and practitioners should keep in mind potential sex and gender-related differences in ASD presentation.^{814,815} Children with TS and comorbid ASD will benefit from early identification and early interventions like autistic children without TS.

Reinhartsen et al. delved more deeply into language skills and discovered a positive neurodevelopmental profile. While clinical assessments of receptive language skills were significantly lower than expressive language skills at 12 and 24 months of age, both were within normal limits.⁸¹⁶ Social and symbolic communication skills were also average and improved significantly from 12 to 24 months. Caregivers reported that use of gestures and production of speech sounds exceeded normative expectations. Interestingly, some aspects of the neuroanatomical phenotype described in older individuals with TS are already present at 12 months of age including volume reductions in primary visual cortex, while others, such as volume reductions in the cuneus and superior parietal lobule, are not. Thus, future research should evaluate early visual processing during this age range.⁸¹⁷

Overall differences between individuals with TS and their peers with typical chromosome complements are milder at this stage, but some children may benefit from early intervention to address motor delays, feeding difficulties, or social behavior. In addition, regular monitoring is important as children transition from early childhood into middle childhood, when the classic neuropsychological features of TS become more evident. It is also important to continue to monitor for ASD symptoms across later childhood and adolescence and consider ASD evaluation if concerns arise with increased social expectations.⁸¹⁸

8.2.3 School age/middle childhood (5-11 years)

During middle childhood in individuals with TS, increased risk emerges for a constellation of cognitive vulnerabilities.

Early research into the cognitive profile of individuals with TS revealed evidence of a lateralized profile, with relative strengths in verbal reasoning abilities compared to non-verbal/visual-spatial reasoning abilities (VIQ-PIQ discrepancy). A cognitive profile involving a significant discrepancy between verbal intellectual abilities and nonverbal/visual-spatial reasoning abilities has been documented in children with TS as young as 4 years of age.⁸¹⁹ This classical cognitive profile tends to be more frequently associated with the 45,X karyotype. Continued vulnerabilities in motor skills noted during early childhood can result in weaknesses in fine motor domains, which affect a child's early visual constructional skills, including handwriting and drawing. These vulnerabilities can be exacerbated by weaknesses in visual-spatial reasoning abilities that affect not only the perception of visual information, but also an individual's ability to recreate visual designs or remember visual-spatial information.

In addition to fine motor and visual-spatial vulnerabilities, individuals with TS are at increased risk for specific learning difficulties in mathematics. Previous research has highlighted a connection between visual-spatial skills and math abilities.⁸²⁰ While some children exhibit vulnerabilities in understanding numeracy concepts early (eg, the ability to count physical objects in order), weaknesses in math concepts may not arise under later childhood as academic topics become more abstract or include visual-spatial concepts (eg, geometry). Prevalence rates for specific learning disabilities in mathematics vary significantly across studies, with rates ranging from 10% to 79% of the study sample.⁸²¹⁻⁸²⁶ In contrast, individuals with TS tend to have age-appropriate verbal and language-based academic skills. Despite these relative strengths, there does appear to be an increased risk for weaknesses in understanding non-literal language (eg, sarcasm). Difficulties with attention and aspects of executive functioning can begin to significantly interfere with academic success as a child progresses through elementary and middle school. There is a higher prevalence of ADHD in individuals with TS—7% to 25% of the sample population—compared to unaffected same-aged peers.^{814,827-830} Of note, girls appear to be at greater risk of the hyperactive/impulsive presentation of ADHD during early childhood than other girls in the general population.⁸²⁸ Executive functioning skills gradually develop over the course of an individual's life with increasing development of the frontal lobes and other areas of the brain involved in mediation of executive functioning skills (eg, planning, organization, task initiation). Weaknesses can also be observed in completion of speeded or timed tasks in individuals with TS and may underlie weaknesses observed on other measures (ie, math).^{825,831}

In addition to the unique cognitive profile observed in school-aged individuals with TS, social-emotional difficulties may emerge or increase during this period for some children. Individuals with TS may experience difficulties with initiation and maintenance of peer relationships, secondary to vulnerabilities in social communication skills. Comorbid conditions such as ASD and ADHD also influence social-emotional function. While there are qualitative reports of increased symptoms of anxiety related to social interactions and medical procedures,⁸³² the prevalence rate of anxiety disorders and symptomatology has not been well defined in early childhood and school-aged children and requires additional research. The interplay between cognitive and social-emotional vulnerabilities can affect an individual's ability to successfully navigate

social and academic settings, leading to reduced self-esteem. It is important to ensure that the child participates in screening and/or evaluation for potential cognitive and social-emotional concerns during early childhood. Some children may benefit from school-based accommodations, while others may require more significant academic interventions. Consideration of therapies to address motor and communication vulnerabilities, if present, are encouraged. Young children with TS may benefit in therapeutic interventions such as behavioral therapy or parent management training, as well as interventions such as Applied Behavioral Analysis (ABA) therapy if needed (<https://www.bacb.com/about-behavior-analysis/>).

8.2.4 Adolescence (12-17 years)

Adolescence marks a developmental epoch encompassing significant changes in social expectations, as well as dramatic biological changes typically triggered by puberty and associated circulating sex steroids. Together, these changes are tied to evolving interpersonal relationships with family members, peers, and potential romantic partners, and signal an emerging need for sophisticated approaches to navigating increasingly complex social and academic environments. Relatedly, adolescence is a particularly critical period in neurodevelopment—since the last clinical practice guidelines,¹ several studies, discussed below, have examined how individuals with TS navigate this developmental period, including examination of neurocognitive and brain outcomes. Particularly relevant to TS, there has also been some examination of the impact of estrogen on these domains which is a putative primary driver for many observed changes in typical puberty.

Regarding neurocognition, features from the neuropsychological profile observed in earlier stages of TS appear to be similar in the adolescent period. This includes findings of persistent visual-spatial differences, arithmetic abilities, and executive function, as components underlying the characteristic and ongoing verbal IQ—performance IQ discrepancy. Recent longitudinal studies in the adolescent period have examined these aspects within individuals across several years, demonstrating stable neuropsychological profiles that progress in parallel to trajectories observed in typically developing female peers in mathematics performance and visual-spatial abilities,⁸²⁰ as well as executive functions and social cognition.³⁶⁷ In other words, these new findings indicate that cognitive differences observed prior to adolescence continue to develop through this period, and do so in parallel to typically developing peers, though the difference in between-group domain scores persist throughout this developmental stage. These neurocognitive findings are partly mirrored in longitudinal findings on MRI, which similarly demonstrate global brain differences, such as smaller total surface area in girls with TS relative to typically developing peers, persisting across ages 8-14 years.⁸³³ Similarly, within the context of known maturational changes in typical puberty where white matter volume continues to increase linearly while gray matter volume decreases under the context of pruning—global cortical thickness differences emerged well into adolescence where individuals with TS appear to demonstrate relatively greater cortical thickness volumes, putatively driven by a slowed rate of thinning.⁸³³ Other specific regional differences that are often observed may arise in part from the absence of expected pubertally related cortical thinning seen in typically developing controls.^{368,833,834} The extent to which these emerging

differences in mid-adolescence derive from estrogen effects remains unclear given the design of existing studies. However, subjects receiving estrogen supplementation were found to have expected maturational decreases in surface area/volume in postcentral gyrus, middle temporal gyrus, parahippocampus, inferior parietal, as well as other regions, compared to individuals with TS who were not receiving estrogen. These estrogen-related findings should be interpreted with caution given that the underlying rationale for timing of estrogen replacement in subjects was not specifically controlled for in these investigations.

Regarding psychiatric symptoms, adolescence is a known developmental period associated with emergence of common mental health conditions. Evidence that rates of anxiety in TS during the adolescent period exceeds prevalence in the general population is mixed. Some studies have reported increased reports on anxiety screening, particularly based on parent reports,⁸³⁵ while others found no differences relative to age-matched peers.³⁶⁷ Specific to mood, while rates of depressive symptoms do not appear elevated in childhood, a recent systematic review indicates emerging depressive burden in adolescence and elevated rates in adulthood.⁸³⁶ Given the inconsistency of methods across several factors,⁷⁹¹ rigorous assessment of anxiety and mood in TS across the lifespan, is needed in future research. Lastly, social skills continue to demonstrate significant deficiencies compared to unaffected adolescents. Recent work demonstrates social skills impairments extending from adolescence into young adulthood and increased rates of meeting diagnostic criteria for ASD both in sample-based findings,⁸¹⁴ as well as large population-based cohorts.^{815,837}

8.2.5 Transitional age/adulthood (>18 years)

Neuropsychological and mental health concerns are elevated in young adults with TS.⁸³⁶ As individuals transition from adolescence to adulthood, it is crucial for healthcare systems to ensure that psychiatric symptoms do not go unnoticed during the change of caregivers as young adults move from pediatric to adult healthcare settings. While research on the neurocognitive function of adult women with TS is not as extensive as that on children and adolescents, it is evident that the cognitive profile remains consistent throughout life.^{369,838} However, how symptoms of neurocognitive and socioemotional deficits in TS are expressed over the lifespan may change. As an example, there seems to be a shift in the manifestation of ADHD symptoms in adult women with TS, with a greater emphasis on inattentive deficits,^{451,829} as opposed to predominantly hyperactive/impulsive symptoms observed in children and adolescents,^{828,839} which parallels broader findings in ADHD.

The occurrence of neurodevelopmental and psychiatric disorders in adults with TS is also reportedly higher in individuals with TS than in the general population.^{815,837} As described above, evidence regarding prevalence of anxiety is mixed,^{835,837} while depression in TS may become more prevalent with age, with the highest risk in adulthood.⁸³⁶ It should be noted however, that significant variability exists in measurement methodologies,⁸³⁶ where obtaining a clinical diagnosis may require comprehensive assessment rather than self-report measures. Attention deficits are also frequently seen among adult women with TS. There is a group of women who do not fully meet DSM-V criteria for ADHD but, to a milder degree, experience problems stemming from executive function, such as weaknesses in attention, regulation of emotions and behavior, and difficulties in organizing and

planning. For these women, training and accommodations based on cognitive-behavior therapy and accommodations at work may demonstrate benefit⁸⁴⁰⁻⁸⁴³; however research examining applications in TS is still needed. For effective healthcare navigation, appropriate recognition and diagnosis of symptoms is critical to facilitate appropriate treatment,⁸⁴⁴ and interventions should primarily be symptom-driven and consistently provided when necessary.⁴⁵¹

Studies on health-related quality of life (HRQoL) do not reveal conclusive outcomes. This may be related to the application of different measuring instruments with differences in outcome measures, groups sizes, and cultural context. A recent large population study revealed no differences in HRQoL between women with TS and the reference population.²⁶¹ HRQoL was not associated with GH treatment, genotype, body composition, hypothyroidism, or the presence of cardiovascular malformations, but appeared to be negatively associated with age, age at diagnosis, hearing impairment, and unemployment/disability.²⁶¹ However, dissatisfaction with body stature and positive evaluation of GH treatment has been observed in older studies.^{260,373,845} Several studies found that large percentages of women had a restricted social network, with increased reports of loneliness and difficulties in initiation and maintenance of social and intimate relationships.⁸⁴⁵⁻⁸⁴⁷ Also, women reported delays in achieving milestones of sexual development such as first romance, first serious partner-relationships, and sexual experiences.^{374,845,848,849} Social communication challenges continue to be described in adult women who have TS. Reduced attention or difficulty interpreting non-verbal communication cues, as well as challenges in understanding ambiguous or non-literal language have been reported,^{1,451,844,850,851} as well as reported difficulties in new, unstructured, or ambiguous social situations. Adult women therefore may benefit from training programs to strengthen their social competence.⁸⁵¹ Recent studies also indicate adult women with TS experience elevated stress and fatigue levels, which is attributed to the associated cognitive profile combined with heightened stress levels,⁸⁵²⁻⁸⁵⁴ potentially related to coping with a congenital disease or a chronic medical condition. In adulthood, optimal neuropsychological functioning, particularly executive functions and social communication, are pivotal for self-dependence and successful social engagement. Conversely, difficulties in these domains present significant functional challenges, which may require ongoing support or accommodations to reduce stress in daily life.^{261,846,847} Vocational counseling, combined with neuropsychological evaluation, may sometimes provide valuable insights in individual profiles of strengths and challenges, to optimize social participation and well-being.

8.3 Clinical recommendations

8.3.1 Evaluation, screening, and surveillance

- **R 8.1** We recommend that cognitive/neuropsychological evaluations and behavioral/social/emotional screenings be integrated into the care of individuals with TS across the lifespan (⊕⊕⊕).

In response to increased life expectancy for individuals with a variety of complex medical conditions, there have been

advances in understanding of related neurocognitive sequelae that affect developmental outcomes and QoL in affected individuals. As a result, there has been an increasing demand for comprehensive neuropsychological evaluations as part of clinical practice guidelines for complex medical conditions,⁸⁵⁵ and should be similarly pursued in clinical care for TS. Unfortunately, access for comprehensive neuropsychological evaluation can be limited due to availability of services in areas, long wait lists, or financial restrictions. In response, there has been increased interest in methods for screening or targeted evaluations for individuals at risk for neurocognitive impairments. These have included alternative methods of neuropsychological evaluations, including monitoring/surveillance, consultation, screening, and targeted evaluation to assist in triaging individuals who might most benefit from comprehensive evaluations.^{856,857} This tiered method of neuropsychological evaluations paired with collaborations with other providers who may be able to complete evaluations assessing cognitive, learning, attentional, or social-emotional vulnerabilities (eg, school personal, community practitioners), may help increase the availability of resources to individuals with TS who historically may not have been able to access a comprehensive neuropsychological evaluation (Figure 8, Table 18 and Text S1).

- **R 8.2** We recommend surveillance of generic risk factors associated with chronic medical conditions that can threaten well-being and QoL (Ungraded Good Practice Statement).

The focus in clinical management in TS is, understandably, on condition-specific features to avoid or minimize the development of more serious medical problems. Less commonly highlighted are those circumstances and experiences shared by individuals affected by a wide range of chronic medical conditions (and their families). Such a “noncategorical approach”⁸⁵⁸ represents a balancing of treatment for specific medical conditions with the need to address related personal, social, and educational/vocational issues related more generally to having a chronic medical condition or caring for an affected child.^{858,859} Holistic strategies for intervention involve counseling and support of patients and families regarding predictable nonspecific experiences of pediatric chronic conditions.

Providers should be aware of caregiver challenges given the psychological strain which can accompany caring for any children with a chronic condition. For example, there are effects on caregivers such as psychological distress related to the diagnosis, negative emotional spill-over effects, and perceived child vulnerability and overprotectiveness.⁸⁶⁰⁻⁸⁶² Chronic pediatric conditions can also exert variable financial and time burdens on caregivers relative to caregiving burdens for healthy children.⁸⁶³ Youth with chronic medical conditions have been shown to experience higher rates of missed school, peer victimization, academic challenges, and threats to body image and self-esteem.^{864,865} More specifically, those with hearing loss tend to encounter social isolation, experience discomfort in interactions with peers, and exhibit signs of immaturity.⁸⁶⁶⁻⁸⁶⁸ Later pubertal onset, a feature of many pediatric chronic conditions,⁸⁶⁹ can perturb healthy psychosocial and psychosexual development.⁷⁴⁵ Chronic medical

conditions are associated with delays or arrest in psychosexual milestones.^{870,871} A final example of a noncategorical or generic factor that threatens positive psychosocial adaptation stems from the influence of chronic medical conditions on employment and career development.⁸⁷²

While there is widespread recognition of cross-condition factors that could jeopardize positive psychosocial adaptation, well-being, and the overall QoL of individuals and their families, these factors might sometimes be overlooked due to the prevailing focus on biomedical treatment advancements and the escalating specialization within the healthcare field. Nevertheless, there are brief screening tools available to assess patient and family risk and resilience at the time of diagnosis and periodically during ongoing care. As an illustration, consider the Psychosocial Assessment Tool™ (PAT) (<https://www.psychosocialassessmenttool.org/>), which is rooted in the Pediatric Psychosocial Preventative Health Model.⁸⁷³ This tool offers a three-tier assessment of patient and family risk (Universal, Targeted, Clinical) based on the cumulative PAT score. It has been implemented across a diverse range of pediatric chronic conditions and is available in multiple languages. The PAT identifies patient and family areas of risk and resiliency across multiple domains (eg, family structure and resources, family problems, social support, child problems, acute stress, sibling problems). Although it has not been validated in TS, the use of the PAT, or similar standardized tool, can be used to triage families to services based on need.

8.3.2 Evidence-based treatment for mental health conditions in TS

- **R 8.3** We recommend that evidence-based interventions for cognitive or psychosocial problems in the general population be adapted to meet the needs of girls/women with TS (⊕⊕⊕○).

While several evidence-based therapies are universally available for symptoms of anxiety, depression and social skills challenges, data demonstrating efficacy of these psychosocial interventions specific to TS has been sorely lacking until recently. Social skills difficulties are among the most consistent challenges faced by girls and women with TS. As outlined above, differences in social interaction are present from childhood, and may become more conspicuous in adolescence, when the complexity of social interaction increases significantly for most girls.^{850,851} By adulthood, women with TS report feeling more socially isolated than their peers and fewer close relationships.⁸⁷⁴ Many of the social difficulties in TS are reminiscent of those experienced by girls with ASD.⁸¹⁴ There is robust evidence from international randomized controlled trials that social skills training interventions, such as the Program for the Education and Enrichment of Relational Skills (PEERS), improve social ability in individuals with ASD, ADHD, anxiety, and depression.⁸⁷⁵⁻⁸⁷⁸ PEERS is a manualized treatment program that can be delivered to preschoolers, adolescents, and young adults over 14-16 weeks. The group sessions are structured to provide didactic instruction as well as social skill rehearsal on topics such as conversational skills, developing friendship networks and finding sources of friends, entering and exiting group conversations, handling teasing and embarrassing feedback, and resolving arguments.⁸⁷⁹

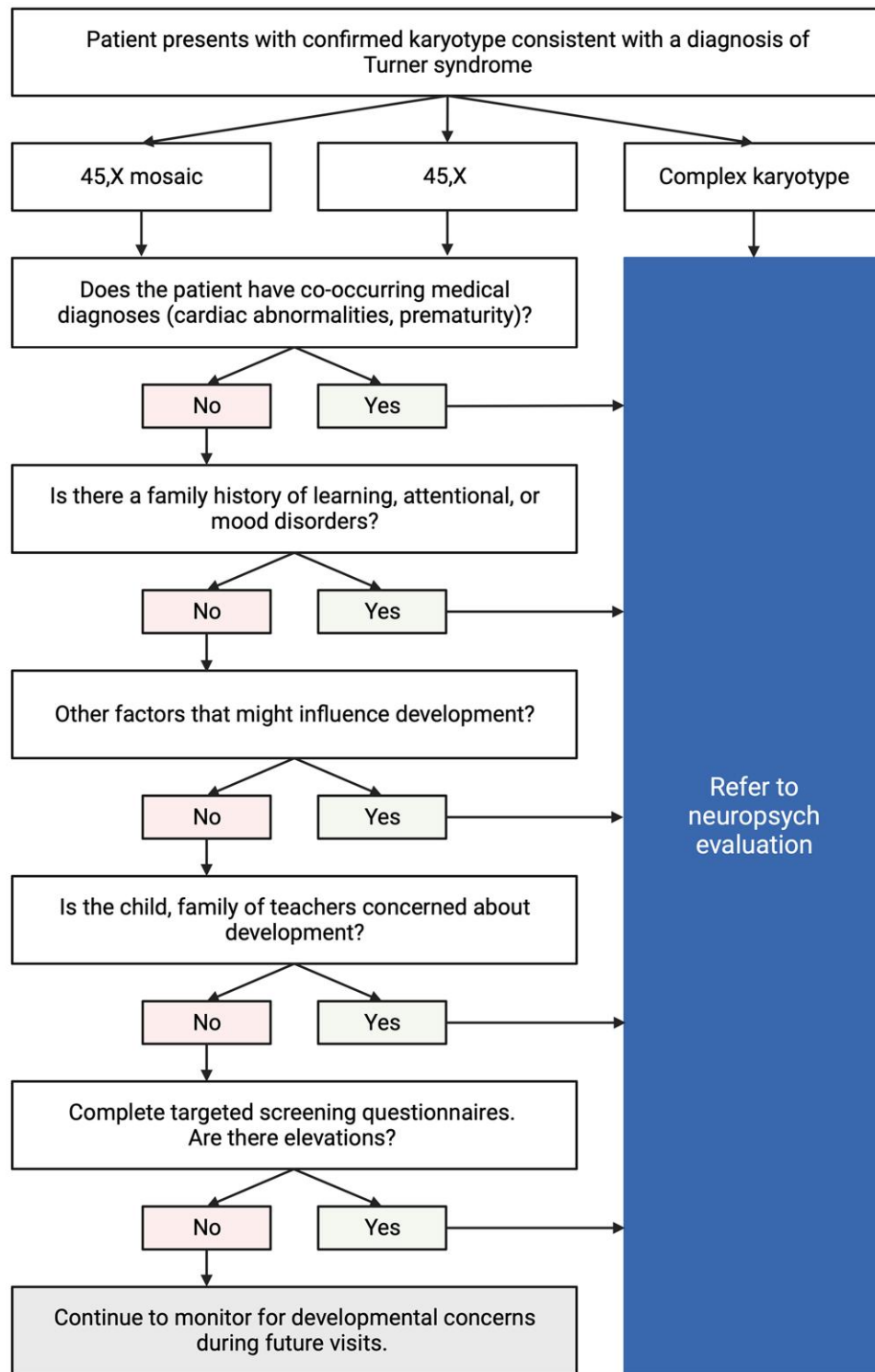


Figure 8. Comprehensive neuropsychological evaluation (see also Table 18).

The young adults program includes additional sessions on relationships and dating.⁸⁷⁸ In TS, a feasibility study found the PEERS adolescents program to be acceptable, feasible and showing promise in improving social outcomes.⁵⁵⁷ This supports the delivery of the PEERS family of interventions, with few adaptations, for girls and young women with TS with social skills challenges. Together with earlier studies examining

cognitive training, these findings indicate psychosocial therapies should be actively pursued in TS whenever impairing symptoms are present, in line with broader clinical indications for management of social skills challenges, anxiety, depression, ADHD or learning difficulties.

Literature examining mechanisms, efficacy, or treatment course for psychopharmacological interventions in TS is

fundamentally lacking, despite the broad evidence for higher rates of psychiatric conditions whose treatment may indicate use of medications. One such example is treatment of ADHD—given the benefit of pharmacological management for ADHD in the general population, psychostimulants, atomoxetine, and alpha-agonists are also frequently utilized in routine management of individuals with TS. Several considerations are relevant given the broader constellation of symptoms and potential comorbidities in TS when using these classes of medication. This includes concerns that catecholaminergic effects in psychostimulants (eg, methylphenidate, mixed amphetamine salts, etc.), and atomoxetine, may be associated with unintended adverse side effects of increased heart rate, hypertension, and potential association with arrhythmia. Specific to TS, there is additional concern for individuals with TS with known structural cardiac defects, particularly the aorta, or history of QT prolongation. Given these considerations, it is recommended that individuals with TS be referred for cardiac consultation and/or ECG prior to starting pharmacological treatment for ADHD, which is also consistent with existing guidelines for ADHD management for individuals with an increased cardiac risk profile.

However, it should also be noted that despite lack of TS-specific literature, expert clinical opinion suggests that with appropriate screening and routine subsequent monitoring, effective management of ADHD with traditional medications may have significant benefit for affected individuals. Another alternative in management of ADHD includes treatment with alpha agonists, such as long-acting clonidine or guanfacine, which may be associated with hypotensive effects. While not a specific treatment target in ADHD management, this should also be considered, in coordination with cardiovascular management. Another aspect of psychostimulant management of ADHD includes recent data demonstrating potential overall decrease in adult height in cohorts of youth with ADHD who consistently took stimulants over an extended period.⁸⁸⁰ This potential adverse side effect should be considered with families to develop shared decision-making treatment plans balancing goals for ADHD symptom management and growth.

8.3.3 Collaboration with schools

- **R 8.4** We recommend that a “support plan” be prepared by the patient’s specialist providers as a tool to empower individuals and their caregivers in advocating for all necessary supports, outside the medical environment (eg, schools, community), to achieve optimal educational and socioemotional development (Ungraded Good Practice Statement).

For children and adolescents with TS, we recommend close communication and collaboration between the individuals’ specialist providers and the school system. This recommendation is in line with best practices for supporting children with health-related conditions (https://www.cdc.gov/healthyschools/chronic_conditions/pdfs/2017_02_15-how-schools-can-students-with-chc_final_508.pdf; <https://www.gov.uk/government/publications/supporting-pupils-at-school-with-medical-conditions--3>). Not all families live near a hospital with TS specialty

providers, which limits how often the patient is able to visit the hospital or clinical setting for intervention/treatment sessions. However, all children spend a large majority of their time in the school setting. Therefore, school staff (eg, teachers, school psychologists, social workers, school nurses) are in an ideal position to be able to support the educational and socioemotional needs of students with TS. Not all school staff, however, are familiar with the neurocognitive and psychosocial features of TS. We recommend that healthcare/specialist providers prepare a “support plan” in collaboration with the individual, the family, and relevant school staff to enhance communication and understanding regarding TS and associated features. Individualized health care plans are often used by the school system for children with chronic health conditions such as diabetes or epilepsy, but we propose that use of an adapted support plan, with increased emphasis on psychosocial support, may be highly beneficial for students with TS. This support plan should include psychoeducation about TS to inform school staff of the primary features and relevant implications. Additionally, the plan should outline the student’s needs in terms of medical and psychosocial care. For example, the plan may include information about a student’s hearing impairment, as well as describe difficulties with processing speed or social interactions. The plan might also outline a specific intervention that will be implemented with the student (eg, social skills group) and identify goals and next steps. As individuals with TS transition into the workforce, this support plan can be adapted to meet vocational needs and can be used as a tool for individuals to advocate for any necessary accommodations in the workplace. It is important to note that not all families will feel comfortable sharing details of their child’s diagnosis or features with their school. Therefore, the use of a support plan should only be considered after engaging the individual and their caregivers in shared decision-making (example template of a support plan for students with TS is provided as [Text S2](#)).

8.3.4 Psychoeducation and health literacy across the lifespan

- **R 8.5** We recommend counseling regarding TS that emphasizes personal understanding and meaning of the features associated with TS (Ungraded Good Practice Statement).

TS may have far-reaching consequences for psychosocial functioning and well-being. Psychoeducation on the neuropsychological and psychosocial consequences enables parents and individuals to anticipate potential neuropsychological and psychosocial needs and to initiate early intervention when indicated. Congenital and chronic conditions require coping and adaptation, however for most parents and affected individuals, role models for coping are often unavailable. Teaching the active use of coping strategies empowers patients’ abilities and improves psychosocial well-being.⁸⁸¹ In the process of acceptance and adaptation, many parents or individuals often benefit from shared understanding of experiences and associated distress, and provision of support.⁸⁸² Relatedly, to obtain required help, caregivers and individuals must be able to effectively communicate on the diagnosis and their neuropsychological or psychosocial problems.⁸⁸³

There are strong reasons for emphasizing openness with girls with TS regarding all aspects of the medical condition and its varied implications. First, successful transition from pediatric to adult care is predicated on the person's full understanding of their condition, its treatment, and its potential impact on their future. Additionally, developing skills in communication, decision-making, and self-advocacy is crucial to support their empowerment.^{884,885} Withholding details about aspects of their condition from girls with TS can only serve to impede a successful transition process. In a recent survey including adults with TS (26 years and older), 86.4% self-reported they were independent in managing their healthcare, whereas only 63.5% of parents perceived their daughters of the same age as being independent.⁵⁵⁰ Similarly, only 59.0% of adults with TS and 47.6% of parents of adults were very confident in the woman's ability to understand her healthcare providers' recommendations. Although gaps in understanding are multifactorial, lack of openness throughout development is a modifiable contributor that should be targeted (additional information in Section 5. Transition).

Another key reason for emphasizing openness in educating the child and teen with TS is the relationship between such communication and the person's emerging self-image. The view of oneself (self-image) and the value ascribed to it (self-esteem) are key elements of the individual's self-concept and significant contributors to emotional well-being. A positive self-concept can serve as a buffer against psychosocial stressors and mitigate emotional distress.⁸⁸⁶⁻⁸⁸⁸ Having a clear and well-defined self-concept, including a realistic understanding of one's strengths and weaknesses, fosters a positive self-image. Research has indicated that individuals with a well-developed self-concept tend to experience less uncertainty and often have greater self-confidence.^{889,890}

Secrecy about the child's medical condition can threaten the development of a positive self-concept, yet reluctance to fully educate youth with chronic medical conditions is common.⁸⁹¹ In the case of TS, barriers to educating the child include caregivers feeling ill-equipped to disclose the diagnosis, and desire to protect their daughter from potential emotional distress related to infertility.^{77,883} Secrecy surrounding a child's medical condition can pose a risk to the development of a positive self-concept. It is important for caregivers and healthcare providers to consider how to provide developmentally appropriate information and support, considering the person's emotional well-being as well as the benefits that can come from a better understanding of the condition and its potential implications. A tool for this purpose has recently been described.⁸⁹² It is crucial to strike a balance between the child's right to privacy and the need for disclosure in certain situations, such as informing healthcare providers, teachers, or close family members who may be involved in the child's care and support. Decisions about when and how to disclose a child's TS, or any chronic condition, should prioritize the child's well-being and best interests.

Narrative methods for chronic illness involve using storytelling and personal narratives as a means of understanding, coping with, and communicating the experience of living with a chronic health condition (Morioka and Nomura 2021). This approach recognizes the importance of individuals' unique stories and perspectives when it comes to a chronic condition. Key components of a narrative approach include storytelling, in which the individual is encouraged to share personal stories through writing or speaking; providing a

more comprehensive understanding of the impact of the medical condition that goes beyond medical symptoms to consider the emotional, social, and psychological implications of the condition and associated medical experiences. Benefits of a narrative approach include empowerment that comes from sharing one's story, making sense of one's experiences, and gaining a sense of control over their lives. In the survey of adult women with TS and parents of adult daughters cited above,⁵⁵⁰ only 48.1% and 40.6%, respectively, felt "very confident" in the woman's ability to explain her healthcare needs to friends and family members.

Narratives can serve as a coping mechanism by providing an outlet for expressing emotions, processing experiences, and developing resilience in facing the challenges stemming from the medical condition. Personal narratives can challenge stereotypes (eg, all women choose to become pregnant) and reduce the stigma associated with a chronic condition (eg, learning disabilities or problems with social communication). Sharing narratives within support groups or online communities can create a sense of belonging and support. Others facing similar challenges can relate to and learn from these stories. Engaging with one's narrative can be a form of healing and self-care. It encourages self-reflection and self-compassion.

- **R 8.6** We recommend that girls and women with TS receive counseling regarding sexual health and sexual well-being (Ungraded Good Practice Statement).

The World Health Organization defines *sexual health* as "...a state of physical, emotional, mental and social well-being in relation to sexuality; it is not merely the absence of disease, dysfunction or infirmity" (https://www.who.int/health-topics/sexual-health#tab=tab_2). While the term "sexual health" encompasses both the public health and personal well-being aspects of sexuality, healthcare systems often prioritize areas such as fertility management, sexual violence prevention, and the prevention and treatment of sexually transmitted infections over the person's subjective sexual experiences and contentment with their sexual life; factors such as enjoyment, comfort, and satisfaction.

It is a recurring finding that women with TS are delayed in psychosexual milestones and less likely to be sexually active or in a stable romantic/sexual relationship, compared to the general population or other comparison groups.^{372,374,569,893,894} Simple accounts, such as specific genetic, hormonal, or other physical features of the syndrome, do not systematically account for these differences across studies,^{372,374,569} but on-time puberty may have a salutary influence.^{371,374} An additional, non-syndromic factor investigated as contributing to poorer sexual well-being in women with TS is poorer self-concept and body image^{894,895} and lower confidence as a sex partner.³⁷⁴ A more consistent observation has been that women with TS who are in a stable relationship report typical levels of sexual satisfaction.^{372,893,894}

Physical appearance and body contentment play a role in shaping self-perceptions and sexual behavior. A negative body image can lead to heightened self-consciousness during intimate encounters, difficulties in initiating sexual interactions, and a reduced likelihood of experiencing satisfying sexual encounters. Keeping in mind the deeply individual

nature of sexual well-being and the role that clinical management can exert in the process. It is noteworthy that one study found that just over a slight majority of women with TS reported being satisfied with their breasts.³⁷³ This level of satisfaction aligns with the results of other studies which have reported relatively low breast satisfaction in women with TS.^{375,896}

In response to these well-documented threats to sexual well-being, it is advised to start discussions related to sexual development during early adolescence. Topics covered include the importance of HRT and the potential impact on sexual well-being. Parents can play a crucial role in initiating these discussions. They may introduce the topic, answer questions, or facilitate communication with healthcare providers and can provide important insights into the teen's readiness and interest. Discussions about sexual well-being can be initiated during routine follow-up appointments with specialists. This can provide a structured and supportive context for these conversations. It is necessary to revisit and adapt these conversations over time as the person's needs and developmental stage evolve.

It is important to discuss the emotional aspects of sexual well-being, including self-esteem, body image, and relationships and to offer support and strategies for dealing with any emotional challenges related to TS. For those who are sexually active, concerns such as pain during intercourse should be addressed with information on treatments or strategies to manage these issues. Encourage participation in TS support groups or counseling services specializing in sexual well-being to connect with others facing similar challenges. Sexual health counselors are well-equipped to assist women with TS or anyone experiencing anxiety related to sexual health by applying a variety of evidence-based therapeutic approaches.⁸⁹⁷⁻⁸⁹⁹

- **R 8.7** We suggest that individuals with TS and their parents be encouraged to network with local/regional/national TS peer support organizations (⊕○○○).

Peer support for those affected by medical conditions refers to a reciprocal and beneficial relationship in which individuals who have encountered or are confronting similar challenges share emotional, informational, and social support. In the case of chronic health conditions, support can be sought directly by the patient or by their caregivers. Peer support may be individual or group-based, in-person or online. Peer support has become a common feature of individual- and family-centered care because of its purported positive effects on various aspects of well-being and health outcomes. A recent systematic review of reviews on peer support for people (children and adults) with chronic conditions found methodological weaknesses across the underlying research literature and lack of consistent significant effects of peer support.⁹⁰⁰ Similarly, a Cochrane systematic review of peer support interventions for caregivers of children with complex healthcare needs found no clear evidence of effects of peer support interventions on any parent outcome; however, the certainty of evidence was low to very low.⁹⁰¹ Importantly, this review found no evidence of harm from participation. Despite these caveats, there is an abundance of qualitative data indicating that

patients and parents value and find emotional support in peer networks. A recent survey involving individuals affiliated with major TS support organizations in the U.S. included items regarding peer support.⁵⁵⁰ Participants included adults with TS (>18 years), parents of adults with TS, and parents of girls with TS (<18 years). Notably, even though these participants were in some way connected to TS support organizations, only a minority (ranging from 25.1% to 38.6%) reported currently utilizing peer support.⁵⁵⁰ It is essential to recognize that the appeal and effectiveness of peer support can vary based on factors like the nature of the chronic illness, and the specific peer support program. To reduce the barrier to girls and women with TS benefiting from peer support, providers may need to facilitate early contacts to overcome hesitancy stemming from anxiety and social communication difficulties frequently observed in this population.

8.3.4 Principles of shared decision-making

Optimal clinical care for TS encompasses a variety of medical procedures and treatments that are not urgently required to address life-threatening or immediately critical medical situations. Elective medical interventions in TS include screening and diagnostic tests, GH therapy, timing of pubertal induction, cosmetic plastic surgery, gonadectomy in girls with Y chromosome material, and fertility treatments, among others.

Shared decision-making (SDM), considered a core feature of patient-centered care,⁹⁰² is a process that recognizes patients (or their caregiver proxies) as active participants in their healthcare, valuing their input and preferences. The principles of SDM are broadly endorsed by national and international medical societies and organizations. SDM holds particular importance in situations where evidence does not decisively favor one option or when a decision requires careful consideration of individual values.

SDM is characterized by three fundamental elements⁹⁰³: first, providers acknowledge, and patients (or caregivers) recognize, the need for a decision; second, all parties involved gain an understanding of the best evidence related to the advantages and disadvantages of all reasonable treatment options, including those not preferred by the clinician; and third, the values and preferences of patients (and for minors, those of the child's parents) are integrated into the decision-making process. Beyond its ethical significance and alignment with clinical guidelines and healthcare policies, SDM offers a range of benefits, including: equipping patients with a deeper understanding of their medical condition and available treatment alternatives; increasing patient satisfaction; enhancing adherence to treatment plans; ensuring a closer alignment between the chosen option and the patient's tailored needs, values, and context; diminishing uncertainty in decision-making; and fostering a collaborative and trusting relationship between individuals and their healthcare providers.⁹⁰⁴ Notwithstanding its importance as an indicator of healthcare quality, evidence that SDM is routinely implemented in pediatric and adult healthcare is difficult to find, whereas reports of barriers and resistance to its application are plentiful.^{905,906}

Patient decision aids (PtDAs) have been introduced as tools or resources to increase the likelihood of adherence to the principles of SDM. These aids have been demonstrated to enhance knowledge, accuracy in understandings of risk, reduced decision-related uncertainty, and better alignment of personal values with the chosen course of action.⁹⁰⁷ PtDAs are designed to complement, rather than replace, counseling from a

healthcare provider. Several recommendations in these clinical practice guidelines are conditioned by the requirement of applying SDM. Clinicians are encouraged to consider using PtDAs in supporting the process of SDM. Information about PtDA development methods, international standards, and a decision aid inventory can be found at the Patient Decision Aids website of The Ottawa Hospital Research Institute (<https://decisionaid.ohri.ca/index.html>).

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Supplementary material

Supplementary material is available at *European Journal of Endocrinology* online.

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References

- Gravholt CH, Andersen NH, Conway GS, *et al.* Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner syndrome meeting. *Eur J Endocrinol.* 2017;177(3):G1-G70. <https://doi.org/10.1530/EJE-17-0430>
- Saenger P, Wikland KA, Conway GS, *et al.* Recommendations for the diagnosis and management of Turner syndrome. *J Clin Endocrinol Metab.* 2001;86(7):3061-3069. <https://doi.org/10.1210/jcem.86.7.7683>
- Bondy CA. Care of girls and women with Turner syndrome: a guideline of the Turner syndrome study group. *J Clin Endocrinol Metab.* 2007;92(1):10-25. <https://doi.org/10.1210/jc.2006-1374>
- Balshem H, Helfand M, Schunemann HJ, *et al.* GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol.* 2011;64(4):401-406. <https://doi.org/10.1016/j.jclinepi.2010.07.015>
- Ullrich O. Uber typische kombinationsbilder multipler abartungen. *Z Kinderheilkd.* 1930;49(3):271-276. <https://doi.org/10.1007/BF02248090>
- Turner HH. A syndrome of infantilism, congenital webbed neck, and cubitus valgus. *Endocrinology.* 1938;23(5):566-574. <https://doi.org/10.1210/endo-23-5-566>
- Rao E, Weiss B, Fukami M, *et al.* Pseudoautosomal deletions encompassing a novel homeobox gene cause growth failure in idiopathic short stature and Turner syndrome. *Nat Genet.* 1997;16(1):54-63. <https://doi.org/10.1038/ng0597-54>
- Rappold G, Blum WF, Shavrikova EP, *et al.* Genotypes and phenotypes in children with short stature: clinical indicators of SHOX haploinsufficiency. *J Med Genet.* 2007;44(5):306-313. <https://doi.org/10.1136/jmg.2006.046581>
- Zinn AR, Tonk VS, Chen Z, *et al.* Evidence for a Turner syndrome locus or loci at Xp11.2-p22.1. *Am J Hum Genet.* 1998;63(6):1757-1766. <https://doi.org/10.1086/302152>
- Russell LM, Strike P, Browne CE, Jacobs PA. X chromosome loss and ageing. *Cytogenet Genome Res.* 2007;116(3):181-185. <https://doi.org/10.1159/000098184>
- Bryman I, Sylven L, Berntorp K, *et al.* Pregnancy rate and outcome in Swedish women with Turner syndrome. *Fertil Steril.* 2011;95(8):2507-2510. <https://doi.org/10.1016/j.fertnstert.2010.12.039>
- El-Mansoury M, Barrenas ML, Bryman I, *et al.* Chromosomal mosaicism mitigates stigmata and cardiovascular risk factors in Turner syndrome. *Clin Endocrinol (Oxf).* 2007;66(5):744-751. <https://doi.org/10.1111/j.1365-2265.2007.02807.x>
- Snyder EA, San Roman AK, Piña-Aguilar RE, *et al.* Genetic counseling for women with 45,X/46,XX mosaicism: towards more personalized management. *Eur J Med Genet.* 2021;64(3):104140. <https://doi.org/10.1016/j.ejmg.2021.104140>
- Sybert VP, McCauley E. Turner's syndrome. *N Engl J Med.* 2004;351(12):1227-1238. <https://doi.org/10.1056/NEJMra030360>
- Davenport ML. Approach to the patient with Turner syndrome. *J Clin Endocrinol Metab.* 2010;95(4):1487-1495. <https://doi.org/10.1210/jc.2009-0926>
- Carvalho AB, Lemos-Marini SHV, Guerra-Junior G, Maciel-Guerra AT. Clinical and cytogenetic features of 516 patients with suspected Turner syndrome—a single-center experience. *J Pediatr Endocrinol Metab.* 2018;31(2):167-173. <https://doi.org/10.1515/jpem-2017-0273>
- Gravholt CH, Viuff M, Just J, *et al.* The changing face of Turner syndrome. *Endocr Rev.* 2023;44(1):33-69. <https://doi.org/10.1210/endo.2022-016>
- Wolff DJ, Van Dyke DL, Powell CM. Laboratory guideline for Turner syndrome. *Genet Med.* 2010;12(1):52-55. <https://doi.org/10.1097/GIM.0b013e3181c684b2>
- Silva M, de Leeuw N, Mann K, *et al.* European guidelines for constitutional cytogenomic analysis. *Eur J Hum Genet.* 2019;27(1):1-16. <https://doi.org/10.1038/s41431-018-0244-x>
- Prakash S, Guo D, Maslen CL, Silberbach M, Milewicz D, Bondy CA. Single-nucleotide polymorphism array genotyping is equivalent to metaphase cytogenetics for diagnosis of Turner syndrome. *Genet Med.* 2014;14(1):53-59. <https://doi.org/10.1038/gim.2013.77>
- Held KR, Kerber S, Kaminsky E, *et al.* Mosaicism in 45,X Turner syndrome: does survival in early pregnancy depend on the presence of two sex chromosomes? *Hum Genet.* 1992;88(3):288-294. <https://doi.org/10.1007/BF00197261>
- Hook EB, Warburton D. The distribution of chromosomal genotypes associated with Turner's syndrome: livebirth prevalence rates and evidence for diminished fetal mortality and severity in genotypes associated with structural X abnormalities or mosaicism. *Hum Genet.* 1983;64(1):24-27. <https://doi.org/10.1007/BF00289473>
- Hook EB, Warburton D. Turner syndrome revisited: review of new data supports the hypothesis that all viable 45,X cases are cryptic mosaics with a rescue cell line, implying an origin by mitotic loss. *Hum Genet.* 2014;133(4):417-424. <https://doi.org/10.1007/s00439-014-1420-x>
- Hassold TJ. Chromosome abnormalities in human reproductive wastage. *Trends Genet.* 1986;2:105-110. [https://doi.org/10.1016/0168-9525\(86\)90194-0](https://doi.org/10.1016/0168-9525(86)90194-0)
- Schoemaker MJ, Swerdlow AJ, Higgins CD, Wright AF, Jacobs PA. Cancer incidence in women with Turner syndrome in Britain: a national cohort study. *Lancet Oncol.* 2008;9(3):239-246. [https://doi.org/10.1016/S1470-2045\(08\)70033-0](https://doi.org/10.1016/S1470-2045(08)70033-0)
- Cameron-Pimblett A, La RC, King TFJ, Davies MC, Conway GS. The Turner syndrome life course project: karyotype-phenotype

- analyses across the lifespan. *Clin Endocrinol (Oxf)*. 2017;87(5):532-538. <https://doi.org/10.1111/cen.13394>
27. Schoemaker MJ, Swerdlow AJ, Higgins CD, Wright AF, Jacobs PA. Mortality in women with Turner syndrome in Great Britain: a national cohort study. *J Clin Endocrinol Metab*. 2008;93(12):4735-4742. <https://doi.org/10.1210/jc.2008-1049>
 28. Stochholm K, Juul S, Juul K, Naeraa RW, Gravholt CH. Prevalence, incidence, diagnostic delay, and mortality in Turner syndrome. *J Clin Endocrinol Metab*. 2006;91(10):3897-3902. <https://doi.org/10.1210/jc.2006-0558>
 29. Viuff MH, Berglund A, Juul S, Andersen NH, Stochholm K, Gravholt CH. Sex hormone replacement therapy in Turner syndrome—impact on morbidity and mortality. *J Clin Endocrinol Metab*. 2020;105(2):468-478. <https://doi.org/10.1210/clinem/dgz039>
 30. Noordman ID, van der Velden JA, Timmers HJ, et al. Karyotype—phenotype associations in patients with Turner syndrome. *Pediatr Endocrinol Rev*. 2019;16(4):431-440. <https://doi.org/10.17458/per.vol16.2019.nvt.karyotypeturnersyndrome>
 31. Sybert VP. Phenotypic effects of mosaicism for a 47,XXX cell line in Turner syndrome. *J Med Genet*. 2002;39(3):217-220. <https://doi.org/10.1136/jmg.39.3.217>
 32. Lindhardt JM, Hagen CP, Rajpert-De ME, et al. 45,X/46,XY mosaicism: phenotypic characteristics, growth, and reproductive function—a retrospective longitudinal study. *J Clin Endocrinol Metab*. 2012;97(8):E1540-E1549. <https://doi.org/10.1210/jc.2012-1388>
 33. Martinerie L, Morel Y, Gay CL, et al. Impaired puberty, fertility, and final stature in 45,X/46,XY mixed gonadal dysgenetic patients raised as boys. *Eur J Endocrinol*. 2012;166(4):687-694. <https://doi.org/10.1530/EJE-11-0756>
 34. Tosson H, Rose SR, Gartner LA. Children with 45,X/46,XY karyotype from birth to adult height. *Horm Res Paediatr*. 2010;74(3):190-200. <https://doi.org/10.1159/000281468>
 35. Tosson H, Rose SR, Gartner LA. Description of children with 45,X/46,XY karyotype. *Eur J Pediatr*. 2012;171(3):521-529. <https://doi.org/10.1007/s00431-011-1600-9>
 36. De Groote K, Cools M, De SJ, et al. Cardiovascular pathology in males and females with 45,X/46,XY mosaicism. *PLoS One*. 2013;8(2):e54977. <https://doi.org/10.1371/journal.pone.0054977>
 37. Hamerton JL, Canning N, Ray M, Smith S. A cytogenetic survey of 14,069 newborn infants. I. Incidence of chromosome abnormalities. *Clin Genet*. 1975;8(4):223-243. <https://doi.org/10.1111/j.1399-0004.1975.tb01498.x>
 38. Nielsen J, Wohler M. Chromosome abnormalities found among 34,910 newborn children: results from a 13-year incidence study in Arhus, Denmark. *Hum Genet*. 1991;87(1):81-83. <https://doi.org/10.1007/BF01213097>
 39. Stochholm K, Holmgård C, Davis SM, Gravholt CH, Berglund A. Incidence, prevalence, age at diagnosis, and mortality in individuals with 45,X/46,XY mosaicism: a population-based registry study. *Genet Med*. 2024;26(1):100987. <https://doi.org/10.1016/j.gim.2023.100987>
 40. Alkhunaizi E, Albrecht JP, Aarabi M, et al. 45,X/46,XY mosaicism: clinical manifestations and long term follow-up. *Am J Med Genet A*. 2024;194(3):e63451. <https://doi.org/10.1002/ajmg.a.63451>
 41. Chang HJ, Clark RD, Bachman H. The phenotype of 45,X/46,XY mosaicism: an analysis of 92 prenatally diagnosed cases. *Am J Hum Genet*. 1990;46:156-167. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1683543/>
 42. Lee PA, Houk CP, Ahmed SF, Hughes IA. Consensus statement on management of intersex disorders. International consensus conference on intersex. *Pediatrics*. 2006;118(2):e488-e500. <https://doi.org/10.1542/peds.2006-0738>
 43. Guzewicz L, Howell S, Crerand CE, et al. Clinical phenotype and management of individuals with mosaic monosomy X with Y chromosome material stratified by genital phenotype. *Am J Med Genet A*. 2021;185(5):1437-1447. <https://doi.org/10.1002/ajmg.a.62127>
 44. Knoll MM, Strickland J, Jacobson JD. Can boys have Turner syndrome? More than a question of semantics. *Sex Dev*. 2022;16(1):19-26. <https://doi.org/10.1159/000518092>
 45. Bronshtein M, Zimmer EZ, Blazer S. A characteristic cluster of fetal sonographic markers that are predictive of fetal Turner syndrome in early pregnancy. *Am J Obstet Gynecol*. 2003;188(4):1016-1020. <https://doi.org/10.1067/mob.2003.230>
 46. Kagan KO, Avgidou K, Molina FS, Gajewska K, Nicolaidis KH. Relation between increased fetal nuchal translucency thickness and chromosomal defects. *Obstet Gynecol*. 2006;107(1):6-10. <https://doi.org/10.1097/01.AOG.0000191301.63871.c6>
 47. Pauta M, Martinez-Portilla RJ, Borrell A. Diagnostic yield of next-generation sequencing in fetuses with isolated increased nuchal translucency: systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. 2022;59(1):26-32. <https://doi.org/10.1002/uog.23746>
 48. Stuurman KE, Joosten M, van der Burgt I, et al. Prenatal ultrasound findings of rasopathies in a cohort of 424 fetuses: update on genetic testing in the NGS era. *J Med Genet*. 2019;56(10):654-661. <https://doi.org/10.1136/jmedgenet-2018-105746>
 49. Bardi F, Bosschietter P, Verheij J, et al. Is there still a role for nuchal translucency measurement in the changing paradigm of first trimester screening? *Prenat Diagn*. 2020;40(2):197-205. <https://doi.org/10.1002/pd.5590>
 50. Surerus E, Huggon IC, Allan LD. Turner's syndrome in fetal life. *Ultrasound Obstet Gynecol*. 2003;22(3):264-267. <https://doi.org/10.1002/uog.151>
 51. Bedei I, Gloning KP, Joyeux L, et al. Turner syndrome-omphalocele association: incidence, karyotype, phenotype and fetal outcome. *Prenat Diagn*. 2023;43(2):183-191. <https://doi.org/10.1002/pd.6302>
 52. Wagner P, Sonek J, Hoopmann M, Abele H, Kagan KO. First-trimester screening for trisomies 18 and 13, triploidy and Turner syndrome by detailed early anomaly scan. *Ultrasound Obstet Gynecol*. 2016;48(4):446-451. <https://doi.org/10.1002/uog.15829>
 53. Baena N, De Vigan C, Cariati E, et al. Turner syndrome: evaluation of prenatal diagnosis in 19 European registries. *Am J Med Genet*. 2004;129A(1):16-20. <https://doi.org/10.1002/ajmg.a.30092>
 54. Kagan KO, Staboulidou I, Syngelaki A, Cruz J, Nicolaidis KH. The 11–13-week scan: diagnosis and outcome of holoprosencephaly, exomphalos and megacystis. *Ultrasound Obstet Gynecol*. 2010;36(1):10-14. <https://doi.org/10.1002/uog.7646>
 55. Levy AT, Berghella V, Al-Kouatly HB. Outcome of 45,X fetuses with cystic hygroma: a systematic review. *Am J Med Genet A*. 2021;185(1):26-32. <https://doi.org/10.1002/ajmg.a.61902>
 56. Koeberl DD, McGillivray B, Sybert VP. Prenatal diagnosis of 45,X/46,XX mosaicism and 45,X: implications for postnatal outcome. *Am J Hum Genet*. 1995;57:661-666. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1801266/>
 57. Gunther DF, Eugster E, Zagar AJ, Bryant CG, Davenport ML, Quigley CA. Ascertainment bias in Turner syndrome: new insights from girls who were diagnosed incidentally in prenatal life. *Pediatrics*. 2004;114(3):640-644. <https://doi.org/10.1542/peds.2003-1122-L>
 58. Tokita MJ, Sybert VP. Postnatal outcomes of prenatally diagnosed 45,X/46,XX. *Am J Med Genet A*. 2016;170A(5):1196-1201. <https://doi.org/10.1002/ajmg.a.37551>
 59. Viuff MH, Stochholm K, Ulbjerg N, Nielsen BB, Danish Fetal Medicine Study Group, Gravholt CH. Only a minority of sex chromosome abnormalities are detected by the Danish national prenatal screening program for Down syndrome. *Hum Reprod*. 2015;30(10):2419-2426. <https://doi.org/10.1093/humrep/dev192>
 60. Maiz N, Valencia C, Kagan KO, Wright D, Nicolaidis KH. Ductus venosus Doppler in screening for trisomies 21, 18 and 13 and Turner syndrome at 11–13 weeks of gestation. *Ultrasound Obstet Gynecol*. 2009;33(5):512-517. <https://doi.org/10.1002/uog.6330>
 61. Shear MA, Swanson K, Garg R, et al. A systematic review and meta-analysis of cell-free DNA testing for detection of fetal sex

- chromosome aneuploidy. *Prenat Diagn.* 2023;43(2):133-143. <https://doi.org/10.1002/pd.6298>
62. Grati FR, Bajaj K, Zanatta V, et al. Implications of fetoplacental mosaicism on cell-free DNA testing for sex chromosome aneuploidies. *Prenat Diagn.* 2017;37(10):1017-1027. <https://doi.org/10.1002/pd.5138>
 63. Hui L, Ellis K, Mayen D, et al. Position statement from the International Society for Prenatal Diagnosis on the use of non-invasive prenatal testing for the detection of fetal chromosomal conditions in singleton pregnancies. *Prenat Diagn.* 2023;43(7):814-828. <https://doi.org/10.1002/pd.6357>
 64. Dungan JS, Klugman S, Darilek S, et al. Noninvasive prenatal screening (NIPS) for fetal chromosome abnormalities in a general-risk population: an evidence-based clinical guideline of the American college of medical genetics and genomics (ACMG). *Genet Med.* 2023;25(2):100336. <https://doi.org/10.1016/j.gim.2022.11.004>
 65. Johnston M, Warton C, Pertile MD, et al. Ethical issues associated with prenatal screening using non-invasive prenatal testing for sex chromosome aneuploidy. *Prenat Diagn.* 2023;43(2):226-234. <https://doi.org/10.1002/pd.6217>
 66. Bedei I, Gehrke T, Gloning KP, et al. Multicenter clinical experience with non-invasive cell-free DNA screening for monosomy X and related X-chromosome variants. *Prenat Diagn.* 2023;43(2):192-206. <https://doi.org/10.1002/pd.6320>
 67. Salomon LJ, Alfirevic Z, Audibert F, et al. ISUOG updated consensus statement on the impact of cfDNA aneuploidy testing on screening policies and prenatal ultrasound practice. *Ultrasound Obstet Gynecol.* 2017;49(6):815-816. <https://doi.org/10.1002/uog.17483>
 68. Beulen L, Faas BHW, Feenstra I, van Vugt JMG, Bekker MN. Clinical utility of non-invasive prenatal testing in pregnancies with ultrasound anomalies. *Ultrasound Obstet Gynecol.* 2017;49(6):721-728. <https://doi.org/10.1002/uog.17228>
 69. Bianchi DW, Parsa S, Bhatt S, et al. Fetal sex chromosome testing by maternal plasma DNA sequencing: clinical laboratory experience and biology. *Obstet Gynecol.* 2015;125(2):375-382. <https://doi.org/10.1097/AOG.0000000000000637>
 70. Bianchi DW. Cherchez la femme: maternal incidental findings can explain discordant prenatal cell-free DNA sequencing results. *Genet Med.* 2018;20(9):910-917. <https://doi.org/10.1038/gim.2017.219>
 71. Wang L, Meng Q, Tang X, et al. Maternal mosaicism of sex chromosome causes discordant sex chromosomal aneuploidies associated with noninvasive prenatal testing. *Taiwan J Obstet Gynecol.* 2015;54(5):527-531. <https://doi.org/10.1016/j.tjog.2014.10.009>
 72. Mardy AH, Norton ME. Diagnostic testing after positive results on cell free DNA screening: CVS or Amnio? *Prenat Diagn.* 2021;41(10):1249-1254. <https://doi.org/10.1002/pd.6021>
 73. Lüthgens K, Grati FR, Sinzel M, Häbig K, Kagan KO. Confirmation rate of cell free DNA screening for sex chromosomal abnormalities according to the method of confirmatory testing. *Prenat Diagn.* 2021;41(10):1258-1263. <https://doi.org/10.1002/pd.5814>
 74. Cornelisse S, Zagers M, Kostova E, Fleischer K, van Wely M, Mastenbroek S. Preimplantation genetic testing for aneuploidies (abnormal number of chromosomes) in in vitro fertilisation. *Cochrane Database Syst Rev.* 2020;9(9):CD005291. <https://doi.org/10.1002/14651858.CD005291.pub3>
 75. De Rycke M, Berckmoes V, De Vos A, et al. PREIMPLANTATION GENETIC TESTING: clinical experience of preimplantation genetic testing. *Reproduction.* 2020;160(5):A45-A58. <https://doi.org/10.1530/REP-20-0082>
 76. Goossens V, Traeger-Synodinos J, Coonen E, et al. ESHRE PGD consortium data collection XI: cycles from January to December 2008 with pregnancy follow-up to October 2009. *Hum Reprod.* 2012;27(7):1887-1911. <https://doi.org/10.1093/humrep/des106>
 77. Sutton EJ, McInerney-Leo A, Bondy CA, Gollust SE, King D, Biesecker B. Turner syndrome: four challenges across the lifespan. *Am J Med Genet A.* 2005;139A(2):57-66. <https://doi.org/10.1002/ajmg.a.30911>
 78. Reimers R, High F, Kremen J, Wilkins-Haug L. Prenatal diagnosis of sex chromosome aneuploidy—what do we tell the prospective parents? *Prenat Diagn.* 2023;43(2):250-260. <https://doi.org/10.1002/pd.6256>
 79. Hamamy HA, Dahoun S. Parental decisions following the prenatal diagnosis of sex chromosome abnormalities. *Eur J Obstet Gynecol Reprod Biol.* 2004;116(1):58-62. <https://doi.org/10.1016/j.ejogrb.2003.12.029>
 80. Hermann M, Khoshnood B, Anselem O, et al. Lack of consensus in the choice of termination of pregnancy for Turner syndrome in France. *BMC Health Serv Res.* 2019;19(1):994. <https://doi.org/10.1186/s12913-019-4833-3>
 81. Jeon KC, Chen LS, Goodson P. Decision to abort after a prenatal diagnosis of sex chromosome abnormality: a systematic review of the literature. *Genet Med.* 2012;14(1):27-38. <https://doi.org/10.1038/gim.0b013e31822e57a7>
 82. Gruchy N, Vialard F, Blondeel E, et al. Pregnancy outcomes of prenatally diagnosed Turner syndrome: a French multicenter retrospective study including a series of 975 cases. *Prenat Diagn.* 2014;34(12):1133-1138. <https://doi.org/10.1002/pd.4439>
 83. Jaramillo C, Nyquist C, Riggan KA, Egginton J, Phelan S, Allyse M. Delivering the diagnosis of sex chromosome aneuploidy: experiences and preferences of parents and individuals. *Clin Pediatr (Phila).* 2019;58(3):336-342. <https://doi.org/10.1177/0009922818817310>
 84. Riggan KA, Gross B, Close S, Weinberg A, Allyse MA. Prenatal genetic diagnosis of a sex chromosome aneuploidy: parent experiences. *J Genet Couns.* 2021;30(5):1407-1417. <https://doi.org/10.1002/jgc4.1407>
 85. Savendahl L, Davenport ML. Delayed diagnoses of Turner's syndrome: proposed guidelines for change. *J Pediatr.* 2000;137(4):455-459. <https://doi.org/10.1067/mpd.2000.107390>
 86. Gravholt CH, Juul S, Naeraa RW, Hansen J. Prenatal and postnatal prevalence of Turner's syndrome: a registry study. *BMJ.* 1996;312(7022):16-21. <https://doi.org/10.1136/bmj.312.7022.16>
 87. Lee MC, Conway GS. Turner's syndrome: challenges of late diagnosis. *Lancet Diabetes Endocrinol.* 2014;2(4):333-338. [https://doi.org/10.1016/S2213-8587\(13\)70153-0](https://doi.org/10.1016/S2213-8587(13)70153-0)
 88. Mohamed S, Roche EF, Hoey HM. Mode of initial presentation and chromosomal abnormalities in Irish patients with Turner syndrome: a single-centre experience. *J Pediatr Endocrinol Metab.* 2015;28(11-12):1215-1218. <https://doi.org/10.1515/jpem-2014-0287>
 89. Rivkees SA, Hager K, Hosono S, et al. A highly sensitive, high-throughput assay for the detection of Turner syndrome. *J Clin Endocrinol Metab.* 2011;96(3):699-705. <https://doi.org/10.1210/jc.2010-1554>
 90. Correa SC, Rocha MN, Richeti F, et al. Neonatal detection of Turner syndrome by real-time PCR gene quantification of the ARSE and MAGEH1 genes. *Genet Mol Res.* 2014;13(4):9068-9076. <https://doi.org/10.4238/2014.October.31.22>
 91. Ibarra-Ramirez M, Zamudio-Osuna MJ, Campos-Acevedo LD, et al. Detection of Turner syndrome by quantitative PCR of SHOX and VAMP7 genes. *Genet Test Mol Biomarkers.* 2015;19(2):88-92. <https://doi.org/10.1089/gtmb.2014.0236>
 92. Campos-Acevedo LD, Ibarra-Ramirez M, de Jesús Lugo-Trampe J, et al. Dosage of sex chromosomal genes in blood deposited on filter paper for neonatal screening of sex chromosome aneuploidy. *Genet Test Mol Biomarkers.* 2016;20(12):786-790. <https://doi.org/10.1089/gtmb.2016.0101>
 93. Ibarra-Ramirez M, Lugo-Trampe JJ, Campos-Acevedo LD, et al. Gene copy number quantification of SHOX, VAMP7, and SRY for the detection of sex chromosome aneuploidies in neonates. *Genet Test Mol Biomarkers.* 2020;24(6):352-358. <https://doi.org/10.1089/gtmb.2019.0226>

94. Murdock DR, Donovan FX, Chandrasekharappa SC, *et al.* Whole-exome sequencing for diagnosis of Turner syndrome: towards next generation sequencing and newborn screening. *J Clin Endocrinol Metab.* 2017;102(5):1529-1537. <https://doi.org/10.1210/clinem.2016-3414>
95. Kemper AR, Green NS, Calonge N, *et al.* Decision-making process for conditions nominated to the recommended uniform screening panel: statement of the US department of health and human services secretary's advisory committee on heritable disorders in newborns and children. *Genet Med.* 2014;16(2):183-187. <https://doi.org/10.1038/gim.2013.98>
96. Swauger S, Backeljauw P, Hornung L, Shafer J, Casnellie L, Gutmark-Little I. Age at and indication for diagnosis of Turner syndrome in the pediatric population. *Am J Med Genet A.* 2021;185(11):3411-3417. <https://doi.org/10.1002/ajmg.a.62459>
97. Woelfle J, Lindberg A, Aydin F, Ong KK, Camacho-Hubner C, Gohlke B. Secular trends on birth parameters, growth, and pubertal timing in girls with Turner syndrome. *Front Endocrinol (Lausanne).* 2018;9:54. <https://doi.org/10.3389/fendo.2018.00054>
98. Wit JM, Kamp GA, Oostdijk W. Towards a rational and efficient diagnostic approach in children referred for growth failure to the general paediatrician. *Horm Res Paediatr.* 2019;91(4):223-240. <https://doi.org/10.1159/000499915>
99. Kruszka P, Addissie YA, Tekendo-Ngongang C, *et al.* Turner syndrome in diverse populations. *Am J Med Genet A.* 2020;182(2):303-313. <https://doi.org/10.1002/ajmg.a.61461>
100. Gurovich Y, Hanani Y, Bar O, *et al.* Identifying facial phenotypes of genetic disorders using deep learning. *Nat Med.* 2019;25(1):60-64. <https://doi.org/10.1038/s41591-018-0279-0>
101. Alexandrou E, Cabrera-Salcedo C, Labilloy G, *et al.* Algorithm-driven electronic health record notification enhances the detection of Turner syndrome. *J Pediatr.* 2020;216:227-231. <https://doi.org/10.1016/j.jpeds.2019.09.023>
102. Yang Z, Shikany A, Ni Y, Zhang G, Weaver KN, Chen J. Using deep learning and electronic health records to detect Noonan syndrome in pediatric patients. *Genet Med.* 2022;24(11):2329-2337. <https://doi.org/10.1016/j.gim.2022.08.002>
103. Viuff M, Skakkebaek A, Johannsen EB, *et al.* X chromosome dosage and the genetic impact across human tissues. *Genome Med.* 2023;15(1):21. <https://doi.org/10.1186/s13073-023-01169-4>
104. Rajpathak SN, Vellarikkal SK, Patowary A, Scaria V, Sivasubbu S, Deobagkar DD. Human 45,X fibroblast transcriptome reveals distinct differentially expressed genes including long noncoding RNAs potentially associated with the pathophysiology of Turner syndrome. *PLoS One.* 2014;9(6):e100076. <https://doi.org/10.1371/journal.pone.0100076>
105. Zhang X, Hong D, Ma S, *et al.* Integrated functional genomic analyses of Klinefelter and Turner syndromes reveal global network effects of altered X chromosome dosage. *Proc Natl Acad Sci U S A.* 2020;117(9):4864-4873. <https://doi.org/10.1073/pnas.1910003117>
106. Trolle C, Nielsen MM, Skakkebaek A, *et al.* Widespread DNA hypomethylation and differential gene expression in Turner syndrome. *Sci Rep.* 2016;6(1):34220. <https://doi.org/10.1038/srep34220>
107. Raznahan A, Parikshak NN, Chandran V, *et al.* Sex-chromosome dosage effects on gene expression in humans. *Proc Natl Acad Sci U S A.* 2018;115(28):7398-7403. <https://doi.org/10.1073/pnas.1802889115>
108. Sharma A, Jamil MA, Nuesgen N, *et al.* DNA methylation signature in peripheral blood reveals distinct characteristics of human X chromosome numerical aberrations. *Clin Epigenetics.* 2015;7:76. <https://doi.org/10.1186/s13148-015-0112-2>
109. Massingham LJ, Johnson KL, Scholl TM, Slonim DK, Wick HC, Bianchi DW. Amniotic fluid RNA gene expression profiling provides insights into the phenotype of Turner syndrome. *Hum Genet.* 2014;133(9):1075-1082. <https://doi.org/10.1007/s00439-014-1448-y>
110. Farooqui A, Tazyeen S, Ahmed MM, *et al.* Assessment of the key regulatory genes and their interologs for Turner syndrome employing network approach. *Sci Rep.* 2018;8(1):10091-28375. <https://doi.org/10.1038/s41598-018-28375-0>
111. Qi X, Wang Q, Yu M, Kong Y, Shi F, Wang S. Bioinformatic analysis identifies the immunological profile of Turner syndrome with different X chromosome origins. *Front Endocrinol (Lausanne).* 2023;14:1024244. <https://doi.org/10.3389/fendo.2023.1024244>
112. Xue R, Tang Q, Zhang Y, *et al.* Integrative analyses of genes associated with otologic disorders in Turner syndrome. *Front Genet.* 2022;13:799783. <https://doi.org/10.3389/fgene.2022.799783>
113. San Roman AK, Skaletsky H, Godfrey AK, *et al.* The human Y and inactive X chromosomes similarly modulate autosomal gene expression. *Cell Genom.* 2024;4(1):100462. <https://doi.org/10.1101/2023.06.05.543763>
114. Sarmiento L, Svensson J, Barchetta I, Giwercman A, Cilio CM. Copy number of the X-linked genes TLR7 and CD40L influences innate and adaptive immune responses. *Scand J Immunol.* 2019;90(2):e12776. <https://doi.org/10.1111/sji.12776>
115. Skakkebaek A, Kjær-Sørensen K, Matchkov VV, *et al.* Dosage of the pseudoautosomal gene SLC25A6 is implicated in QTc interval duration. *Sci Rep.* 2023;13(1):12089. <https://doi.org/10.1038/s41598-023-38867-3>
116. Ottesen AM, Aksglaede L, Garn I, *et al.* Increased number of sex chromosomes affects height in a nonlinear fashion: a study of 305 patients with sex chromosome aneuploidy. *Am J Med Genet A.* 2010;152A(5):1206-1212. <https://doi.org/10.1002/ajmg.a.33334>
117. Abu-Halima M, Oberhoffer FS, El Rahman MA, *et al.* Insights from circulating microRNAs in cardiovascular entities in Turner syndrome patients. *PLoS One.* 2020;15(4):e0231402. <https://doi.org/10.1371/journal.pone.0231402>
118. Abu-Halima M, Oberhoffer FS, Wagner V, *et al.* MicroRNA-126-3p/5p and aortic stiffness in patients with Turner syndrome. *Children (Basel).* 2022;9(8):1109. <https://doi.org/10.3390/children9081109>
119. Sun YX, Zhang YX, Zhang D, *et al.* XCI-escaping gene KDM5C contributes to ovarian development via downregulating miR-320a. *Hum Genet.* 2017;136(2):227-239. <https://doi.org/10.1007/s00439-016-1752-9>
120. Johannsen EB, Just J, Viuff MH, *et al.* Sex chromosome aneuploidies give rise to changes in the circular RNA profile: a circular transcriptome-wide study of Turner and Klinefelter syndrome across different tissues. *Front Genet.* 2022;13:928874. <https://doi.org/10.3389/fgene.2022.928874>
121. Barrientos-Rios R, Frias S, Velázquez-Aragón JA, *et al.* Low bone mineral density and renal malformation in Mexican patients with Turner syndrome are associated with single nucleotide variants in vitamin D-metabolism genes. *Gynecol Endocrinol.* 2019;35(9):772-776. <https://doi.org/10.1080/09513590.2019.1582626>
122. Peralta López M, Centeno V, Miras M, *et al.* Association of vitamin D receptor gene Cdx2 polymorphism with bone markers in Turner syndrome patients. *J Pediatr Endocrinol Metab.* 2012;25(7-8):669-671. <https://doi.org/10.1515/jpem-2012-0098>
123. Corbitt H, Morris SA, Gravholt CH, *et al.* TIMP3 and TIMP1 are risk genes for bicuspid aortic valve and aortopathy in Turner syndrome. *PLoS Genet.* 2018;14(10):e1007692. <https://doi.org/10.1371/journal.pgen.1007692>
124. Gutierrez J, Davis BA, Nevenon KA, Ward S, Carbone L, Maslen CL. DNA methylation analysis of Turner syndrome BAV. *Front Genet.* 2022;13:872750. <https://doi.org/10.3389/fgene.2022.872750>
125. Pinnaro CT, Beck CB, Major HJ, Darbro BW. CRELD1 variants are associated with bicuspid aortic valve in Turner syndrome. *Hum Genet.* 2023;142(4):523-530. <https://doi.org/10.1007/s00439-023-02538-0>
126. Bianco B, Verreschi IT, Oliveira KC, *et al.* PTPN22 polymorphism is related to autoimmune disease risk in patients with Turner

- syndrome. *Scand J Immunol.* 2010;72(3):256-259. <https://doi.org/10.1111/j.1365-3083.2010.02438.x>
127. Santos LOD, Bispo AVS, Barros JV, et al. CTLA-4 gene polymorphisms are associated with obesity in Turner syndrome. *Genet Mol Biol.* 2018;41(4):727-734. <https://doi.org/10.1590/1678-4685-gmb-2017-0312>
 128. Álvarez-Nava F, Salinas M, Bastidas D, Vicuña Y, Racines-Orbe M. PPARGC1A promoter DNA-methylation level and glucose metabolism in Ecuadorian women with Turner syndrome. *Horm Mol Biol Clin Investig.* 2020;42(2):159-165. <https://doi.org/10.1515/hmbci-2020-0076>
 129. Calcaterra V, Gamba G, Montani N, et al. Thrombophilic screening in Turner syndrome. *J Endocrinol Invest.* 2011;34(9):676-679. <https://doi.org/10.3275/7724>
 130. Binder G, Baur F, Schweizer R, Ranke MB. The d3-growth hormone (GH) receptor polymorphism is associated with increased responsiveness to GH in Turner syndrome and short small-for-gestational-age children. *J Clin Endocrinol Metab.* 2006;91(2):659-664. <https://doi.org/10.1210/jc.2005-1581>
 131. Binder G, Trebar B, Baur F, Schweizer R, Ranke MB. Homozygosity of the d3-growth hormone receptor polymorphism is associated with a high total effect of GH on growth and a low BMI in girls with Turner syndrome. *Clin Endocrinol (Oxf).* 2008;68(4):567-572. <https://doi.org/10.1111/j.1365-2265.2007.03090.x>
 132. Braz AF, Costalonga EF, Trarbach EB, et al. Genetic predictors of long-term response to growth hormone (GH) therapy in children with GH deficiency and Turner syndrome: the influence of a SOCS2 polymorphism. *J Clin Endocrinol Metab.* 2014;99(9):E1808-E1813. <https://doi.org/10.1210/jc.2014-1744>
 133. Alvarez-Nava F, Marcano H, Pardo T, et al. GHR and VDR genes do not contribute to the growth hormone (GH) response in GH deficient and Turner syndrome patients. *J Pediatr Endocrinol Metab.* 2010;23(8):773-782. <https://doi.org/10.1515/jpem.2010.127>
 134. Braz AF, Costalonga EF, Montenegro LR, et al. The interactive effect of GHR-exon 3 and -202 A/C IGFBP3 polymorphisms on rhGH responsiveness and treatment outcomes in patients with Turner syndrome. *J Clin Endocrinol Metab.* 2012;97(4):E671-E677. <https://doi.org/10.1210/jc.2011-2521>
 135. Ko JM, Kim JM, Cheon CK, et al. The common exon 3 polymorphism of the growth hormone receptor gene and the effect of growth hormone therapy on growth in Korean patients with Turner syndrome. *Clin Endocrinol (Oxf).* 2010;72(2):196-202. <https://doi.org/10.1111/j.1365-2265.2009.03681.x>
 136. Stevens A, Murray P, De Leonibus C, et al. Gene expression signatures predict response to therapy with growth hormone. *Pharmacogenomics J.* 2021;21(5):594-607. <https://doi.org/10.1038/s41397-021-00237-5>
 137. FitzSimmons J, Fantel A, Shepard TH. Growth parameters in mid-trimester fetal Turner syndrome. *Early Hum Dev.* 1994;38(2):121-129. [https://doi.org/10.1016/0378-3782\(94\)90223-2](https://doi.org/10.1016/0378-3782(94)90223-2)
 138. Bernasconi S, Larizza D, Benso L, et al. Turner's syndrome in Italy: familial characteristics, neonatal data, standards for birth weight and for height and weight from infancy to adulthood. *Acta Paediatr.* 1994;83(3):292-298. <https://doi.org/10.1111/j.1651-2227.1994.tb18097.x>
 139. Isojima T, Yokoya S, Ito J, Horikawa R, Tanaka T. New reference growth charts for Japanese girls with Turner syndrome. *Pediatr Int.* 2009;51(5):709-714. <https://doi.org/10.1111/j.1442-200X.2009.02838.x>
 140. Even L, Cohen A, Marbach N, et al. Longitudinal analysis of growth over the first 3 years of life in Turner's syndrome. *J Pediatr.* 2000;137(4):460-464. <https://doi.org/10.1067/mpd.2000.109110>
 141. Davenport ML, Punyasavatsut N, Stewart PW, Gunther DF, Savendahl L, Sybert VP. Growth failure in early life: an important manifestation of Turner syndrome. *Horm Res.* 2002;57(5-6):157-164. <https://doi.org/10.1159/000058376>
 142. Lyon AJ, Preece MA, Grant DB. Growth curve for girls with Turner syndrome. *Arch Dis Child.* 1985;60(10):932-935. <https://doi.org/10.1136/adc.60.10.932>
 143. Rongen-Westerlaken C, Corel L, Van den Broeck J, et al. Reference values for height, height velocity and weight in Turner's syndrome. Swedish study group for GH treatment. *Acta Paediatr.* 1997;86(9):937-942. <https://doi.org/10.1111/j.1651-2227.1997.tb15174.x>
 144. Isojima T, Yokoya S. Growth in girls with Turner syndrome. *Front Endocrinol (Lausanne).* 2022;13:1068128. <https://doi.org/10.3389/fendo.2022.1068128>
 145. Ellison JW, Wardak Z, Young MF, Robey PG, Laig-Webster M, Chiong W. PHOG, a candidate gene for involvement in the short stature of Turner syndrome. *Hum Mol Genet.* 1997;6(8):1341-1347. <https://doi.org/10.1093/hmg/6.8.1341>
 146. Ranke MB, Blum WF, Haug F, et al. Growth hormone, somatomedin levels and growth regulation in Turner's syndrome. *Acta Endocrinol.* 1987;116:305-313. <https://doi.org/10.1530/acta.0.1160305>
 147. Ross JL, Long LM, Loriaux DL, Cutler GBJ. Growth hormone secretory dynamics in Turner syndrome. *J Pediatr.* 1985;106(2):202-206. [https://doi.org/10.1016/S0022-3476\(85\)80287-0](https://doi.org/10.1016/S0022-3476(85)80287-0)
 148. Zadik Z, Landau H, Chen M, Altman Y, Lieberman E. Assessment of growth hormone (GH) axis in Turner's syndrome using 24-hour integrated concentrations of GH, insulin-like growth factor-I, plasma GH-binding activity, GH binding to IM9 cells, and GH response to pharmacological stimulation. *J Clin Endocrinol Metab.* 1992;75(2):412-416. <https://doi.org/10.1210/jcem.75.2.1386373>
 149. Hochberg Z, Aviram M, Rubin D, Pollack S. Decreased sensitivity to insulin-like growth factor I in Turner's syndrome: a study of monocytes and T lymphocytes. *Eur J Clin Invest.* 1997;27(7):543-547. <https://doi.org/10.1046/j.1365-2362.1997.1640702.x>
 150. Lebl J, Pruhova S, Zapletalova J, Pechova M. IGF-I resistance and Turner's syndrome. *J Pediatr Endocrinol Metab.* 2001;14(1):37-41. <https://doi.org/10.1515/JPEM.2001.14.1.37>
 151. Gravholt CH, Frystyk J, Flyvbjerg A, Orskov H, Christiansen JS. Reduced free IGF-I and increased IGFBP-3 proteolysis in Turner syndrome: modulation by female sex steroids. *Am J Physiol.* 2001;280:E308-E314. <https://doi.org/10.1152/ajpendo.2001.280.2.E308>
 152. Rongen Westerlaken C, Rikken B, Vastrick P, et al. Body proportions in individuals with Turner syndrome. The Dutch growth hormone working group. *Eur J Pediatr.* 1993;152(10):813-817. <https://doi.org/10.1007/BF02073377>
 153. Uematsu A, Yorifuji T, Muroi J, Yamanaka C, Momoi T. Relatively longer hand in patients with Ullrich-Turner syndrome. *Am J Med Genet.* 1999;82(3):254-256. [https://doi.org/10.1002/\(SICI\)1096-8628\(19990129\)82:3<254::AID-AJMG11>3.0.CO;2-J](https://doi.org/10.1002/(SICI)1096-8628(19990129)82:3<254::AID-AJMG11>3.0.CO;2-J)
 154. Binder G, Fritsch H, Schweizer R, Ranke MB. Radiological signs of Leri-Weill dyschondrosteosis in Turner syndrome. *Horm Res.* 2001;55(2):71-76. <https://doi.org/10.1159/000049973>
 155. Kim JY, Rosenfeld SR, Keyak JH. Increased prevalence of scoliosis in Turner syndrome. *J Pediatr Orthop.* 2001;21(6):765-766. <https://doi.org/10.1097/01241398-200111000-00012>
 156. Baxter L, Bryant J, Cave CB, Milne R. Recombinant growth hormone for children and adolescents with Turner syndrome. *Cochrane Database Syst Rev.* 2007;(3):CD003887. <https://doi.org/10.1002/14651858.CD003887.pub2>
 157. Kollmann F, Damm M, Reinhardt D, et al. Growth-promoting effects of human recombinant growth hormone in subjects with Ullrich-Turner syndrome (UTS). In: Ranke MB, Rosenfeld RG, eds. *Turner Syndrome: Growth Promoting Therapies.* Elsevier Science Publishing; 2016:201-207.
 158. Stephure DK. Impact of growth hormone supplementation on adult height in Turner syndrome: results of the Canadian randomized controlled trial. *J Clin Endocrinol Metab.* 2005;90(6):3360-3366. <https://doi.org/10.1210/jc.2004-2187>

159. Rosenfeld RG, Attie KM, Frane J, *et al.* Growth hormone therapy of Turner's syndrome: beneficial effect on adult height. *J Pediatr.* 1998;132(2):319-324. [https://doi.org/10.1016/S0022-3476\(98\)70452-4](https://doi.org/10.1016/S0022-3476(98)70452-4)
160. Ross JL, Quigley CA, Cao D, *et al.* Growth hormone plus childhood low-dose estrogen in Turner's syndrome. *N Engl J Med.* 2011;364(13):1230-1242. <https://doi.org/10.1056/NEJMoa1005669>
161. Quigley CA, Crowe BJ, Anglin DG, Chipman JJ. Growth hormone and low dose estrogen in Turner syndrome: results of a United States multi-center trial to near-final height. *J Clin Endocrinol Metab.* 2002;87(5):2033-2041. <https://doi.org/10.1210/jcem.87.5.8477>
162. Davenport ML, Crowe BJ, Travers SH, *et al.* Growth hormone treatment of early growth failure in toddlers with Turner syndrome: a randomized, controlled, multi-center trial. *J Clin Endocrinol Metab.* 2007;92(9):3406-3416. <https://doi.org/10.1210/jc.2006-2874>
163. Quigley CA, Fechner PY, Geffner ME, *et al.* Prevention of growth failure in Turner syndrome: long-term results of early growth hormone treatment in the "toddler Turner" cohort. *Horm Res Paediatr.* 2021;94(1-2):18-35. <https://doi.org/10.1159/000513788>
164. Pasquino AM, Pucarelli I, Segni M, Tarani L, Calcaterra V, Larizza D. Adult height in sixty girls with Turner syndrome treated with growth hormone matched with an untreated group. *J Endocrinol Invest.* 2005;28(6):350-356. <https://doi.org/10.1007/BF03347202>
165. Attanasio A, James D, Reinhardt R, Rekers Mombarg L. Final height and long-term outcome after growth hormone therapy in Turner syndrome: results of a German multicentre trial. *Horm Res.* 1995;43(4):147-149. <https://doi.org/10.1159/000184263>
166. Van den BJ, van Teunenbroek A, Hokken-Koelega A, Wit JM. Efficacy of long-term growth hormone treatment in Turner's syndrome. European study group. *J Pediatr Endocrinol Metab.* 1999;12(5):673-676. <https://doi.org/10.1515/jpem.1999.12.5.673>
167. Chernausek SD, Attie KM, Cara JF, Rosenfeld RG, Frane J. Growth hormone therapy of Turner syndrome: the impact of age of estrogen replacement on final height. Genentech, Inc., collaborative study group. *J Clin Endocrinol Metab.* 2000;85(7):2439-2445. <https://doi.org/10.1210/jcem.85.7.6684>
168. Li P, Cheng F, Xiu L. Height outcome of the recombinant human growth hormone treatment in Turner syndrome: a meta-analysis. *Endocr Connect.* 2018;7(4):573-583. <https://doi.org/10.1530/EC-18-0115>
169. Carel JC, Mathivon L, Gendrel C, Ducret JP, Chaussain JL. Near normalization of final height with adapted doses of growth hormone in Turner's syndrome. *J Clin Endocrinol Metab.* 1998;83(5):1462-1466. <https://doi.org/10.1210/jcem.83.5.4777>
170. Sas TC, Muinck Keizer-Schrama SM, Stijnen T, *et al.* Normalization of height in girls with Turner syndrome after long-term growth hormone treatment: results of a randomized dose-response trial. *J Clin Endocrinol Metab.* 1999;84(12):4607-4612. <https://doi.org/10.1210/jcem.84.12.6241>
171. Van Pareden YK, de Muinck Keizer-Schrama SM, Stijnen T, *et al.* Final height in girls with Turner syndrome after long-term growth hormone treatment in three dosages and low dose estrogens. *J Clin Endocrinol Metab.* 2003;88(3):1119-1125. <https://doi.org/10.1210/jc.2002-021171>
172. Plotnick L, Attie KM, Blethen SL, Sy JP. Growth hormone treatment of girls with Turner syndrome: the national cooperative growth study experience. *Pediatrics.* 1998;102 (2 Pt 3):479-481. <https://doi.org/10.1542/peds.102.S3.479>
173. Maghnie M, Ranke MB, Geffner ME, *et al.* Safety and efficacy of pediatric growth hormone therapy: results from the full KIGS cohort. *J Clin Endocrinol Metab.* 2022;107(12):3287-3301. <https://doi.org/10.1210/clinem/dgac517>
174. Kriström B, Ankarberg-Lindgren C, Barrenäs ML, Nilsson KO, Albertsson-Wikland K. Normalization of puberty and adult height in girls with Turner syndrome: results of the Swedish growth hormone trials initiating transition into adulthood. *Front Endocrinol (Lausanne).* 2023;14:1197897. <https://doi.org/10.3389/fendo.2023.1197897>
175. Reiter EO, Blethen SL, Baptista J, Price L. Early initiation of growth hormone treatment allows age-appropriate estrogen use in Turner's syndrome. *J Clin Endocrinol Metab.* 2001;86(5):1936-1941. <https://doi.org/10.1210/jcem.86.5.7466>
176. Ranke MB, Lindberg A, Longas AF, *et al.* Major determinants of height development in Turner syndrome (TS) patients treated with GH: analysis of 987 patients from KIGS. *Pediatr Res.* 2007;61(1):105-110. <https://doi.org/10.1203/01.pdr.0000250039.42000.c9>
177. Ranke MB, Lindberg A, Brosz M, *et al.* Accurate long-term prediction of height during the first four years of growth hormone treatment in prepubertal children with growth hormone deficiency or Turner syndrome. *Horm Res Paediatr.* 2012;78(1):8-17. <https://doi.org/10.1159/000339468>
178. Stevens A, Murray P, Wojcik J, *et al.* Validating genetic markers of response to recombinant human growth hormone in children with growth hormone deficiency and Turner syndrome: the PREDICT validation study. *Eur J Endocrinol.* 2016;175(6):633-643. <https://doi.org/10.1530/EJE-16-0357>
179. Linglart A, Cabrol S, Berlier P, *et al.* Growth hormone treatment before the age of 4 years prevents short stature in young girls with Turner syndrome. *Eur J Endocrinol.* 2011;164(6):891-897. <https://doi.org/10.1530/EJE-10-1048>
180. Wasniewska M, De Luca F, Bergamaschi R, *et al.* Early treatment with GH alone in Turner syndrome: prepubertal catch-up growth and waning effect. *Eur J Endocrinol.* 2004;151:567-572. <https://doi.org/10.1530/eje.0.1510567>
181. Quigley CA, Wan X, Garg S, Kowal K, Cutler GB, Jr., Ross JL. Effects of low-dose estrogen replacement during childhood on pubertal development and gonadotropin concentrations in patients with Turner syndrome: results of a randomized, double-blind, placebo-controlled clinical trial. *J Clin Endocrinol Metab.* 2014;99(9):E1754-E1764. <https://doi.org/10.1210/jc.2013-4518>
182. Ross JL, Lee PA, Gut R, Germak J. Increased height standard deviation scores in response to growth hormone therapy to near-adult height in older children with delayed skeletal maturation: results from the ANSWER program. *Int J Pediatr Endocrinol.* 2015;2015(1):1. <https://doi.org/10.1186/1687-9856-2015-1>
183. Bettendorf M, Inta IM, Doerr HG, Hauffa BP, Mehls O, Ranke MB. Height gain in Ullrich-Turner syndrome after early and late growth hormone treatment start: results from a large retrospective German study and potential basis for an individualized treatment approach. *Horm Res Paediatr.* 2013;80(5):356-362. <https://doi.org/10.1159/000356045>
184. Sas TC, Muinck Keizer-Schrama SM, Stijnen T, Aanstoot HJ, Drop SL. Carbohydrate metabolism during long-term growth hormone (GH) treatment and after discontinuation of GH treatment in girls with Turner syndrome participating in a randomized dose-response study. Dutch advisory group on growth hormone. *J Clin Endocrinol Metab.* 2000;85(2):769-775. <https://doi.org/10.1210/jcem.85.2.6334>
185. Blankenstein O, Snajderova M, Blair J, Pournara E, Pedersen BT, Petit IO. Real-life GH dosing patterns in children with GHD, TS or born SGA: a report from the NordiNet® international outcome study. *Eur J Endocrinol.* 2017;177(2):145-155. <https://doi.org/10.1530/EJE-16-1055>
186. Backeljauw P, Kanumakala S, Loche S, *et al.* Safety and effectiveness of recombinant human growth hormone in children with Turner syndrome: data from the PATRO children study. *Horm Res Paediatr.* 2021;94(3-4):133-143. <https://doi.org/10.1159/000515875>
187. Cleemann Wang A, Hagen CP, Nedaeifard L, Juul A, Jensen RB. Growth and adult height in girls with Turner syndrome following IGF-1 titrated growth hormone treatment. *J Clin Endocrinol Metab.* 2020;105(8):dgaa274. <https://doi.org/10.1210/clinem/dgaa274>
188. Polak M, Konrad D, Tønnes Pedersen B, Puras G, Šnajderová M. Still too little, too late? Ten years of growth hormone therapy

- baseline data from the NordiNet® international outcome study. *J Pediatr Endocrinol Metab.* 2018;31(5):521-532. <https://doi.org/10.1515/jpem-2017-0489>
189. Coutant R, Nicolino M, Cammas B, de Buyst V, Tauber M, Hamel JF. Yearly height gain is dependent on the truly received dose of growth hormone and the duration of periods of poor adherence: practical lessons from the French EasyPod™ connect multicenter observational study. *Front Endocrinol (Lausanne).* 2021;12:790169. <https://doi.org/10.3389/fendo.2021.790169>
 190. Hughes IP, Choong C, Rath S, et al. Early cessation and non-response are important and possibly related problems in growth hormone therapy: an OZGROW analysis. *Growth Horm IGF Res.* 2016;29:63-70. <https://doi.org/10.1016/j.ghir.2016.04.006>
 191. Bannink EM, van der Palen RL, Mulder PG, de Muinck Keizer-Schrama SM. Long-term follow-up of GH-treated girls with Turner syndrome: BMI, blood pressure, body proportions. *Horm Res.* 2009;71(6):336-342. <https://doi.org/10.1159/000223418>
 192. Van Pareren YK, de Muinck Keizer-Schrama SM, Stijnen T, Sas TC, Drop SL. Effect of discontinuation of long-term growth hormone treatment on carbohydrate metabolism and risk factors for cardiovascular disease in girls with Turner syndrome. *J Clin Endocrinol Metab.* 2002;87(12):5442-5448. <https://doi.org/10.1210/jc.2002-020789>
 193. Sas TC, Cromme-Dijkhuis AH, de Muinck K, Stijnen T, van Teunenbroek A, Drop SL. The effects of long-term growth hormone treatment on cardiac left ventricular dimensions and blood pressure in girls with Turner's syndrome. *J Pediatr.* 1999;135(4):470-476. [https://doi.org/10.1016/S0022-3476\(99\)70170-8](https://doi.org/10.1016/S0022-3476(99)70170-8)
 194. Radetti G, Crepaz R, Milanese O, et al. Cardiac performance in Turner's syndrome patients on growth hormone therapy. *Horm Res.* 2001;55(5):240-244. <https://doi.org/10.1159/000050003>
 195. Child CJ, Quigley CA, Cutler GB, et al. Height gain and safety outcomes in growth hormone-treated children with idiopathic short stature: experience from a prospective observational study. *Horm Res Paediatr.* 2019;91(4):241-251. <https://doi.org/10.1159/000500087>
 196. Pfäffle R, Bidlingmaier M, Kreitschmann-Andermahr I, et al. Safety and effectiveness of omnitrope®, a biosimilar recombinant human growth hormone: more than 10 years' experience from the PATRO children study. *Horm Res Paediatr.* 2020;93(3):154-163. <https://doi.org/10.1159/000508190>
 197. Quigley CA, Child CJ, Zimmermann AG, Rosenfeld RG, Robison LL, Blum WF. Mortality in children receiving growth hormone treatment of growth disorders: data from the genetics and neuroendocrinology of short stature international study. *J Clin Endocrinol Metab.* 2017;102(9):3195-3205. <https://doi.org/10.1210/jc.2017-00214>
 198. Coutant R, Bosch Muñoz J, Dumitrescu CP, et al. Effectiveness and overall safety of NutropinAq® for growth hormone deficiency and other paediatric growth hormone disorders: completion of the international cooperative growth study, NutropinAq® European Registry (iNCGS). *Front Endocrinol (Lausanne).* 2021;12:676083. <https://doi.org/10.3389/fendo.2021.676083>
 199. Rhie YJ, Yoo JH, Choi JH, et al. Long-term safety and effectiveness of growth hormone therapy in Korean children with growth disorders: 5-year results of LG growth study. *PLoS One.* 2019;14(5):e0216927. <https://doi.org/10.1371/journal.pone.0216927>
 200. Bannink EM, van der Palen RL, Mulder PG, de Muinck Keizer-Schrama SM. Long-term follow-up of GH-treated girls with Turner syndrome: metabolic consequences. *Horm Res.* 2009;71(6):343-349. <https://doi.org/10.1159/000223419>
 201. Mazzanti L, Bergamaschi R, Castiglioni L, Zappulla F, Pirazzoli P, Cicognani A. Turner syndrome, insulin sensitivity and growth hormone treatment. *Horm Res.* 2005;64(Suppl 3):51-57. <https://doi.org/10.1159/000089318>
 202. Wooten N, Bakalov VK, Hill S, Bondy CA. Reduced abdominal adiposity and improved glucose tolerance in growth hormone-treated girls with Turner syndrome. *J Clin Endocrinol Metab.* 2008;93(6):2109-2114. <https://doi.org/10.1210/jc.2007-2266>
 203. Ari M, Bakalov VK, Hill S, Bondy CA. The effects of growth hormone treatment on bone mineral density and body composition in girls with Turner syndrome. *J Clin Endocrinol Metab.* 2006;91(11):4302-4305. <https://doi.org/10.1210/jc.2006-1351>
 204. Nour MA, Burt LA, Perry RJ, Stephure DK, Hanley DA, Boyd SK. Impact of growth hormone on adult bone quality in Turner syndrome: a HR-pQCT study. *Calcif Tissue Int.* 2016;98(1):49-59. <https://doi.org/10.1007/s00223-015-0064-8>
 205. Sas TC, Gerver WJ, De Bruin R, et al. Body proportions during long-term growth hormone treatment in girls with Turner syndrome participating in a randomized dose-response trial. *J Clin Endocrinol Metab.* 1999;84(12):4622-4628. <https://doi.org/10.1210/jcem.84.12.6225>
 206. McVey LC, Fletcher A, Murtaza M, Donaldson M, Wong SC, Mason A. Skeletal disproportion in girls with Turner syndrome and longitudinal change with growth-promoting therapy. *Clin Endocrinol (Oxf).* 2021;94(5):797-803. <https://doi.org/10.1111/cen.14413>
 207. Davenport ML, Roush J, Liu C, et al. Growth hormone treatment does not affect incidences of middle ear disease or hearing loss in infants and toddlers with Turner syndrome. *Horm Res Paediatr.* 2010;74(1):23-32. <https://doi.org/10.1159/000313964>
 208. Bell J, Parker KL, Swinford RD, Hoffman AR, Maneatis T, Lippe B. Long-term safety of recombinant human growth hormone in children. *J Clin Endocrinol Metab.* 2010;95(1):167-177. <https://doi.org/10.1210/jc.2009-0178>
 209. Darendeliler F, Karagiannis G, Wilton P. Headache, idiopathic intracranial hypertension and slipped capital femoral epiphysis during growth hormone treatment: a safety update from the KIGS database. *Horm Res.* 2007;68(Suppl 5):41-47. <https://doi.org/10.1159/000110474>
 210. Child CJ, Zimmermann AG, Scott RS, Cutler GB, Jr., Battelino T, Blum WF. Prevalence and incidence of diabetes mellitus in GH-treated children and adolescents: analysis from the GeNeSIS observational research program. *J Clin Endocrinol Metab.* 2011;96(6):E1025-E1034. <https://doi.org/10.1210/jc.2010-3023>
 211. Säwendahl L, Cooke R, Tidblad A, et al. Long-term mortality after childhood growth hormone treatment: the SAGHe cohort study. *Lancet Diabetes Endocrinol.* 2020;8(8):683-692. [https://doi.org/10.1016/S2213-8587\(20\)30163-7](https://doi.org/10.1016/S2213-8587(20)30163-7)
 212. Säwendahl L, Polak M, Backeljauw P, et al. Long-term safety of growth hormone treatment in childhood: two large observational studies: NordiNet IOS and ANSWER. *J Clin Endocrinol Metab.* 2021;106(6):1728-1741. <https://doi.org/10.1210/clinem/dgab080>
 213. Stochholm K, Kiess W. Long-term safety of growth hormone—A combined registry analysis. *Clin Endocrinol (Oxf).* 2018;88(4):515-528. <https://doi.org/10.1111/cen.13502>
 214. Allen DB. Safety of human growth hormone therapy: current topics. *J Pediatr.* 1996;128(5):S8-S13. [https://doi.org/10.1016/S0022-3476\(96\)70003-3](https://doi.org/10.1016/S0022-3476(96)70003-3)
 215. Marx JS, Pagadala M, Carney J, et al. Scoliosis and kyphosis prevalence in Turner syndrome: a retrospective review at a pediatric tertiary care medical center. *J Pediatr Orthop.* 2023;43(5):299-302. <https://doi.org/10.1097/BPO.0000000000002367>
 216. Irzyniec T, Jeż W, Lepska K, Maciejewska-Paszek I, Frelich J. Childhood growth hormone treatment in women with Turner syndrome—benefits and adverse effects. *Sci Rep.* 2019;9(1):15951. <https://doi.org/10.1038/s41598-019-52332-0>
 217. Cabanas P, Garcia-Caballero T, Barreiro J, et al. Papillary thyroid carcinoma after recombinant GH therapy for Turner syndrome. *Eur J Endocrinol.* 2005;153(4):499-502. <https://doi.org/10.1530/eje.1.01988>
 218. Hong YH, Kim DG, Lee JH, Jung MJ, Choi CY. The unusual case of fibroma of tendon sheath in a young girl with Turner syndrome undergoing growth hormone treatment. *J Clin Res Pediatr Endocrinol.* 2021;13(1):104-108. <https://doi.org/10.4274/jcrpe.galenos.2020.2019.0223>

219. Mathara Diddhenipothage SAD, Goindoo RJ, Bragg F, *et al.* Tumour occurrence in women with Turner syndrome: a narrative review and single-centre case series. *Clin Endocrinol (Oxf)*. 2023;99(1):64-72. <https://doi.org/10.1111/cen.14910>
220. Morotti RA, Killackey M, Shneider BL, Repucci A, Emre S, Thung SN. Hepatocellular carcinoma and congenital absence of the portal vein in a child receiving growth hormone therapy for Turner syndrome. *Semin Liver Dis*. 2007;27(4):427-431. <https://doi.org/10.1055/s-2007-991518>
221. Larizza D, Albanesi M, de SA, *et al.* Neoplasia in Turner syndrome. The importance of clinical and screening practices during follow-up. *Eur J Med Genet*. 2016;59(5):269-273. <https://doi.org/10.1016/j.ejmg.2016.03.005>
222. Bolar K, Hoffman AR, Maneatis T, Lippe B. Long-term safety of recombinant human growth hormone in Turner syndrome. *J Clin Endocrinol Metab*. 2008;93(2):344-351. <https://doi.org/10.1210/jc.2007-1723>
223. Swerdlow AJ, Cooke R, Beckers D, *et al.* Cancer risks in patients treated with growth hormone in childhood: the SAGhE European cohort study. *J Clin Endocrinol Metab*. 2017;102(5):1661-1672. <https://doi.org/10.1210/jc.2016-2046>
224. Backeljauw P, Blair JC, Ferran JM, *et al.* Early GH treatment is effective and well tolerated in children with Turner syndrome: NordiNet® IOS and ANSWER program. *J Clin Endocrinol Metab*. 2023;108(10):2653-2665. <https://doi.org/10.1210/clinem/dgad159>
225. Child CJ, Zimmermann AG, Chrousos GP, *et al.* Safety outcomes during pediatric GH therapy: final results from the prospective GeNeSIS observational program. *J Clin Endocrinol Metab*. 2019;104(2):379-389. <https://doi.org/10.1210/jc.2018-01189>
226. Radetti G, Pasquino B, Gottardi E, Boscolo CI, Aimaretti G, Rigon F. Insulin sensitivity in Turner's syndrome: influence of GH treatment. *Eur J Endocrinol*. 2004;151:351-354. <https://doi.org/10.1530/eje.0.1510351>
227. Bakalov VK, Cooley MM, Quon MJ, *et al.* Impaired insulin secretion in the Turner metabolic syndrome. *J Clin Endocrinol Metab*. 2004;89(7):3516-3520. <https://doi.org/10.1210/jc.2004-0122>
228. Caprio S, Boulware S, Diamond M, *et al.* Insulin resistance: an early metabolic defect of Turner's syndrome. *J Clin Endocrinol Metab*. 1991;72(4):832-836. <https://doi.org/10.1210/jcem-72-4-832>
229. Baronio F, Mazzanti L, Girtler Y, *et al.* The influence of GH treatment on glucose homeostasis in girls with Turner syndrome: a 7-year study. *J Clin Endocrinol Metab*. 2017;102(3):878-883. <https://doi.org/10.1210/jc.2016-3179>
230. Gnacińska M, Magnuszewska H, Sworcak K. Metabolic consequences of recombinant human growth hormone therapy in patients with Turner syndrome. *Pediatr Endocrinol Diabetes Metab*. 2023;29(1):16-21. <https://doi.org/10.5114/pedm.2022.123204>
231. Cutfield WS, Wilton P, Bennmarker H, *et al.* Incidence of diabetes mellitus and impaired glucose tolerance in children and adolescents receiving growth-hormone treatment. *Lancet*. 2000;355(9204):610-613. [https://doi.org/10.1016/S0140-6736\(99\)04055-6](https://doi.org/10.1016/S0140-6736(99)04055-6)
232. Thunström S, Thunström E, Naessén S, *et al.* Aortic size predicts aortic dissection in Turner syndrome—a 25-year prospective cohort study. *Int J Cardiol*. 2022;373:47-54. <https://doi.org/10.1016/j.ijcard.2022.11.023>
233. Duijnhouwer AL, Bons LR, Timmers H, *et al.* Aortic dilatation and outcome in women with Turner syndrome. *Heart*. 2019;105(9):693-700. <https://doi.org/10.1136/heartjnl-2018-313716>
234. Quezada E, Lapidus J, Shaughnessy R, Chen Z, Silberbach M. Aortic dimensions in Turner syndrome. *Am J Med Genet A*. 2015;167A(11):2527-2532. <https://doi.org/10.1002/ajmg.a.37208>
235. Uçar A, Tuğrul M, Erol BO, *et al.* Determinants of increased aortic diameters in young normotensive patients with Turner syndrome without structural heart disease. *Pediatr Cardiol*. 2018;39(4):786-793. <https://doi.org/10.1007/s00246-018-1821-z>
236. Bondy CA, Van PL, Bakalov VK, Ho VB. Growth hormone treatment and aortic dimensions in Turner syndrome. *J Clin Endocrinol Metab*. 2006;91(5):1785-1788. <https://doi.org/10.1210/jc.2005-2625>
237. Grimberg A, DiVall SA, Polychronakos C, *et al.* Guidelines for growth hormone and insulin-like growth factor-I treatment in children and adolescents: growth hormone deficiency, idiopathic short stature, and primary insulin-like growth factor-I deficiency. *Horm Res Paediatr*. 2016;86(6):361-397. <https://doi.org/10.1159/000452150>
238. Collett-Solberg PF, Pessoa de Queiroz AN, Cardoso ME, Jusan RC, Vaisman M, Guimaraes MM. The correlation of the IGF-I, IGFBP-3, and ALS generation test to height velocity after 6 months of recombinant growth hormone therapy in girls with Turner syndrome. *Growth Horm IGF Res*. 2006;16(4):240-246. <https://doi.org/10.1016/j.gHIR.2006.06.002>
239. van Teunenbroek A, de Muinck Keizer Schrama S, Stijnen T, *et al.* Growth response and levels of growth factors after two years growth hormone treatment are similar for a once and twice daily injection regimen in girls with Turner syndrome (Dutch working group on growth hormone). *Clin Endocrinol Oxf*. 1997;46(4):451-459. <https://doi.org/10.1046/j.1365-2265.1997.1610972.x>
240. Juul A. Serum levels of insulin-like growth factor I and its binding proteins in health and disease. *Growth Horm IGF Res*. 2003;13(4):113-170. [https://doi.org/10.1016/S1096-6374\(03\)00038-8](https://doi.org/10.1016/S1096-6374(03)00038-8)
241. Frystyk J, Freda P, Clemmons DR. The current status of IGF-I assays—a 2009 update. *Growth Horm IGF Res*. 2010;20(1):8-18. <https://doi.org/10.1016/j.gHIR.2009.09.004>
242. Mohammed-Ali Z, Delaney S, Singh R, *et al.* Bias in IGF-1 concentrations and interpretation across three different clinical laboratory assays. *Clin Biochem*. 2022;108:14-19. <https://doi.org/10.1016/j.clinbiochem.2022.06.009>
243. Chanson P, Arnoux A, Mavromati M, *et al.* Reference values for IGF-I serum concentrations: comparison of six immunoassays. *J Clin Endocrinol Metab*. 2016;101(9):3450-3458. <https://doi.org/10.1210/jc.2016-1257>
244. Renehan AG, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM, Egger M. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. *Lancet*. 2004;363(9418):1346-1353. [https://doi.org/10.1016/S0140-6736\(04\)16044-3](https://doi.org/10.1016/S0140-6736(04)16044-3)
245. Menke LA, Sas TC, de Muinck Keizer-Schrama SM, *et al.* Efficacy and safety of oxandrolone in growth hormone-treated girls with Turner syndrome. *J Clin Endocrinol Metab*. 2010;95(3):1151-1160. <https://doi.org/10.1210/jc.2009-1821>
246. Sas TC, Gault EJ, Bardsley MZ, *et al.* Safety and efficacy of oxandrolone in growth hormone-treated girls with Turner syndrome: evidence from recent studies and recommendations for use. *Horm Res Paediatr*. 2014;81(5):289-297. <https://doi.org/10.1159/000358195>
247. Freriks K, Verhaak CM, Sas TC, *et al.* Long-term effects of oxandrolone treatment in childhood on neurocognition, quality of life and social-emotional functioning in young adults with Turner syndrome. *Horm Behav*. 2015;69:59-67. <https://doi.org/10.1016/j.yhbeh.2014.12.008>
248. Gault EJ, Cole TJ, Casey S, *et al.* Effect of oxandrolone and timing of pubertal induction on final height in Turner syndrome: final analysis of the UK randomised placebo-controlled trial. *Arch Dis Child*. 2019;106(1):74-76. <https://doi.org/10.1136/archdischild-2019-317695>
249. Gault EJ, Perry RJ, Cole TJ, *et al.* Effect of oxandrolone and timing of pubertal induction on final height in Turner's syndrome: randomised, double blind, placebo controlled trial. *BMJ*. 2011;342:d1980. <https://doi.org/10.1136/bmj.d1980.d1980>
250. Mohamed S, Alkofide H, Adi YA, Amer YS, AlFaleh K. Oxandrolone for growth hormone-treated girls aged up to 18 years with Turner syndrome. *Cochrane Database Syst Rev*. 2019;2019(10):CD010736. <https://doi.org/10.1002/14651858.CD010736.pub2>

251. Sheanon NM, Backeljauw PF. Effect of oxandrolone therapy on adult height in Turner syndrome patients treated with growth hormone: a meta-analysis. *Int J Pediatr Endocrinol*. 2015;2015(1):18-0013. <https://doi.org/10.1186/s13633-015-0013-3>
252. Freriks K, Sas TC, Traas MA, et al. Long-term effects of previous oxandrolone treatment in adult women with Turner syndrome. *Eur J Endocrinol*. 2013;168(1):91-99. <https://doi.org/10.1530/EJE-12-0404>
253. Verver EJ, Freriks K, Sas TC, et al. Karyotype-specific ear and hearing problems in young adults with Turner syndrome and the effect of oxandrolone treatment. *Otol Neurotol*. 2014;35(9):1577-1584. <https://doi.org/10.1097/MAO.0000000000000406>
254. Ross JL, Roeltgen D, Feuillan P, Kushner H, Cutler GB. Use of estrogen in young girls with Turner syndrome: effects on memory. *Neurology*. 2000;54(1):164-170. <https://doi.org/10.1212/WNL.54.1.164>
255. Ross JL, Roeltgen D, Feuillan P, Kushner H, Cutler GB, Jr. Effects of estrogen on nonverbal processing speed and motor function in girls with Turner's syndrome. *J Clin Endocrinol Metab*. 1998;83(9):3198-3204. <https://doi.org/10.1210/jcem.83.9.5087>
256. Steiner M, Frank J, Saenger P. Long-acting growth hormone in 2022. *Pediatr Investig*. 2023;7(1):36-42. <https://doi.org/10.1002/ped4.12358>
257. Gao X, Chen J, Cao B, et al. First clinical study on long-acting growth hormone therapy in children with Turner syndrome. *Horm Metab Res*. 2022;54(6):389-395. <https://doi.org/10.1055/a-1842-0724>
258. Kim SJ, Pierce W, Sabharwal S. The etiology of short stature affects the clinical outcome of lower limb lengthening using external fixation. A systematic review of 18 trials involving 547 patients. *Acta Orthop*. 2014;85(2):181-186. <https://doi.org/10.3109/17453674.2014.899856>
259. Hahn SB, Park HW, Park HJ, Seo YJ, Kim HW. Lower limb lengthening in Turner dwarfism. *Yonsei Med J*. 2003;44(3):502-507. <https://doi.org/10.3349/ymj.2003.44.3.502>
260. Carel JC, Ecosse E, Bastie-Sigeac I, et al. Quality of life determinants in young women with Turner's syndrome after growth hormone treatment: results of the StaTur population-based cohort study. *J Clin Endocrinol Metab*. 2005;90(4):1992-1997. <https://doi.org/10.1210/jc.2004-1395>
261. Krantz E, Landin-Wilhelmsen K, Trimpou P, Bryman I, Wide U. Health-related quality of life in Turner syndrome and the influence of growth hormone therapy: a 20-year follow-up. *J Clin Endocrinol Metab*. 2019;104(11):5073-5083. <https://doi.org/10.1210/jc.2019-00340>
262. Reis CT, de Assumpcao MS, Guerra-Junior G, de Lemos-Marini SHV. Systematic review of quality of life in Turner syndrome. *Qual Life Res*. 2018;27(8):1985-2006. <https://doi.org/10.1007/s11136-018-1810-y>
263. Borgstrom B, Hreinsson JG, Rasmussen C, et al. Fertility preservation in girls with Turner syndrome: prognostic signs of the presence of ovarian follicles. *J Clin Endocrinol Metab*. 2009;94(1):74-80. <https://doi.org/10.1210/jc.2008-0708>
264. Boechar MI, Westra SJ, Lippe B. Normal US appearance of ovaries and uterus in four patients with Turner's syndrome and 45,X karyotype. *Pediatr Radiol*. 1996;26(1):37-39. <https://doi.org/10.1007/BF01403702>
265. Pasquino AM, Passeri F, Pucarelli I, Segni M, Mucicchi G. Spontaneous pubertal development in Turner's syndrome. Italian study group for Turner's syndrome. *J Clin Endocrinol Metab*. 1997;82(6):1810-1813. <https://doi.org/10.1210/jcem.82.6.3970>
266. Hagen CP, Main KM, Kjaergaard S, Juul A. FSH, LH, inhibin B and estradiol levels in Turner syndrome depend on age and karyotype: longitudinal study of 70 Turner girls with or without spontaneous puberty. *Hum Reprod*. 2010;25(12):3134-3141. <https://doi.org/10.1093/humrep/deq291>
267. Hankus M, Soltysik K, Szeliga K, et al. Prediction of spontaneous puberty in Turner syndrome based on mid-childhood gonadotropin concentrations, karyotype, and ovary visualization: a longitudinal study. *Horm Res Paediatr*. 2018;89(2):90-97. <https://doi.org/10.1159/000485321>
268. Conte FA, Grumbach MM, Kaplan SL. A diphasic pattern of gonadotropin secretion in patients with the syndrome of gonadal dysgenesis. *J Clin Endocrinol Metab*. 1975;40(4):670-674. <https://doi.org/10.1210/jcem-40-4-670>
269. Gravholt CH, Naeraa RW, Andersson AM, Christiansen JS, Skakkebaek NE. Inhibin A and B in adolescents and young adults with Turner's syndrome and no sign of spontaneous puberty. *Hum Reprod*. 2002;17(8):2049-2053. <https://doi.org/10.1093/humrep/17.8.2049>
270. Lunding SA, Aksglaede L, Anderson RA, et al. AMH as predictor of premature ovarian insufficiency: a longitudinal study of 120 Turner syndrome patients. *J Clin Endocrinol Metab*. 2015;100(7):E1030-E1038. <https://doi.org/10.1210/jc.2015-1621>
271. Ruszala A, Wójcik M, Starzyk J. Evaluation of the usefulness of antimüllerian hormone and inhibin B as markers of ovarian activity in patients with Turner syndrome—preliminary results. *Pediatr Endocrinol Diabetes Metab*. 2020;26(2):84-88. <https://doi.org/10.5114/pedm.2020.95622>
272. Hamza RT, Mira MF, Hamed AI, Ezzat T, Sallam MT. Anti-Müllerian hormone levels in patients with Turner syndrome: relation to karyotype, spontaneous puberty, and replacement therapy. *Am J Med Genet A*. 2018;176(9):1929-1934. <https://doi.org/10.1002/ajmg.a.40473>
273. Boncompagni A, McNeilly J, Murtaza M, et al. Clinical utility of urinary gonadotrophins in hypergonadotrophic states as Turner syndrome. *J Pediatr Endocrinol Metab*. 2020;33(11):1373-1381. <https://doi.org/10.1515/jpem-2020-0170>
274. Dabrowski E, Jensen R, Johnson EK, Habiby RL, Brickman WJ, Finlayson C. Turner syndrome systematic review: spontaneous thelarche and menarche stratified by karyotype. *Horm Res Paediatr*. 2019;92(3):143-149. <https://doi.org/10.1159/000502902>
275. Fitz VW, Law JR, Peavey M. Karyotype is associated with timing of ovarian failure in women with Turner syndrome. *J Pediatr Endocrinol Metab*. 2021;34(3):319-323. <https://doi.org/10.1515/jpem-2020-0304>
276. Folsom LJ, Slaven JE, Nabhan ZM, Eugster EA. Characterization of spontaneous and induced puberty in girls with Turner syndrome. *Endocr Pract*. 2017;23(7):768-774. <https://doi.org/10.4158/EP161738.OR>
277. Obara-Moszynska M, Dzialach L, Rabska-Pietrzak B, Niedziela M, Kapczuk K. Uterine development during induced puberty in girls with Turner syndrome. *Front Endocrinol (Lausanne)*. 2021;12:707031. <https://doi.org/10.3389/fendo.2021.707031>
278. Norjavaara E, Ankarberg C, Albertsson WK. Diurnal rhythm of 17 beta-estradiol secretion throughout pubertal development in healthy girls: evaluation by a sensitive radioimmunoassay. *J Clin Endocrinol Metab*. 1996;81(11):4095-4102. <https://doi.org/10.1210/jcem.81.11.8923866>
279. Backeljauw P, Klein K. Sex hormone replacement therapy for individuals with Turner syndrome. *Am J Med Genet C Semin Med Genet*. 2019;181(1):13-17. <https://doi.org/10.1002/ajmg.c.31685>
280. Cintron D, Rodriguez-Gutierrez R, Serrano V, Latortue-Albino P, Erwin PJ, Murad MH. Effect of estrogen replacement therapy on bone and cardiovascular outcomes in women with Turner syndrome: a systematic review and meta-analysis. *Endocrine*. 2017;55(2):366-375. <https://doi.org/10.1007/s12020-016-1046-y>
281. Dowlut-McElroy T, Shankar RK. The care of adolescents and young adults with Turner syndrome: a pediatric and adolescent gynecology perspective. *J Pediatr Adolesc Gynecol*. 2022;35(4):429-434. <https://doi.org/10.1016/j.jpjg.2022.02.002>
282. Giordano Imbroll M, Gruppetta M. A current perspective into young female sex hormone replacement: a review. *Expert Rev Endocrinol Metab*. 2020;15(6):405-414. <https://doi.org/10.1080/17446651.2020.1816820>
283. Webber L, Anderson RA, Davies M, Janse F, Vermeulen N. HRT for women with premature ovarian insufficiency: a comprehensive

- review. *Hum Reprod Open*. 2017;2017(2):hox007. <https://doi.org/10.1093/hropen/hox007>
284. Cameron-Pimblett A, Davies MC, Burt E, *et al*. Effects of estrogen therapies on outcomes in Turner syndrome: assessment of induction of puberty and adult estrogen use. *J Clin Endocrinol Metab*. 2019;104(7):2820-2826. <https://doi.org/10.1210/jc.2018-02137>
 285. Mauras N, Torres-Santiago L, Santen R, *et al*. Impact of route of administration on genotoxic oestrogens concentrations using oral vs transdermal oestradiol in girls with Turner syndrome. *Clin Endocrinol (Oxf)*. 2019;90(1):155-161. <https://doi.org/10.1111/cen.13869>
 286. Taboada M, Santen R, Lima J, *et al*. Pharmacokinetics and pharmacodynamics of oral and transdermal 17beta estradiol in girls with Turner syndrome. *J Clin Endocrinol Metab*. 2011;96(11):3502-3510. <https://doi.org/10.1210/jc.2011-1449>
 287. Ankarberg-Lindgren C, Elfving M, Wikland KA, Norjavaara E. Nocturnal application of transdermal estradiol patches produces levels of estradiol that mimic those seen at the onset of spontaneous puberty in girls. *J Clin Endocrinol Metab*. 2001;86(7):3039-3044. <https://doi.org/10.1210/jcem.86.7.7667>
 288. Ankarberg-Lindgren C, Gawlik A, Kriström B, Mazzanti L, Ruijgrok EJ, Sas TCJ. Estradiol matrix patches for pubertal induction: stability of cut pieces at different temperatures. *Endocr Connect*. 2019;8(4):360-366. <https://doi.org/10.1530/EC-19-0025>
 289. Labarta JI, Moreno ML, Lopez-Siguero JP, *et al*. Individualised vs fixed dose of oral 17beta-oestradiol for induction of puberty in girls with Turner syndrome: an open-randomised parallel trial. *Eur J Endocrinol*. 2012;167(4):523-529. <https://doi.org/10.1530/EJE-12-0444>
 290. Matthews D, Bath L, Högler W, Mason A, Smyth A, Skae M. Hormone supplementation for pubertal induction in girls. *Arch Dis Child*. 2017;102(10):975-980. <https://doi.org/10.1136/archdischild-2016-311372>
 291. Donaldson M, Kristrom B, Ankarberg-Lindgren C, *et al*. Optimal pubertal induction in girls with Turner syndrome using either oral or transdermal estradiol: a proposed modern strategy. *Horm Res Paediatr*. 2019;91(3):1-11. <https://doi.org/10.1159/000500050>
 292. Verdonk SJE, Vesper HW, Martens F, Sluss PM, Hillebrand JJ, Heijboer AC. Estradiol reference intervals in women during the menstrual cycle, postmenopausal women and men using an LC-MS/MS method. *Clin Chim Acta*. 2019;495:198-204. <https://doi.org/10.1016/j.cca.2019.04.062>
 293. Gawlik AM, Hankus M, Szeliga K, *et al*. Late-onset puberty induction by transdermal estrogen in Turner syndrome girls—a longitudinal study. *Front Endocrinol (Lausanne)*. 2018;9:23. <https://doi.org/10.3389/fendo.2018.00023>
 294. Hasegawa Y, Ariyasu D, Izawa M, *et al*. Gradually increasing ethinyl estradiol for Turner syndrome may produce good final height but not ideal BMD. *Endocr J*. 2017;64(2):221-227. <https://doi.org/10.1507/endocrj.EJ16-0170>
 295. Lanes R, Lindberg A, Carlsson M, *et al*. Near adult height in girls with Turner syndrome treated with growth hormone following either induced or spontaneous puberty. *J Pediatr*. 2019;212:172-179.e171. <https://doi.org/10.1016/j.jpeds.2019.04.056>
 296. Golden NH. Bones and birth control in adolescent girls. *J Pediatr Adolesc Gynecol*. 2020;33(3):249-254. <https://doi.org/10.1016/j.jpag.2020.01.003>
 297. Stute P, Neulen J, Wildt L. The impact of micronized progesterone on the endometrium: a systematic review. *Climacteric*. 2016;19(4):316-328. <https://doi.org/10.1080/13697137.2016.1187123>
 298. Stanczyk FZ, Hapgood JP, Winer S, Mishell DR. Progestogens used in postmenopausal hormone therapy: differences in their pharmacological properties, intracellular actions, and clinical effects. *Endocr Rev*. 2013;34(2):171-208. <https://doi.org/10.1210/er.2012-1008>
 299. Hipolito Rodrigues MA, Gompel A. Micronized progesterone, progestins, and menopause hormone therapy. *Women Health*. 2021;61(1):3-14. <https://doi.org/10.1080/03630242.2020.1824956>
 300. Panay N, Anderson RA, Nappi RE, *et al*. Premature ovarian insufficiency: an international menopause society white paper. *Climacteric*. 2020;23(5):426-446. <https://doi.org/10.1080/13697137.2020.1804547>
 301. Cleemann L, Holm K, Kobbernagel H, *et al*. Dosage of estradiol, bone and body composition in Turner syndrome: a 5-year randomized controlled clinical trial. *Eur J Endocrinol*. 2017;176(2):233-242. <https://doi.org/10.1530/EJE-16-0582>
 302. Burt E, Davies MC, Yasmin E, *et al*. Reduced uterine volume after induction of puberty in women with hypogonadism. *Clin Endocrinol (Oxf)*. 2019;91(6):798-804. <https://doi.org/10.1111/cen.14092>
 303. Viuff MH, Just J, Brun S, *et al*. Women with Turner syndrome are both estrogen and androgen deficient—the impact of hormone replacement therapy. *J Clin Endocrinol Metab*. 2022;107(7):1983-1993. <https://doi.org/10.1210/clinem/dgac167>
 304. Whitehead MI, Townsend PT, Pryse-Davies J, *et al*. Effects of various types and dosages of progestogens on the postmenopausal endometrium. *J Reprod Med*. 1982;27(Suppl 8):539-548.
 305. Hamoda H, Panay N, Pedder H, Arya R, Savvas M. The British Menopause Society & Women's Health Concern 2020 recommendations on hormone replacement therapy in menopausal women. *Post Reprod Health*. 2020;26(4):181-209. <https://doi.org/10.1177/2053369120957514>
 306. Bachelot A, Nicolas C, Gricourt S, *et al*. Poor compliance to hormone therapy and decreased bone mineral density in women with premature ovarian insufficiency. *PLoS One*. 2016;11(12):e0164638. <https://doi.org/10.1371/journal.pone.0164638>
 307. Burt E, Yasmin E, Davies MC, *et al*. Variability of response to early puberty induction demonstrated by transverse uterine diameter measurement and a novel method of 3D breast imaging. *Clin Endocrinol (Oxf)*. 2022;97(1):91-99. <https://doi.org/10.1111/cen.14740>
 308. Hagen CP, Mouritsen A, Mieritz MG, *et al*. Uterine volume and endometrial thickness in healthy girls evaluated by ultrasound (3-dimensional) and magnetic resonance imaging. *Fertil Steril*. 2015;104(2):452-459.e452. <https://doi.org/10.1016/j.fertnstert.2015.04.042>
 309. Asi N, Mohammed K, Haydour Q, *et al*. Progesterone vs. synthetic progestins and the risk of breast cancer: a systematic review and meta-analysis. *Syst Rev*. 2016;5(1):121. <https://doi.org/10.1186/s13643-016-0294-5>
 310. Shim S, Streich-Tilles T, Gutmark-Little I, *et al*. Abnormal uterine bleeding during pubertal induction with transdermal estrogen in individuals with Turner syndrome. *J Pediatr Adolesc Gynecol*. 2023;36(4):358-362. <https://doi.org/10.1016/j.jpag.2023.03.004>
 311. Mathez ALG, Monteagudo PT, do Nascimento Verreschi IT, Dias-da-Silva MR. Levonorgestrel correlates with less weight gain than other progestins during hormonal replacement therapy in Turner syndrome patients. *Sci Rep*. 2020;10(1):8298. <https://doi.org/10.1038/s41598-020-64992-4>
 312. Deeb A, AlSaffar H, Hamza RT, Abass M, Habeb AM. Availability and access to medications for puberty induction and maintenance in adolescents with hypogonadism in the Arab Region. *Int J Clin Pract*. 2022;2022:9142433. <https://doi.org/10.1155/2022/9142433>
 313. Briggs P, Barber K, Cooke K, *et al*. Consensus-led recommendations supporting choice and personalisation of hormone replacement therapy in menopause care. *Post Reprod Health*. 2022;28(2):71-78. <https://doi.org/10.1177/20533691221084827>
 314. Dam TV, Dalgaard LB, Sevdalis V, *et al*. Muscle performance during the menstrual cycle correlates with psychological well-being, but not fluctuations in sex hormones. *Med Sci Sports Exerc*. 2022;54(10):1678-1689. <https://doi.org/10.1249/MSS.0000000000002961>
 315. Richardson H, Ho V, Pasquet R, *et al*. Baseline estrogen levels in postmenopausal women participating in the MAP.3 breast cancer chemoprevention trial. *Menopause*. 2020;27(6):693-700. <https://doi.org/10.1097/GME.0000000000001568>

316. Fruzzetti F, Palla G, Gambacciani M, Simoncini T. Tailored hormonal approach in women with premature ovarian insufficiency. *Climacteric*. 2020;23(1):3-8. <https://doi.org/10.1080/13697137.2019.1632284>
317. Costa GPO, Ferreira-Filho ES, Simoes RDS, Soares-Junior JM, Baracat EC, Maciel GAR. Impact of hormone therapy on the bone density of women with premature ovarian insufficiency: a systematic review. *Maturitas*. 2023;167:105-112. <https://doi.org/10.1016/j.maturitas.2022.09.011>
318. Shah S, Forghani N, Durham E, Neely EK. A randomized trial of transdermal and oral estrogen therapy in adolescent girls with hypogonadism. *Int J Pediatr Endocrinol*. 2014;2014(1):12. <https://doi.org/10.1186/1687-9856-2014-12>
319. Frederiksen H, Johannsen TH, Andersen SE, *et al.* Sex-specific estrogen levels and reference intervals from infancy to late adulthood determined by LC-MS/MS. *J Clin Endocrinol Metab*. 2020;105(3):754-768. <https://doi.org/10.1210/clinem/dgz196>
320. Torres-Santiago L, Mericq V, Taboada M, *et al.* Metabolic effects of oral vs. Transdermal 17beta estradiol (E2): a randomized clinical trial in girls with Turner syndrome. *J Clin Endocrinol Metab*. 2013;98(7):2716-2724. <https://doi.org/10.1210/jc.2012-4243>
321. Cleemann L, Holm K, Fallentin E, *et al.* Effect of dosage of 17beta-estradiol on uterine growth in Turner syndrome—a randomized controlled clinical pilot trial. *J Clin Endocrinol Metab*. 2020;105(3):dgz061. <https://doi.org/10.1210/clinem/dgz061>
322. Cleemann L, Holm K, Fallentin E, *et al.* Uterus and ovaries in girls and young women with Turner syndrome evaluated by ultrasound and magnetic resonance imaging. *Clin Endocrinol (Oxf)*. 2011;74(6):756-761. <https://doi.org/10.1111/j.1365-2265.2011.03995.x>
323. Lindsay Mart F, Gutmark-Little I, Streich-Tilles T, *et al.* Current recommended estrogen dosing for pubertal induction in Turner syndrome results in normal uterine growth. *J Clin Endocrinol Metab*. 2023;109(3):e1040-e1047. <https://doi.org/10.1210/clinem/dgad649>
324. Jivraj S, Stillwell S. Turner syndrome through the lens of a gynaecologist. *Post Reprod Health*. 2021;27(2):98-108. <https://doi.org/10.1177/2053369120958593>
325. Schoenaker DA, Jackson CA, Rowlands JV, Mishra GD. Socioeconomic position, lifestyle factors and age at natural menopause: a systematic review and meta-analyses of studies across six continents. *Int J Epidemiol*. 2014;43(5):1542-1562. <https://doi.org/10.1093/ije/dyu094>
326. Klein KO, Rosenfield RL, Santen RJ, *et al.* Estrogen replacement in Turner syndrome: literature review and practical considerations. *J Clin Endocrinol Metab*. 2018;103(5):1790-1803. <https://doi.org/10.1210/jc.2017-02183>
327. Son KA, Lee DY, Yoon BK, Choi D. The efficacy of long-term estrogen replacement therapy in Turner syndrome women with premature ovarian insufficiency. *J Pediatr Adolesc Gynecol*. 2019;32(5):530-534. <https://doi.org/10.1016/j.jpag.2019.05.008>
328. Brun S, Cleemann L, Holm K, *et al.* Five-year randomized study demonstrates blood pressure increases in young women with Turner syndrome regardless of estradiol dose. *Hypertension*. 2019;73(1):242-248. <https://doi.org/10.1161/HYPERTENSIONAHA.118.11742>
329. Itonaga T, Koga E, Nishigaki S, Kawai M, Sakakibara H, Hasegawa Y. A retrospective multicenter study of bone mineral density in adolescents and adults with Turner syndrome in Japan. *Endocr J*. 2020;67(10):1023-1028. <https://doi.org/10.1507/endocrj.EJ20-0083>
330. Christ JP, Gunning MN, Palla G, *et al.* Estrogen deprivation and cardiovascular disease risk in primary ovarian insufficiency. *Fertil Steril*. 2018;109(4):594-600.e591. <https://doi.org/10.1016/j.fertnstert.2017.11.035>
331. Sandahl KJ, Just J, Erlandsen M, Mortensen KH, Andersen NH, Gravholt CH. A prospective study of lipids in adult women with Turner syndrome. *J Endocr Soc*. 2023;7(11):bvad124. <https://doi.org/10.1210/jendso/bvad124>
332. Viuff MH, Stochholm K, Lin A, Berglund A, Juul S, Gravholt CH. Cancer occurrence in Turner syndrome and the effect of sex hormone substitution therapy. *Eur J Endocrinol*. 2021;184(1):79-88. <https://doi.org/10.1530/EJE-20-0702>
333. Bosze P, Toth A, Torok M. Hormone replacement and the risk of breast cancer in Turner's syndrome. *N Engl J Med*. 2006;355(24):2599-2600. <https://doi.org/10.1056/NEJMc062795>
334. Vincent AJ, Nguyen HH, Ranasinha S, Vollenhoven B. Increased detection of co-morbidities with evaluation at a dedicated adult Turner syndrome clinic. *Climacteric*. 2017;20(5):442-447. <https://doi.org/10.1080/13697137.2017.1350841>
335. Nabhan ZM, Dimeglio LA, Qi R, Perkins SM, Eugster EA. Conjugated oral versus transdermal estrogen replacement in girls with Turner syndrome: a pilot comparative study. *J Clin Endocrinol Metab*. 2009;94(6):2009-2014. <https://doi.org/10.1210/jc.2008-2123>
336. Mauras N, Shulman D, Hsiang HY, Balagopal P, Welch S. Metabolic effects of oral versus transdermal estrogen in growth hormone-treated girls with Turner syndrome. *J Clin Endocrinol Metab*. 2007;92(11):4154-4160. <https://doi.org/10.1210/jc.2007-0671>
337. Jospe N, Orłowski CC, Furlanetto RW. Comparison of transdermal and oral estrogen therapy in girls with Turner's syndrome. *J Pediatr Endocrinol Metab*. 1995;8(2):111-116. <https://doi.org/10.1515/JPEM.1995.8.2.111>
338. Ruzsala A, Wojcik M, Zygmunt-Gorska A, Janus D, Wojtys J, Starzyk JB. Prepubertal ultra-low-dose estrogen therapy is associated with healthier lipid profile than conventional estrogen replacement for pubertal induction in adolescent girls with Turner syndrome: preliminary results. *J Endocrinol Invest*. 2017;40(8):875-879. <https://doi.org/10.1007/s40618-017-0665-3>
339. Guttmann H, Weiner Z, Nikolski E, *et al.* Choosing an oestrogen replacement therapy in young adult women with Turner syndrome. *Clin Endocrinol (Oxf)*. 2001;54(2):159-164. <https://doi.org/10.1046/j.1365-2265.2001.01181.x>
340. Naeraa RW, Gravholt CH, Kastrup KW, Svenstrup B, Christiansen JS. Morning versus evening administration of estradiol to girls with Turner syndrome receiving growth hormone: impact on growth hormone and metabolism. A randomized placebo-controlled crossover study. *Acta Paediatr*. 2001;90(5):526-531.
341. Alves ST, Gallichio CT, Guimaraes MM. Insulin resistance and body composition in Turner syndrome: effect of sequential change in the route of estrogen administration. *Gynecol Endocrinol*. 2006;22(10):590-594. <https://doi.org/10.1080/08916930600929586>
342. Koulouri O, Ostberg J, Conway GS. Liver dysfunction in Turner's syndrome: prevalence, natural history and effect of exogenous oestrogen. *Clin Endocrinol (Oxf)*. 2008;69(2):306-310. <https://doi.org/10.1111/j.1365-2265.2008.03203.x>
343. Singh I, Noel G, Barker JM, *et al.* Hepatic abnormalities in youth with Turner syndrome. *Liver Int*. 2022;42(10):2237-2246. <https://doi.org/10.1111/liv.15358>
344. Viuff MH, Stochholm K, Grønbaek H, Berglund A, Juul S, Gravholt CH. Increased occurrence of liver and gastrointestinal diseases and anaemia in women with Turner syndrome—a nationwide cohort study. *Aliment Pharmacol Ther*. 2021;53(7):821-829. <https://doi.org/10.1111/apt.16277>
345. Roulot D, Degott C, Chazouilleres O, *et al.* Vascular involvement of the liver in Turner's syndrome. *Hepatology*. 2004;39(1):239-247. <https://doi.org/10.1002/hep.20026>
346. Gravholt CH, Naeraa RW, Fisker S, Christiansen JS. Body composition and physical fitness are major determinants of the growth hormone-IGF axis aberrations in adult Turner syndrome, with important modulations by treatment with 17-beta-estradiol. *J Clin Endocrinol Metab*. 1997;82(8):2570-2577. <https://doi.org/10.1210/jcem.82.8.4127>
347. Gravholt CH, Poulsen HE, Ott P, Christiansen JS, Vilstrup H. Quantitative liver functions in Turner syndrome with and without

- hormone replacement therapy. *Eur J Endocrinol.* 2007;156(6):679-686. <https://doi.org/10.1530/EJE-07-0070>
348. Larizza D, Locatelli M, Vitali L, *et al.* Serum liver enzymes in Turner syndrome. *Eur J Pediatr.* 2000;159(3):143-148. <https://doi.org/10.1007/s004310050038>
349. Elsheikh M, Hodgson HJ, Wass JA, Conway GS. Hormone replacement therapy may improve hepatic function in women with Turner's syndrome. *Clin Endocrinol (Oxf).* 2001;55(2):227-231. <https://doi.org/10.1046/j.1365-2265.2001.01321.x>
350. Wójcik M, Ruzsała A, Januś D, Starzyk JB. Liver biochemical abnormalities in adolescent patients with Turner syndrome. *J Clin Res Pediatr Endocrinol.* 2019;11(4):395-399. <https://doi.org/10.4274/jcrpe.galenos.2019.2018.0271>
351. Soucek O, Schönau E, Lebl J, Willnecker J, Hlavka Z, Sumnik Z. A 6-year follow-up of fracture incidence and volumetric bone mineral density development in girls with Turner syndrome. *J Clin Endocrinol Metab.* 2018;103(3):1188-1197. <https://doi.org/10.1210/jc.2017-02381>
352. Nishigaki S, Itonaga T, Hasegawa Y, Kawai M. Starting age of oestrogen-progestin therapy is negatively associated with bone mineral density in young adults with Turner syndrome independent of age and body mass index. *Clin Endocrinol (Oxf).* 2021;95(1):84-91. <https://doi.org/10.1111/cen.14484>
353. Nguyen HH, Wong P, Strauss BJ, Ebeling PR, Milat F, Vincent A. A cross-sectional and longitudinal analysis of trabecular bone score in adults with Turner syndrome. *J Clin Endocrinol Metab.* 2018;103(10):3792-3800. <https://doi.org/10.1210/jc.2018-00854>
354. Saito S, Koga E, Okada Y, *et al.* Effects of age at estrogen replacement therapy initiation on trabecular bone score in Japanese adults with Turner syndrome. *Osteoporos Int.* 2021;32(4):671-680. <https://doi.org/10.1007/s00198-020-05652-1>
355. Nguyen HH, Wong P, Strauss BJ, *et al.* Delay in estrogen commencement is associated with lower bone mineral density in Turner syndrome. *Climacteric.* 2017;20(5):436-441. <https://doi.org/10.1080/13697137.2017.1325461>
356. Mortensen KH, Andersen NH, Gravholt CH. Cardiovascular phenotype in Turner syndrome—integrating cardiology, genetics, and endocrinology. *Endocr Rev.* 2012;33(5):677-714. <https://doi.org/10.1210/er.2011-1059>
357. Gravholt CH, Naeraa RW, Nyholm B, *et al.* Glucose metabolism, lipid metabolism, and cardiovascular risk factors in adult Turner's syndrome. The impact of sex hormone replacement. *Diabetes Care.* 1998;21(7):1062-1070. <https://doi.org/10.2337/diacare.21.7.1062>
358. Peppas M, Pavlidis G, Mavroei I, *et al.* Effects of hormone replacement therapy on endothelial function, arterial stiffness and myocardial deformation in women with Turner syndrome. *J Hypertens.* 2021;39(10):2051-2057. <https://doi.org/10.1097/HJH.0000000000002903>
359. Langrish JP, Mills NL, Bath LE, *et al.* Cardiovascular effects of physiological and standard sex steroid replacement regimens in premature ovarian failure. *Hypertension.* 2009;53(5):805-811. <https://doi.org/10.1161/HYPERTENSIONAHA.108.126516>
360. Stachenfeld NS, DiPietro L, Palter SF, Nadel ER. Estrogen influences osmotic secretion of AVP and body water balance in postmenopausal women. *Am J Physiol.* 1998;274(1):R187-R195. <https://doi.org/10.1152/ajpregu.1998.274.1.R187>
361. Oelkers W, Foidart JM, Dombrovicz N, Welter A, Heithecker R. Effects of a new oral contraceptive containing an antimineralocorticoid progestogen, drospirenone, on the renin-aldosterone system, body weight, blood pressure, glucose tolerance, and lipid metabolism. *J Clin Endocrinol Metab.* 1995;80(6):1816-1821. <https://doi.org/10.1210/jcem.80.6.7775629>
362. Mohammed K, Abu Dabrh AM, Benkhadra K, *et al.* Oral vs transdermal estrogen therapy and vascular events: a systematic review and meta-analysis. *J Clin Endocrinol Metab.* 2015;100(11):4012-4020. <https://doi.org/10.1210/jc.2015-2237>
363. Paterson WF, Hollman AS, Donaldson MD. Poor uterine development in Turner syndrome with oral oestrogen therapy. *Clin Endocrinol (Oxf).* 2002;56(3):359-365. <https://doi.org/10.1046/j.1365-2265.2002.01477.x>
364. Bakalov VK, Shawker T, Ceniceros I, Bondy CA. Uterine development in Turner syndrome. *J Pediatr.* 2007;151(5):528-531. <https://doi.org/10.1016/j.jpeds.2007.04.031>
365. Rodrigues EB, Braga J, Gama J, Guimaraes MM. Turner syndrome patients' ultrasound profile. *Gynecol Endocrinol.* 2013;29(7):704-706. <https://doi.org/10.3109/09513590.2013.797391>
366. Elsedfy HH, Hamza RT, Farghaly MH, Ghazy MS. Uterine development in patients with Turner syndrome: relation to hormone replacement therapy and karyotype. *J Pediatr Endocrinol Metab.* 2012;25(5-6):441-445. <https://doi.org/10.1515/jpem-2012-0040>
367. Jordan TL, Klabunde M, Green T, *et al.* Longitudinal investigation of cognition, social competence, and anxiety in children and adolescents with Turner syndrome. *Horm Behav.* 2023;149:105300. <https://doi.org/10.1016/j.yhbeh.2022.105300>
368. O'Donoghue S, Green T, Ross JL, *et al.* Brain development in school-age and adolescent girls: effects of Turner syndrome, estrogen therapy, and genomic imprinting. *Biol Psychiatry.* 2020;87(2):113-122. <https://doi.org/10.1016/j.biopsych.2019.07.032>
369. Ross JL, Stefanatos GA, Kushner H, Zinn A, Bondy C, Roeltgen D. Persistent cognitive deficits in adult women with Turner syndrome. *Neurology.* 2002;58(2):218-225. <https://doi.org/10.1212/WNL.58.2.218>
370. Li M, Zhao C, Xie S, *et al.* Effects of hypogonadism on brain development during adolescence in girls with Turner syndrome. *Hum Brain Mapp.* 2019;40(17):4901-4911. <https://doi.org/10.1002/hbm.24745>
371. Carel JC, Elie C, Ecosse E, *et al.* Self-esteem and social adjustment in young women with Turner syndrome—influence of pubertal management and sexuality: population-based cohort study. *J Clin Endocrinol Metab.* 2006;91(8):2972-2979. <https://doi.org/10.1210/jc.2005-2652>
372. Sheaffer AT, Lange E, Bondy CA. Sexual function in women with Turner syndrome. *J Womens Health (Larchmt).* 2008;17(1):27-33. <https://doi.org/10.1089/jwh.2007.0488>
373. Bannink EM, Raat H, Mulder PG, de Muinck Keizer-Schrama SM. Quality of life after growth hormone therapy and induced puberty in women with Turner syndrome. *J Pediatr.* 2006;148(1):95-101. <https://doi.org/10.1016/j.jpeds.2005.08.043>
374. Naess EE, Bahr D, Gravholt CH. Health status in women with Turner syndrome: a questionnaire study on health status, education, work participation and aspects of sexual functioning. *Clin Endocrinol (Oxf).* 2010;72(5):678-684. <https://doi.org/10.1111/j.1365-2265.2009.03715.x>
375. Idkowiak J, Smyth A, Mundy L, Wanaguru A, Gleeson H, Högler W. Breast satisfaction in adult women with Turner syndrome—an international survey employing the BREAST-Q questionnaire. *Clin Endocrinol (Oxf).* 2023;98(1):82-90. <https://doi.org/10.1111/cen.14755>
376. Cardona AC, Cameron-Pimblett A, Puri D, *et al.* Relationship and sexual experiences in women with early onset oestrogen deficiency: comparison between women with Turner syndrome and premature ovarian insufficiency. *Clin Endocrinol (Oxf).* 2020;93(4):473-481. <https://doi.org/10.1111/cen.14271>
377. Weissberger AJ, Ho KK, Lazarus L. Contrasting effects of oral and transdermal routes of estrogen replacement therapy on 24-hour growth hormone (GH) secretion, insulin-like growth factor I, and GH-binding protein in postmenopausal women. *J Clin Endocrinol Metab.* 1991;72(2):374-381. <https://doi.org/10.1210/jcem-72-2-374>
378. Kam GY, Leung KC, Baxter RC, Ho KK. Estrogens exert route- and dose-dependent effects on insulin-like growth factor (IGF)-binding protein-3 and the acid-labile subunit of the IGF ternary complex. *J Clin Endocrinol Metab.* 2000;85(5):1918-1922. <https://doi.org/10.1210/jcem.85.5.6527>
379. Reinehr T, Lindberg A, Toschke C, Cara J, Chrysis D, Camacho-Hubner C. Weight gain in Turner syndrome: association to puberty induction?—longitudinal analysis of KIGS data.

- Clin Endocrinol (Oxf)*. 2016;85(1):85-91. <https://doi.org/10.1111/cen.13044>
380. Hamoda H. The British Menopause Society and women's health concern recommendations on the management of women with premature ovarian insufficiency. *Post Reprod Health*. 2017;23(1):22-35. <https://doi.org/10.1177/2053369117699358>
 381. Zuckerman-Levin N, Frolova-Bishara T, Militianu D, Levin M, Aharon-Peretz J, Hochberg Z. Androgen replacement therapy in Turner syndrome: a pilot study. *J Clin Endocrinol Metab*. 2009;94(12):4820-4827. <https://doi.org/10.1210/jc.2009-0514>
 382. Meccanici F, de Bruijn JWC, Dommissie JS, Takkenberg JJM, van den Bosch AE, Roos-Hesslink JW. Prevalence and development of aortic dilation and dissection in women with Turner syndrome: a systematic review and meta-analysis. *Expert Rev Cardiovasc Ther*. 2023;21(2):133-144. <https://doi.org/10.1080/14779072.2023.2172403>
 383. Lopez L, Arheart KL, Colan SD, et al. Turner syndrome is an independent risk factor for aortic dilation in the young. *Pediatrics*. 2008;121(6):e1622-e1627. <https://doi.org/10.1542/peds.2007-2807>
 384. Gambineri A, Scarano E, Rucci P, et al. New insights into the comorbid conditions of Turner syndrome: results from a long-term monocentric cohort study. *J Endocrinol Invest*. 2022;45(12):2247-2256. <https://doi.org/10.1007/s40618-022-01853-z>
 385. Mazzanti L, Cacciari E. Congenital heart disease in patients with Turner's syndrome. Italian study group for Turner syndrome (ISGTS). *J. Pediatr*. 1998;133(5):688-692. [https://doi.org/10.1016/S0022-3476\(98\)70119-2](https://doi.org/10.1016/S0022-3476(98)70119-2)
 386. Sybert VP. Cardiovascular malformations and complications in Turner syndrome. *Pediatrics*. 1998;101(1):E11-E17. <https://doi.org/10.1542/peds.101.1.e11>
 387. Volkl TM, Degenhardt K, Koch A, Simm D, Dorr HG, Singer H. Cardiovascular anomalies in children and young adults with Ullrich-Turner syndrome the Erlangen experience. *Clin Cardiol*. 2005;28(2):88-92. <https://doi.org/10.1002/clc.4960280209>
 388. Kim HK, Gottliebson W, Hor K, et al. Cardiovascular anomalies in Turner syndrome: spectrum, prevalence, and cardiac MRI findings in a pediatric and young adult population. *AJR Am J Roentgenol* 2011;196(2):454-460. <https://doi.org/10.2214/AJR.10.4973>
 389. Gotzsche CO, Krag Olsen B, Nielsen J, Sorensen KE, Kristensen BO. Prevalence of cardiovascular malformations and association with karyotypes in Turner's syndrome. *Arch Dis Child*. 1994;71(5):433-436. <https://doi.org/10.1136/adc.71.5.433>
 390. Noordman I, Duijnhouwer A, Kapusta L, et al. Phenotype in girls and women with Turner syndrome: association between dysmorphic features, karyotype and cardio-aortic malformations. *Eur J Med Genet*. 2018;61(6):301-306. <https://doi.org/10.1016/j.ejmg.2018.01.004>
 391. Birjiniuk A, Weisman AG, Laternser C, et al. Cardiovascular manifestations of Turner syndrome: phenotypic differences between karyotype subtypes [published online ahead of print May 5, 2023]. *Pediatr Cardiol*. <https://doi.org/10.1007/s00246-023-03159-0>
 392. Clark EB. Neck web and congenital heart defects: a pathogenic association in 45 X-O Turner syndrome? *Teratology*. 1984;29(3):355-361. <https://doi.org/10.1002/tera.1420290305>
 393. Loscalzo ML, Van PL, Ho VB, et al. Association between fetal lymphedema and congenital cardiovascular defects in Turner syndrome. *Pediatrics*. 2005;115(3):732-735. <https://doi.org/10.1542/peds.2004-1369>
 394. Eckhauser A, South ST, Meyers L, Bleyl SB, Botto LD. Turner syndrome in girls presenting with coarctation of the aorta. *J Pediatr*. 2015;167(5):1062-1066. <https://doi.org/10.1016/j.jpeds.2015.08.002>
 395. Ho VB, Bakalov VK, Cooley M, et al. Major vascular anomalies in Turner syndrome: prevalence and magnetic resonance angiographic features. *Circulation*. 2004;110(12):1694-1700. <https://doi.org/10.1161/01.CIR.0000142290.35842.BO>
 396. Koenraadt WMC, Siebelink HJ, Bartelings MM, et al. Coronary anatomy in Turner syndrome versus patients with isolated bicuspid aortic valves. *Heart*. 2019;105(9):701-707. <https://doi.org/10.1136/heartjnl-2018-313724>
 397. Gentile F, Castiglione V, De Caterina R. Coronary artery anomalies. *Circulation*. 2021;144(12):983-996. <https://doi.org/10.1161/CIRCULATIONAHA.121.055347>
 398. Naito S, Petersen J, Reichenspurner H, Girdauskas E. The impact of coronary anomalies on the outcome in aortic valve surgery: comparison of bicuspid aortic valve versus tricuspid aortic valve morphotype. *Interact Cardiovasc Thorac Surg*. 2018;26(4):617-622. <https://doi.org/10.1093/icvts/ivx396>
 399. Dowlut-McElroy T, Davis S, Howell S, et al. Cell-free DNA screening positive for monosomy X: clinical evaluation and management of suspected maternal or fetal Turner syndrome. *Am J Obstet Gynecol*. 2022;227(6):862-870. <https://doi.org/10.1016/j.ajog.2022.07.004>
 400. Donofrio MT, Moon-Grady AJ, Hornberger LK, et al. Diagnosis and treatment of fetal cardiac disease: a scientific statement from the American heart association. *Circulation*. 2014;129(21):2183-2242. <https://doi.org/10.1161/01.cir.0000437597.44550.5d>
 401. Dotters-Katz SK, Humphrey WM, Senz KL, Lee VR, Shaffer BL, Caughey AB. The effects of Turner syndrome, 45,X on obstetric and neonatal outcomes: a retrospective cohort evaluation. *Am J Perinatol* 2016;33(12):1152-1158. <https://doi.org/10.1055/s-0036-1585083>
 402. Papp C, Beke A, Mezei G, Szigeti Z, Ban Z, Papp Z. Prenatal diagnosis of Turner syndrome: report on 69 cases. *J Ultrasound Med*. 2006;25(6):711-717. <https://doi.org/10.7863/jum.2006.25.6.711>
 403. Mahle WT, Newburger JW, Matherne GP, et al. Role of pulse oximetry in examining newborns for congenital heart disease: a scientific statement from the AHA and AAP. *Pediatrics*. 2009;124(2):823-836. <https://doi.org/10.1542/peds.2009-1397>
 404. Olivieri LJ, Baba RY, Arai AE, et al. Spectrum of aortic valve abnormalities associated with aortic dilation across age groups in Turner syndrome. *Circ Cardiovasc Imaging*. 2013;6(6):1018-1023. <https://doi.org/10.1161/CIRCIMAGING.113.000526>
 405. Niaz T, Poterucha JT, Olson TM, et al. Characteristic morphologies of the bicuspid aortic valve in patients with genetic syndromes. *J Am Soc Echocardiogr*. 2018;31(2):194-200. <https://doi.org/10.1016/j.echo.2017.10.008>
 406. Szöcs K, Toprak B, Schön G, et al. Concomitant cardiovascular malformations in isolated bicuspid aortic valve disease: a retrospective cross-sectional study and meta-analysis. *Cardiovasc Diagn Ther*. 2022;12(4):400-414. <https://doi.org/10.21037/cdt-22-112>
 407. Stout KK, Daniels CJ, Aboulhosn JA, et al. 2018 AHA/ACC guideline for the management of adults with congenital heart disease: executive summary: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. *Circulation*. 2019;139(14):e637-e697. <https://doi.org/10.1161/CIR.0000000000000602>
 408. Baumgartner H, De Backer J, Babu-Narayan SV, et al. 2020 ESC Guidelines for the management of adult congenital heart disease. *Eur Heart J*. 2021;42(6):563-645. <https://doi.org/10.1093/eurheartj/ehaa554>
 409. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. 2022;43(7):561-632. <https://doi.org/10.1093/eurheartj/ehab395>
 410. Madriago E, Nguyen T, McFerson M, et al. Frequency and outcomes of cardiac operations and catheter interventions in Turner syndrome. *Am J Cardiol*. 2012;110(4):580-585. <https://doi.org/10.1016/j.amjcard.2012.04.036>
 411. Fuchs MM, Attenhofer Jost CH, Said SM, et al. Cardiovascular surgery in Turner syndrome—early outcome and long-term follow-up. *World J Cardiol*. 2020;12(3):97-106. <https://doi.org/10.4330/wjc.v12.i3.97>

412. Chew JD, Soslow JH, Thurm C, *et al.* Heart transplantation in children with Turner syndrome: analysis of a linked dataset. *Pediatr Cardiol.* 2018;39(3):610-616. <https://doi.org/10.1007/s00246-017-1801-8>
413. Chew JD, Hill KD, Jacobs ML, *et al.* Congenital heart surgery outcomes in Turner syndrome: the society of thoracic surgeons database analysis. *Ann Thorac Surg.* 2019;108(5):1430-1437. <https://doi.org/10.1016/j.athoracsur.2019.05.047>
414. Fuchs MM, Attenhofer Jost C, Babovic-Vuksanovic D, Connolly HM, Egbe A. Long-term outcomes in patients with Turner syndrome: a 68-year follow-up. *J Am Heart Assoc.* 2019;8(11):e011501. <https://doi.org/10.1161/JAHA.118.011501>
415. Cramer JW, Bartz PJ, Simpson PM, Zangwill SD. The spectrum of congenital heart disease and outcomes after surgical repair among children with Turner syndrome: a single-center review. *Pediatr Cardiol.* 2014;35(2):253-260. <https://doi.org/10.1007/s00246-013-0766-5>
416. Ribé L, Shihadeh FD, Afifi RO, Estrera AL, Prakash SK. Outcomes of cardiothoracic surgery in women with Turner syndrome. *Ann Cardiothorac Surg.* 2023;12(6):569-576. <https://doi.org/10.21037/acs-2023-adw-0083>
417. van den Hoven AT, Duijnhouwer AL, Eicken A, *et al.* Adverse outcome of coarctation stenting in patients with Turner syndrome. *Catheter Cardiovasc Interv.* 2017;89(2):280-287. <https://doi.org/10.1002/ccd.26728>
418. Obara-Moszyńska M, Rajewska-Tabor J, Rozmiarek S, *et al.* The usefulness of magnetic resonance imaging of the cardiovascular system in the diagnostic work-up of patients with Turner syndrome. *Front Endocrinol (Lausanne).* 2018;9:609. <https://doi.org/10.3389/fendo.2018.00609>
419. Mortensen KH, Hjerrild BE, Andersen NH, *et al.* Abnormalities of the major intra-thoracic arteries in Turner syndrome: a magnetic resonance imaging study. *Cardiol Young.* 2010;20(2):191-200. <https://doi.org/10.1017/S1047951110000041>
420. van den Hoven AT, Chelu RG, Duijnhouwer AL, *et al.* Partial anomalous pulmonary venous return in Turner syndrome. *Eur J Radiol.* 2017;95:141-146. <https://doi.org/10.1016/j.ejrad.2017.07.024>
421. Mortensen KH, Wen J, Erlandsen M, *et al.* Aortic growth rates are not increased in Turner syndrome—a prospective CMR study. *Eur Heart J Cardiovasc Imaging.* 2019;20(10):1164-1170. <https://doi.org/10.1093/ehjci/jez065>
422. Viuff MH, Trolle C, Wen J, *et al.* Coronary artery anomalies in Turner syndrome. *J Cardiovasc Comput Tomogr.* 2016;10(6):480-484. <https://doi.org/10.1016/j.jcct.2016.08.004>
423. Mortensen KH, Gravholt CH, Hjerrild BE, Stochholm K, Andersen NH. Left ventricular hypertrophy in Turner syndrome: a prospective echocardiographic study. *Echocardiography.* 2012;29(9):1022-1030. <https://doi.org/10.1111/j.1540-8175.2012.01754.x>
424. Kahlert E, Blaschke M, Brockmann K, *et al.* Deficient knowledge in adult care as an incentives for founding Turner centers in Germany. *Endocr Connect.* 2019;8(11):1483-1492. <https://doi.org/10.1530/EC-19-0418>
425. Mortensen KH, Young L, De BJ, *et al.* Cardiovascular imaging in Turner syndrome: state-of-the-art practice across the lifespan. *Heart.* 2018;104(22):1823-1831. <https://doi.org/10.1136/heartjnl-2017-312658>
426. Yetman AT, Starr L, Sanmann J, Wilde M, Murray M, Cramer JW. Clinical and echocardiographic prevalence and detection of congenital and acquired cardiac abnormalities in girls and women with the Turner syndrome. *Am J Cardiol.* 2018;122(2):327-330. <https://doi.org/10.1016/j.amjcard.2018.03.357>
427. Lanzarini L, Larizza D, Prete G, *et al.* Aortic dimensions in Turner's syndrome: two-dimensional echocardiography versus magnetic resonance imaging. *J Cardiovasc Med (Hagerstovun).* 2007;8(6):428-437. <https://doi.org/10.2459/01.JCM.0000269716.33435.d3>
428. Miller MJ, Geffner ME, Lippe BM, *et al.* Echocardiography reveals a high incidence of bicuspid aortic valve in Turner syndrome. *J Pediatr.* 1983;102(1):47-50. [https://doi.org/10.1016/S0022-3476\(83\)80284-4](https://doi.org/10.1016/S0022-3476(83)80284-4)
429. Kriksčiūnienė R, Navickaitė I, Ereminienė E, Lukoševičius S, Žilaitienė B, Verkauskienė R. Relationship between echocardiographic and magnetic resonance-derived measurements of the thoracic aorta in Turner syndrome patients. *Int J Endocrinol.* 2019;2019:9258726. <https://doi.org/10.1155/2019/9258726>
430. Somerville S, Rosolowsky E, Suntratonpipat S, Girgis R, Goot BH, Tham EB. Cardiac magnetic resonance imaging in pediatric Turner syndrome. *J Pediatr.* 2016;175:111-115.e111. <https://doi.org/10.1016/j.jpeds.2016.04.080>
431. Nejatian A, Yu J, Geva T, White MT, Prakash A. Aortic measurements in patients with aortopathy are larger and more reproducible by cardiac magnetic resonance compared with echocardiography. *Pediatr Cardiol.* 2015;36(8):1761-1773. <https://doi.org/10.1007/s00246-015-1231-4>
432. Ostberg JE, Brookes JA, McCarthy C, Halcox J, Conway GS. A comparison of echocardiography and magnetic resonance imaging in cardiovascular screening of adults with Turner syndrome. *J Clin Endocrinol Metab.* 2004;89(12):5966-5971. <https://doi.org/10.1210/jc.2004-1090>
433. De Groote K, Devos D, Van Herck K, *et al.* Abnormal aortic arch morphology in Turner syndrome patients is a risk factor for hypertension. *Heart Vessels.* 2014;30(5):618-625. <https://doi.org/10.1007/s00380-014-0529-0>
434. Meccanici F, Schotte MH, Snoeren M, *et al.* Aortic dilation and growth in women with Turner syndrome. *Heart.* 2022;109(2):102-110. <https://doi.org/10.1136/heartjnl-2022-320922>
435. Carlson M, Airhart N, Lopez L, Silberbach M. Moderate aortic enlargement and bicuspid aortic valve are associated with aortic dissection in Turner syndrome: report of the international Turner syndrome aortic dissection registry. *Circulation.* 2012;126(18):2220-2226. <https://doi.org/10.1161/CIRCULATIONAHA.111.088633>
436. Chalard F, Ferey S, Teinturier C, Kalifa G. Aortic dilatation in Turner syndrome: the role of MRI in early recognition. *Pediatr Radiol.* 2005;35(3):323-326. <https://doi.org/10.1007/s00247-004-1359-5>
437. Baguet JP, Douchin S, Pierre H, Rossignol AM, Bost M, Mallion JM. Structural and functional abnormalities of large arteries in the Turner syndrome. *Heart.* 2005;91(11):1442-1446. <https://doi.org/10.1136/hrt.2004.048371>
438. Mortensen KH, Hjerrild BE, Stochholm K, *et al.* Dilation of the ascending aorta in Turner syndrome—a prospective cardiovascular magnetic resonance study. *J Cardiovasc Magn Reson.* 2011;13(1):24. <https://doi.org/10.1186/1532-429X-13-24>
439. Isselbacher EM, Preventza O, Hamilton Black J, *et al.* 2022 ACC/AHA guideline for the diagnosis and management of aortic disease: a report of the American heart association/American college of cardiology joint committee on clinical practice guidelines. *Circulation.* 2022;146(24):e334-e482. <https://doi.org/10.1161/CIR.0000000000001106>
440. Davies RR, Gallo A, Coady MA, *et al.* Novel measurement of relative aortic size predicts rupture of thoracic aortic aneurysms. *Ann Thorac Surg.* 2006;81(1):169-177. <https://doi.org/10.1016/j.athoracsur.2005.06.026>
441. Los E, Quezada E, Chen Z, Lapidus J, Silberbach M. Pilot study of blood pressure in girls with Turner syndrome: an awareness gap, clinical associations, and new hypotheses. *Hypertension.* 2016;68(1):133-136. <https://doi.org/10.1161/HYPERTENSIONAHA.115.07065>
442. Prakash S, Milewicz D. Turner syndrome-specific and general population Z-scores are equivalent for most adults with Turner syndrome. *Am J Med Genet A.* 2017;173(4):1094-1096. <https://doi.org/10.1002/ajmg.a.38100>
443. Zafar MA, Li Y, Rizzo JA, *et al.* Height alone, rather than body surface area, suffices for risk estimation in ascending aortic aneurysm. *J Thorac Cardiovasc Surg.* 2018;155(5):1938-1950. <https://doi.org/10.1016/j.jtcvs.2017.10.140>

444. Campens L, Demulier L, De Groote K, *et al.* Reference values for echocardiographic assessment of the diameter of the aortic root and ascending aorta spanning all age categories. *Am J Cardiol.* 2014;114(6):914-920. <https://doi.org/10.1016/j.amjcard.2014.06.024>
445. Cleemann L, Mortensen KH, Holm K, *et al.* Aortic dimensions in girls and young women with Turner syndrome: a magnetic resonance imaging study. *Pediatr Cardiol.* 2010;31(4):497-504. <https://doi.org/10.1007/s00246-009-9626-8>
446. Erbel R, Aboyans V, Boileau C, *et al.* 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The task force for the diagnosis and treatment of aortic diseases of the European Society of Cardiology (ESC). *Eur Heart J.* 2014;35:2873-2926. <https://doi.org/10.1093/eurheartj/ehu281>
447. De Groote K, Demulier L, De Backer J, *et al.* Arterial hypertension in Turner syndrome: a review of the literature and a practical approach for diagnosis and treatment. *J Hypertens.* 2015;33(7):1342-1351. <https://doi.org/10.1097/HJH.0000000000000599>
448. Hiratzka LF, Bakris GL, Beckman JA, *et al.* 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: executive summary. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. *Catheter Cardiovasc Interv.* 2010;76(2):E43-E86. <https://doi.org/10.1002/ccd.22537>
449. Matura LA, Ho VB, Rosing DR, Bondy CA. Aortic dilatation and dissection in Turner syndrome. *Circulation.* 2007;116(15):1663-1670. <https://doi.org/10.1161/CIRCULATIONAHA.106.685487>
450. Leibelthal Y, Levy S, Sofrin-Drucker E, *et al.* The natural history of metabolic comorbidities in Turner syndrome from childhood to early adulthood: comparison between 45,X monosomy and other karyotypes. *Front Endocrinol (Lausanne).* 2018;9:27. <https://doi.org/10.3389/fendo.2018.00027>
451. Lin AE, Prakash SK, Andersen NH, *et al.* Recognition and management of adults with Turner syndrome: from the transition of adolescence through the senior years. *Am J Med Genet A.* 2019;179(10):1987-2033. <https://doi.org/10.1002/ajmg.a.61310>
452. Sandahl K, Wen J, Erlandsen M, Andersen NH, Gravholt CH. Natural history of hypertension in Turner syndrome during a 12-year pragmatic interventional study. *Hypertension.* 2020;76(5):1608-1615. <https://doi.org/10.1161/HYPERTENSIONAHA.120.15292>
453. McCarrison S, Carr A, Wong SC, Mason A. The prevalence of hypertension in paediatric Turner syndrome: a systematic review and meta-analysis. *J Hum Hypertens.* 2023;37(8):675-688. <https://doi.org/10.1038/s41371-022-00777-8>
454. Gravholt CH, Hansen KW, Erlandsen M, Ebbelohj E, Christiansen JS. Nocturnal hypertension and impaired sympathovagal tone in Turner syndrome. *J Hypertens.* 2006;24(2):353-360. <https://doi.org/10.1097/01.hjh.0000200509.17947.0f>
455. Landin-Wilhelmsen K, Bryman I, Wilhelmsen L. Cardiac malformations and hypertension, but not metabolic risk factors, are common in Turner syndrome. *J Clin Endocrinol Metab.* 2001;86(9):4166-4170. <https://doi.org/10.1210/jcem.86.9.7818>
456. Elsheikh M, Casadei B, Conway GS, Wass JA. Hypertension is a major risk factor for aortic root dilatation in women with Turner's syndrome. *Clin Endocrinol (Oxf).* 2001;54(1):69-73. <https://doi.org/10.1046/j.1365-2265.2001.01154.x>
457. Van De Kelft AS, Lievens C, De Groote K, *et al.* Disproportion and dysmorphism in an adult Belgian population with Turner syndrome: risk factors for chronic diseases? *Acta Clin Belg.* 2020;75(4):258-266. <https://doi.org/10.1080/17843286.2019.1606761>
458. Jones L, Blair J, Hawcutt DB, Lip GYH, Shantsila A. Hypertension in Turner syndrome: a review of proposed mechanisms, management and new directions. *J Hypertens.* 2023;41(2):203-211. <https://doi.org/10.1097/HJH.0000000000003321>
459. Kjaer ASL, Petersen JH, Cleemann Wang A, *et al.* Clinical assessment of blood pressure in 60 girls with Turner syndrome compared to 1888 healthy Danish girls. *Clin Endocrinol (Oxf).* 2022;96(3):428-438. <https://doi.org/10.1111/cen.14669>
460. Andersen NH, Hjerrild BE, Sørensen K, *et al.* Subclinical left ventricle dysfunction in normotensive women with Turner's syndrome. *Heart.* 2006;92(10):1516-1517. <https://doi.org/10.1136/hrt.2005.081471>
461. Sozen AB, Cefle K, Kudat H, *et al.* Left ventricular thickness is increased in nonhypertensive Turner's syndrome. *Echocardiography.* 2009;26(8):943-949. <https://doi.org/10.1111/j.1540-8175.2009.00902.x>
462. De Groote K, Devos D, Van HK, *et al.* Increased aortic stiffness in prepubertal girls with Turner syndrome. *J Cardiol.* 2017;69(1):201-207. <https://doi.org/10.1016/j.jjcc.2016.03.006>
463. Wen J, Trolle C, Viuff MH, *et al.* Impaired aortic distensibility and elevated central blood pressure in Turner syndrome: a cardiovascular magnetic resonance study. *J Cardiovasc Magn Reson.* 2018;20(1):80-0497. <https://doi.org/10.1186/s12968-018-0497-0>
464. Devos DG, De Groote K, Babin D, *et al.* Proximal aortic stiffening in Turner patients may be present before dilation can be detected: a segmental functional MRI study. *J Cardiovasc Magn Reson.* 2017;19(1):27-0331. <https://doi.org/10.1186/s12968-017-0331-0>
465. Fox DA, Kang KT, Potts JE, *et al.* Non-invasive assessment of aortic stiffness and blood pressure in young Turner syndrome patients. *J Pediatr Endocrinol Metab.* 2019;32(5):489-498. <https://doi.org/10.1515/jpem-2018-0346>
466. Fudge EB, Constantacos C, Fudge JC, Davenport M. Improving detection of hypertension in girls with Turner syndrome using ambulatory blood pressure monitoring. *Horm Res Paediatr.* 2014;81(1):25-31. <https://doi.org/10.1159/000355510>
467. Akyurek N, Atabek ME, Eklioglu BS, Alp H. Ambulatory blood pressure and subclinical cardiovascular disease in children with Turner syndrome. *Pediatr Cardiol.* 2014;35(1):57-62. <https://doi.org/10.1007/s00246-013-0740-2>
468. Nathwani NC, Unwin R, Brook CG, Hindmarsh PC. Blood pressure and Turner syndrome. *Clin Endocrinol (Oxf).* 2000;52(3):363-370. <https://doi.org/10.1046/j.1365-2265.2000.00960.x>
469. Nuckols VR, Stroud AK, Armstrong MK, *et al.* Postpartum ambulatory and home blood pressure monitoring in women with history of preeclampsia: diagnostic agreement and detection of masked hypertension. *Pregnancy Hypertens.* 2022;29:23-29. <https://doi.org/10.1016/j.preghy.2022.05.003>
470. Koletsos N, Dipla K, Triantafyllou A, *et al.* A brief submaximal isometric exercise test 'unmasks' systolic and diastolic masked hypertension. *J Hypertens.* 2019;37(4):710-719. <https://doi.org/10.1097/HJH.0000000000001943>
471. Flynn JT, Kaelber DC, Baker-Smith CM, *et al.* Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics.* 2017;140(3):e20171904. <https://doi.org/10.1542/peds.2017-1904>
472. Whelton PK, Carey RM, Aronow WS, *et al.* 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Hypertension.* 2018;71:e13-e115. <https://doi.org/10.1161/HYP.0000000000000065>
473. Lurbe E, Agabiti-Rosei E, Cruickshank JK, *et al.* 2016 European society of hypertension guidelines for the management of high blood pressure in children and adolescents. *J Hypertens.* 2016;34(10):1887-1920. <https://doi.org/10.1097/HJH.0000000000001039>

474. Gravholt CH, Mortensen KH, Andersen NH, Ibsen L, Ingerslev J, Hjerrild BE. Coagulation and fibrinolytic disturbances are related to carotid intima thickness and arterial blood pressure in Turner syndrome. *Clin Endocrinol (Oxf)*. 2012;76(5):649-656. <https://doi.org/10.1111/j.1365-2265.2011.04190.x>
475. Sigakis CJG, Browne LP, Bang T, Khanna A, Prunte R, Vargas D. Computed tomography and magnetic resonance imaging of cardiovascular anomalies associated with Turner syndrome. *J Thorac Imaging*. 2019;34(3):W23-W35. <https://doi.org/10.1097/RTI.0000000000000372>
476. Kozłowska-Wojciechowska M, Jez W, Zdrojewski T, Chwojnicky K. Are young women with Turner syndrome at greater risk of coronary artery disease? *Eur J Cardiovasc Prev Rehabil*. 2006;13(3):467-469. <https://doi.org/10.1097/01.hjr.0000216545.99807.fd>
477. O'Gorman CS, Syme C, Lang J, Bradley TJ, Wells GD, Hamilton JK. An evaluation of early cardiometabolic risk factors in children and adolescents with Turner syndrome. *Clin Endocrinol (Oxf)*. 2013;78(6):907-913. <https://doi.org/10.1111/cen.12079>
478. Delabays B, de La Harpe R, Vollenweider P, et al. Comparison of the European and U.S. Guidelines for lipid-lowering therapy in primary prevention of cardiovascular disease. *Eur J Prev Cardiol*. 2023;30(17):1856-1864. <https://doi.org/10.1093/eurjpc/zwad193>
479. Alvarez-Jimenez L, Morales-Palomo F, Moreno-Cabañas A, Ortega JF, Mora-Rodríguez R. Effects of statin therapy on glycaemic control and insulin resistance: a systematic review and meta-analysis. *Eur J Pharmacol*. 2023;947:175672. <https://doi.org/10.1016/j.ejphar.2023.175672>
480. Abbasi F, Lamendola C, Harris CS, et al. Statins are associated with increased insulin resistance and secretion. *Arterioscler Thromb Vasc Biol*. 2021;41(11):2786-2797. <https://doi.org/10.1161/ATVBAHA.121.316159>
481. Davis SM, Geffner ME. Cardiometabolic health in Turner syndrome. *Am J Med Genet C Semin Med Genet*. 2019;181(1):52-58. <https://doi.org/10.1002/ajmg.c.31678>
482. Schoepp M, Hannah-Shmouni F, Matta J, et al. Coronary calcification in adults with Turner syndrome. *Genet Med*. 2017;20(6):664-668. doi:10.1038/gim.2017.149
483. Funck KL, Budde RPJ, Viuff MH, et al. Coronary plaque burden in Turner syndrome a coronary computed tomography angiography study. *Heart Vessels*. 2021;36(1):14-23. <https://doi.org/10.1007/s00380-020-01660-7>
484. Wang T, Chen L, Yang T, et al. Congenital heart disease and risk of cardiovascular disease: a meta-analysis of cohort studies. *J Am Heart Assoc*. 2019;8(10):e012030. <https://doi.org/10.1161/JAHA.119.012030>
485. Lindholt JS, Søgaard R, Rasmussen LM, et al. Five-year outcomes of the Danish Cardiovascular Screening (DANCAVAS) trial. *N Engl J Med*. 2022;387(15):1385-1394. <https://doi.org/10.1056/NEJMoa2208681>
486. Shantsila E, Koziel-Siołkowska M, Lip GY. Antiplatelet agents and anticoagulants for hypertension. *Cochrane Database Syst Rev*. 2022;7:CD003186. <https://doi.org/10.1002/14651858.CD003186.pub4>
487. Bondy CA, Van PL, Bakalov VK, et al. Prolongation of the cardiac QTc interval in Turner syndrome. *Medicine (Baltimore)*. 2006;85(2):75-81. <https://doi.org/10.1097/01.md.0000205629.16302.bc>
488. Sozen AB, Cefle K, Kudat H, et al. Atrial and ventricular arrhythmogenic potential in Turner syndrome. *Pacing Clin Electrophysiol*. 2008;31(9):1140-1145. <https://doi.org/10.1111/j.1540-8159.2008.01154.x>
489. Cho JH, Choi EK, Moon IK, et al. Chromosomal abnormalities and atrial fibrillation and ischemic stroke incidence: a nationwide population-based study. *Sci Rep*. 2020;10(1):15872-72678. <https://doi.org/10.1038/s41598-020-72678-0>
490. Bondy CA, Ceniceros I, Van PL, Bakalov VK, Rosing DR. Prolonged rate-corrected QT interval and other electrocardiogram abnormalities in girls with Turner syndrome. *Pediatrics*. 2006;118(4):e1220-e1225. <https://doi.org/10.1542/peds.2006-0776>
491. Noordman ID, Fejzic Z, Bos M, et al. Cardiac abnormalities in girls with Turner syndrome: ECG abnormalities, myocardial strain imaging, and karyotype-phenotype associations. *Am J Med Genet A*. 2021;185(8):2399-2408. <https://doi.org/10.1002/ajmg.a.62259>
492. Rautaharju PM, Surawicz B, Gettes LS, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part IV: the ST segment, T and U waves, and the QT interval: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. *J Am Coll Cardiol*. 2009;53(11):982-991. <https://doi.org/10.1016/j.jacc.2008.12.014>
493. Noordman ID, Duijnhouwer AL, Coert M, et al. No QTc prolongation in girls and women with Turner syndrome. *J Clin Endocrinol Metab*. 2020;105(11):e4148-e4156. <https://doi.org/10.1210/clinem/dgaa552>
494. Harrahill NJ, Yetman AT, Danford DA, Starr LJ, Sanmann JN, Robinson JA. The QT interval in patients with the Turner syndrome. *Am J Cardiol*. 2021;140:118-121. <https://doi.org/10.1016/j.amjcard.2020.09.061>
495. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). *Heart Rhythm*. 2011;8(8):1308-1339. <https://doi.org/10.1016/j.hrthm.2011.05.020>
496. Santi M, Flück CE, Hauschild M, Kuhlmann B, Kuehni CE, Sommer G. Health behaviour of women with Turner syndrome. *Acta Paediatr*. 2021;110(8):2424-2429. <https://doi.org/10.1111/apa.15814>
497. Thompson T, Zieba B, Howell S, Karakash W, Davis S. A mixed methods study of physical activity and quality of life in adolescents with Turner syndrome. *Am J Med Genet A*. 2020;182(2):386-396. <https://doi.org/10.1002/ajmg.a.61439>
498. Arnold L, Bacova M, Dalla-Pozza R, Haas NA, Oberhoffer FS. Physical activity and diet quality: effects on cardiovascular morbidity in women with Turner syndrome-results from an online patient survey. *J Clin Med*. 2021;11(1):167. <https://doi.org/10.3390/jcm11010167>
499. West SL, O'Gorman CS, Elzibak AH, et al. Skeletal muscle microvascular function in girls with Turner syndrome. *BBA Clin*. 2015;3:25-30. <https://doi.org/10.1016/j.bbaci.2014.12.002>
500. Brun S, Berglund A, Mortensen KH, et al. Blood pressure, sympathovagal tone, exercise capacity and metabolic status are linked in Turner syndrome. *Clin Endocrinol (Oxf)*. 2019;91(1):148-155. <https://doi.org/10.1111/cen.13983>
501. Thijsen CGE, Bons LR, Gökalp AL, et al. Exercise and sports participation in patients with thoracic aortic disease: a review. *Expert Rev Cardiovasc Ther*. 2019;17(4):251-266. <https://doi.org/10.1080/14779072.2019.1585807>
502. Li J, Boyd A, Huang M, Berookhim J, Prakash SK. Safety of exercise for adults with thoracic aortic aneurysms and dissections. *Front Sports Act Living*. 2022;4:888534. <https://doi.org/10.3389/fspor.2022.888534>
503. Feng D, Ke J, Huang S, Lang X. A scoping review of exercise-based cardiac rehabilitation for patients with aortic dissection. *Rev Cardiovasc Med*. 2021;22(3):613-624. <https://doi.org/10.31083/j.rcm2203072>
504. Mas-Stachurska A, Siegert AM, Battle M, et al. Cardiovascular benefits of moderate exercise training in Marfan syndrome: insights from an animal model. *J Am Heart Assoc*. 2017;6(9):e006438. <https://doi.org/10.1161/JAHA.117.006438>

505. Selamet Tierney ES, Chung S, Stauffer KJ, et al. Can 10 000 healthy steps a day slow aortic root dilation in pediatric patients with Marfan syndrome? *J Am Heart Assoc.* 2022;11(23):e027598. <https://doi.org/10.1161/JAHA.122.027598>
506. Piercy KL, Troiano RP, Ballard RM, et al. The physical activity guidelines for Americans. *JAMA.* 2018;320(19):2020-2028. <https://doi.org/10.1001/jama.2018.14854>
507. Sheppard MB, Braverman AC. Sports participation and physical activity in individuals with heritable thoracic aortic disease and aortopathy conditions. *Clin Sports Med.* 2022;41(3):511-527. <https://doi.org/10.1016/j.csm.2022.02.009>
508. Budts W, Pieles GE, Roos-Hesselink JW, et al. Recommendations for participation in competitive sport in adolescent and adult athletes with Congenital Heart Disease (CHD): position statement of the Sports Cardiology & Exercise Section of the European Association of Preventive Cardiology (EAPC), the European Society of Cardiology (ESC) Working Group on Adult Congenital Heart Disease and the Sports Cardiology, Physical Activity and Prevention Working Group of the Association for European Paediatric and Congenital Cardiology (AEPCC). *Eur Heart J.* 2020;41(43):4191-4199. <https://doi.org/10.1093/eurheartj/ehaa501>
509. Karnis MF, Zimon AE, Lalwani SI, Timmreck LS, Klipstein S, Reindollar RH. Risk of death in pregnancy achieved through oocyte donation in patients with Turner syndrome: a national survey. *Fertil Steril.* 2003;80(3):498-501. [https://doi.org/10.1016/S0015-0282\(03\)00974-9](https://doi.org/10.1016/S0015-0282(03)00974-9)
510. Grewal J, Valente AM, Egbe AC, et al. Cardiovascular outcomes of pregnancy in Turner syndrome. *Heart.* 2021;107(1):61-66. <https://doi.org/10.1136/heartjnl-2020-316719>
511. Calanchini M, Aye CYL, Orchard E, et al. Fertility issues and pregnancy outcomes in Turner syndrome. *Fertil Steril.* 2020;114(1):144-154. <https://doi.org/10.1016/j.fertnstert.2020.03.002>
512. Kooijman SS, Duijnhouwer AL, van Kimmenade RRJ, et al. Influence of pregnancy on aortic diameter in women with the Turner syndrome. *Am J Cardiol.* 2021;140:122-127. <https://doi.org/10.1016/j.amjcard.2020.10.047>
513. Cadoret F, Parinaud J, Bettiol C, et al. Pregnancy outcome in Turner syndrome: a French multi-center study after the 2009 guidelines. *Eur J Obstet Gynecol Reprod Biol.* 2018;229:20-25. <https://doi.org/10.1016/j.ejogrb.2018.08.005>
514. Masoudian P, Nasr A, de Nanassy J, Fung-Kee-Fung K, Bainbridge SA, El Demellawy D. Oocyte donation pregnancies and the risk of preeclampsia or gestational hypertension: a systematic review and metaanalysis. *Am J Obstet Gynecol.* 2016;214(3):328-339. <https://doi.org/10.1016/j.ajog.2015.11.020>
515. Januzzi JL, Isselbacher EM, Fattori R, et al. Characterizing the young patient with aortic dissection: results from the international registry of aortic dissection (IRAD). *J Am Coll Cardiol.* 2004;43(4):665-669. <https://doi.org/10.1016/j.jacc.2003.08.054>
516. Nasiell J, Lindqvist PG. Aortic dissection in pregnancy: the incidence of a life-threatening disease. *Eur J Obstet Gynecol Reprod Biol.* 2010;149(1):120-121. <https://doi.org/10.1016/j.ejogrb.2009.10.029>
517. Hynes JS, Kuller JA, Goldstein SA, Ward CC, Muasher SJ. Increased risk of aortic dissection associated with pregnancy in women with Turner syndrome: a systematic review. *Obstet Gynecol Surv.* 2020;75(9):566-575. <https://doi.org/10.1097/OGX.0000000000000833>
518. Orwat S, Diller GP, van Hagen IM, et al. Risk of pregnancy in moderate and severe aortic stenosis: from the multinational ROPAC registry. *J Am Coll Cardiol.* 2016;68(16):1727-1737. <https://doi.org/10.1016/j.jacc.2016.07.750>
519. Chang SA, Khakh P, Janzen M, Kiess M, Rychel V, Grewal J. Pregnancy related changes in Doppler gradients and left ventricular mechanics in women with sub-valvular or valvular aortic stenosis. *Echocardiography.* 2021;38(10):1754-1761. <https://doi.org/10.1111/echo.15208>
520. Ramlakhan KP, Tobler D, Greutmann M, et al. Pregnancy outcomes in women with aortic coarctation. *Heart.* 2020;107(4):290-298. <https://doi.org/10.1136/heartjnl-2020-317513>
521. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, et al. 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy. *Eur Heart J.* 2018;39(34):3165-3241. <https://doi.org/10.1093/eurheartj/ehy340>
522. Mercadal BA, Imbert R, Demeestere I, Englert Y, Delbaere A. Pregnancy outcome after oocyte donation in patients with Turner's syndrome and partial X monosomy. *Hum Reprod.* 2011;26(8):2061-2068. <https://doi.org/10.1093/humrep/der166>
523. Chevalier N, Letur H, Lelannou D, et al. Materno-fetal cardiovascular complications in Turner syndrome after oocyte donation: insufficient prepregnancy screening and pregnancy follow-up are associated with poor outcome. *J Clin Endocrinol Metab.* 2011;96(2):E260-E267. <https://doi.org/10.1210/jc.2010-0925>
524. Hagman A, Loft A, Wennerholm UB, et al. Obstetric and neonatal outcome after oocyte donation in 106 women with Turner syndrome: a Nordic cohort study. *Hum Reprod.* 2013;28(6):1598-1609. <https://doi.org/10.1093/humrep/det082>
525. Steegers EA, von DP, Duvetkot JJ, Pijnenborg R. Pre-eclampsia. *Lancet.* 2010;376(9741):631-644. [https://doi.org/10.1016/S0140-6736\(10\)60279-6](https://doi.org/10.1016/S0140-6736(10)60279-6)
526. Ersbøll AS, Hedegaard M, Sondergaard L, Ersbøll M, Johansen M. Treatment with oral beta-blockers during pregnancy complicated by maternal heart disease increases the risk of fetal growth restriction. *BJOG.* 2014;121(5):618-626. <https://doi.org/10.1111/1471-0528.12522>
527. Ruys TP, Maggioni A, Johnson MR, et al. Cardiac medication during pregnancy, data from the ROPAC. *Int J Cardiol.* 2014;177(1):124-128. <https://doi.org/10.1016/j.ijcard.2014.09.013>
528. Henderson JT, Vesco KK, Senger CA, Thomas RG, Redmond N. Aspirin use to prevent preeclampsia and related morbidity and mortality: updated evidence report and systematic review for the US preventive services task force. *JAMA.* 2021;326(12):1192-1206. <https://doi.org/10.1001/jama.2021.8551>
529. Berntsen S, Larsen EC, la Cour Freiesleben N, Pinborg A. Pregnancy outcomes following oocyte donation. *Best Pract Res Clin Obstet Gynaecol.* 2021;70:81-91. <https://doi.org/10.1016/j.bpobgyn.2020.07.008>
530. Webber L, Davies M, Anderson R, et al. ESHRE guideline: management of women with premature ovarian insufficiency. *Hum Reprod.* 2016;31(5):926-937. <https://doi.org/10.1093/humrep/dew027>
531. Sharma N, O'Hare K, Antonelli RC, Sawicki GS. Transition care: future directions in education, health policy, and outcomes research. *Acad Pediatr.* 2014;14(2):120-127. <https://doi.org/10.1016/j.acap.2013.11.007>
532. White PH, Cooley WC. Supporting the health care transition from adolescence to adulthood in the medical home. *Pediatrics.* 2018;142(5):e20182587. <https://doi.org/10.1542/peds.2018-2587>
533. Pape L, Ernst G. Health care transition from pediatric to adult care: an evidence-based guideline. *Eur J Pediatr.* 2022;181(5):1951-1958. <https://doi.org/10.1007/s00431-022-04385-z>
534. Prior M, McManus M, White P, Davidson L. Measuring the "triple aim" in transition care: a systematic review. *Pediatrics.* 2014;134(6):e1648-e1661. <https://doi.org/10.1542/peds.2014-1704>
535. Campbell F, Biggs K, Aldiss SK, et al. Transition of care for adolescents from paediatric services to adult health services. *Cochrane Database Syst Rev.* 2016;4(4):CD009794. <https://doi.org/10.1002/14651858.CD009794.pub2>
536. Gabriel P, McManus M, Rogers K, White P. Outcome evidence for structured pediatric to adult health care transition interventions: a systematic review. *J Pediatr.* 2017;188:263-269.e15. <https://doi.org/10.1016/j.jpeds.2017.05.066>
537. Varty M, Popejoy LL. A systematic review of transition readiness in youth with chronic disease. *West J Nurs Res.* 2020;42(7):554-566. <https://doi.org/10.1177/0193945919875470>

538. Bernard V, Donadille B, Le Poulennec T, Nedelcu M, Martinerie L, Christin-Maitre S. MANAGEMENT OF ENDOCRINE DISEASE: transition of care for young adult patients with Turner syndrome. *Eur J Endocrinol*. 2019;180(1):R1-R7. <https://doi.org/10.1530/EJE-18-0238>
539. Patel N, Davis S, Nahata L. Transition-related discussions among adolescent females with Turner syndrome: current practices and associated factors. *Endocr Pract*. 2021;27(1):56-62. <https://doi.org/10.4158/EP-2020-0287>
540. Aversa T, De Sanctis L, Faienza MF, et al. Transition from pediatric to adult care in patients with Turner syndrome in Italy: a consensus statement by the TRAMITI project [published online ahead of print February 20, 2024]. *J Endocrinol Invest*. <https://doi.org/10.1007/s40618-024-02315-4>
541. Kosteria I, Kanaka-Gantenbein C. Turner syndrome: transition from childhood to adolescence. *Metabolism*. 2018;86:145-153. <https://doi.org/10.1016/j.metabol.2017.12.016>
542. Stinson J, Kohut SA, Spiegel L, et al. A systematic review of transition readiness and transfer satisfaction measures for adolescents with chronic illness. *Int J Adolesc Med Health*. 2014;26(2):159-174. <https://doi.org/10.1515/ijamh-2013-0512>
543. Sawicki GS, Lukens-Bull K, Yin X, et al. Measuring the transition readiness of youth with special healthcare needs: validation of the TRAQ—transition readiness assessment questionnaire. *J Pediatr Psychol*. 2011;36(2):160-171. <https://doi.org/10.1093/jpepsy/jsp128>
544. Beal SJ, Riddle IK, Kichler JC, et al. The associations of chronic condition type and individual characteristics with transition readiness. *Acad Pediatr*. 2016;16(7):660-667. <https://doi.org/10.1016/j.acap.2016.06.007>
545. Culen C, Herle M, Ertl DA, et al. Less ready for adulthood?—Turner syndrome has an impact on transition readiness. *Clin Endocrinol (Oxf)*. 2020;93(4):449-455. <https://doi.org/10.1111/cen.14293>
546. Patel N, Klamer B, Davis S, Nahata L. Patient-parent perceptions of transition readiness in Turner syndrome and associated factors. *Clin Endocrinol (Oxf)*. 2022;96(2):155-164. <https://doi.org/10.1111/cen.14584>
547. Davids K, van Staa A, Geilvoet W, et al. We mind your step: understanding and preventing drop-out in the transfer from paediatric to adult tertiary endocrine healthcare. *Endocr Connect*. 2022;11(5):e220025. <https://doi.org/10.1530/EC-22-0025>
548. Gray WN, Schaefer MR, Resmini-Rawlinson A, Wagoner ST. Barriers to transition from pediatric to adult care: a systematic review. *J Pediatr Psychol*. 2018;43(5):488-502. <https://doi.org/10.1093/jpepsy/jsx142>
549. Sheanon NM, Beal SJ, Kichler JC, Casnellie L, Backeljauw P, Corathers S. Readiness for transition to adult care in adolescents and young adults with Turner syndrome. *J Pediatr Endocrinol Metab*. 2020;33(9):1165-1171. <https://doi.org/10.1515/jpem-2020-0155>
550. Streur CS, Floody EA, Lapham ZK, Sandberg DE. The transition to independence and adult care for women with Turner syndrome: current status and priorities of 1338 women and parents. *Am J Med Genet A*. 2022;188(2):400-413. <https://doi.org/10.1002/ajmg.a.62564>
551. Zahra B, Lyall H, Sastry A, Freel EM, Dominiczak AF, Mason A. Evaluating transition in Turner syndrome in the west of Scotland. *J Pediatr Endocrinol Metab*. 2021;34(4):473-477. <https://doi.org/10.1515/jpem-2020-0242>
552. Gleeson H, Turner G. Transition to adult services. *Arch Dis Child Educ Pract Ed*. 2012;97(3):86-92. <https://doi.org/10.1136/archdischild-2011-300261>
553. Liao LM, Tacconelli E, Wood D, Conway G, Creighton SM. Adolescent girls with disorders of sex development: a needs analysis of transitional care. *J Pediatr Urol*. 2010;6(6):609-613. <https://doi.org/10.1016/j.jpuro.2010.07.006>
554. Thomsen EL, Boisen KA, Hanghøj S, et al. A comprehensive transfer program from pediatrics to adult care for parents of adolescents with chronic illness (ParTNERSTEPS): study protocol for a randomized controlled trial. *Trials*. 2022;23(1):1034. <https://doi.org/10.1186/s13063-022-06997-0>
555. Devernay M, Ecosse E, Coste J, Carel JC. Determinants of medical care for young women with Turner syndrome. *J Clin Endocrinol Metab*. 2009;94(9):3408-3413. <https://doi.org/10.1210/jc.2009-0495>
556. Freriks K, Timmermans J, Beerendonk CC, et al. Standardized multidisciplinary evaluation yields significant previously undiagnosed morbidity in adult women with Turner syndrome. *J Clin Endocrinol Metab*. 2011;96(9):E1517-E1526. <https://doi.org/10.1210/jc.2011-0346>
557. Wolstencroft J, Kerry E, Denyer H, Watkins A, Mandy W, Skuse D. New approaches to social skills training: blended group interventions for girls with social communication difficulties. *Autism Res*. 2021;14(5):1061-1072. <https://doi.org/10.1002/aur.2495>
558. de Brouwer IJ, Suijkerbuijk M, van de Grift TC, Kreukels BPC. First adolescent romantic and sexual experiences in individuals with differences of sex development/intersex conditions. *J Adolesc Health*. 2022;71(6):688-695. <https://doi.org/10.1016/j.jadohealth.2022.07.012>
559. Lucaccioni L, Wong SC, Smyth A, et al. Turner syndrome—issues to consider for transition to adulthood. *Br Med Bull*. 2015;113(1):45-58. <https://doi.org/10.1093/bmb/ldu038>
560. Ertl DA, Gleiss A, Schubert K, et al. Health status, quality of life and medical care in adult women with Turner syndrome. *Endocr Connect*. 2018;7(4):534-543. <https://doi.org/10.1530/EC-18-0053>
561. Bernard V, Donadille B, Zenaty D, et al. Spontaneous fertility and pregnancy outcomes amongst 480 women with Turner syndrome. *Hum Reprod*. 2016;31(4):782-788. <https://doi.org/10.1093/humrep/dew012>
562. Birkebaek N, Cruger D, Hansen J, Nielsen J, Bruun-Petersen G. Fertility and pregnancy outcome in Danish women with Turner syndrome. *Clin Genet*. 2002;61(1):35-39. <https://doi.org/10.1034/j.1399-0004.2002.610107.x>
563. Hadnott TN, Gould HN, Gharib AM, Bondy CA. Outcomes of spontaneous and assisted pregnancies in Turner syndrome: the U.S. National institutes of health experience. *Fertil Steril*. 2011;95(7):2251-2256. <https://doi.org/10.1016/j.fertnstert.2011.03.085>
564. Słowikowska-Hilczler J, Hirschberg AL, Claahsen-van der Grinten H, et al. Fertility outcome and information on fertility issues in individuals with different forms of disorders of sex development: findings from the dsd-LIFE study. *Fertil Steril*. 2017;108(5):822-831. <https://doi.org/10.1016/j.fertnstert.2017.08.013>
565. Sylven L, Magnusson C, Hagenfeldt K, von Schultzb B. Life with Turner's syndrome—a psychosocial report from 22 middle-aged women. *Acta Endocrinol Copenh*. 1993;129(3):188-194. <https://doi.org/10.1530/acta.0.1290188>
566. Falsey E, Cirino AL, Snyder E, Steeves M, Lin AE. Parenthood among individuals with Turner syndrome: results of an online survey of attitudes towards pregnancy, adoption, and surrogacy. *J Community Genet*. 2022;13(3):263-270. <https://doi.org/10.1007/s12687-022-00588-x>
567. van Hagen IM, Duijnhouwer AL, Ten Kate-Booij MJ, et al. Wish to conceive and concerns to develop cardiovascular complications during pregnancy in patients with Turner syndrome. *J Psychosom Obstet Gynaecol*. 2017;38(1):45-52. <https://doi.org/10.1080/0167482X.2016.1216961>
568. Schmidt PJ, Cardoso GM, Ross JL, Haq N, Rubinow DR, Bondy CA. Shyness, social anxiety, and impaired self-esteem in Turner syndrome and premature ovarian failure. *JAMA*. 2006;295(12):1374-1376. <https://doi.org/10.1001/jama.295.12.1374>
569. Ros C, Alobid I, Balasch J, Mullol J, Castelo-Branco C. Turner's syndrome and other forms of congenital hypogonadism impair quality of life and sexual function. *Am J Obstet Gynecol*. 2013;208(6):484.e1-484.e6. <https://doi.org/10.1016/j.ajog.2013.01.011>

570. Stochholm K, Hjerrild B, Mortensen KH, Juul S, Frydenberg M, Gravholt CH. Socio-economic parameters and mortality in Turner syndrome. *Eur J Endocrinol.* 2012;166(6):1013-1019. <https://doi.org/10.1530/EJE-11-1066>
571. Gould HN, Bakalov VK, Tankersley C, Bondy CA. High levels of education and employment among women with Turner syndrome. *J Womens Health (Larchmt).* 2013;22(3):230-235. <https://doi.org/10.1089/jwh.2012.3931>
572. van der Coelen S, van der Velden J, Nadesapillai S, *et al.* The decision-making process regarding ovarian tissue cryopreservation in girls with Turner syndrome by patients, parents, and healthcare providers: a mixed-methods study. *Horm Res Paediatr.* 2022;95(4):374-383. <https://doi.org/10.1159/000525374>
573. Schleedoorn M, van der Velden J, Braat D, *et al.* TurnerFertility trial: PROTOCOL for an observational cohort study to describe the efficacy of ovarian tissue cryopreservation for fertility preservation in females with Turner syndrome. *BMJ Open.* 2019;9(12):e030855. <https://doi.org/10.1136/bmjopen-2019-030855>
574. Graff A, Donadille B, Morel H, *et al.* Added value of buccal cell FISH analysis in the diagnosis and management of Turner syndrome. *Hum Reprod.* 2020;35(10):2391-2398. <https://doi.org/10.1093/humrep/deaa197>
575. Schleedoorn MJ, Fleischer K, Braat D, Oerlemans A, van der Velden A, Peek R. Why Turner patients with 45, X monosomy should not be excluded from fertility preservation services. *Reprod Biol Endocrinol.* 2022;20(1):143. <https://doi.org/10.1186/s12958-022-01015-z>
576. Nadesapillai S, van der Velden J, Smeets D, *et al.* Why are some patients with 45,X Turner syndrome fertile? A young girl with classical 45,X Turner syndrome and a cryptic mosaicism in the ovary. *Fertil Steril.* 2021;115(5):1280-1287. <https://doi.org/10.1016/j.fertnstert.2020.11.006>
577. Mortensen KH, Rohde MD, Ulbjerg N, Gravholt CH. Repeated spontaneous pregnancies in 45 X Turner syndrome. *Obstet Gynecol.* 2010;115(2):446-449. <https://doi.org/10.1097/AOG.0b013e3181cb5b2a>
578. Nadesapillai S, Mol F, Broer SL, *et al.* Reproductive outcomes of women with Turner syndrome undergoing oocyte vitrification: a retrospective multicenter cohort study. *J Clin Med.* 2023;12(20):6502. <https://doi.org/10.3390/jcm12206502>
579. Mamsen LS, Charkiewicz K, Anderson RA, *et al.* Characterization of follicles in girls and young women with Turner syndrome who underwent ovarian tissue cryopreservation. *Fertil Steril.* 2019;111(6):1217-1225.e3. <https://doi.org/10.1016/j.fertnstert.2019.02.003>
580. Weenen C, Laven JS, Von Bergh AR, *et al.* Anti-Müllerian hormone expression pattern in the human ovary: potential implications for initial and cyclic follicle recruitment. *Mol Hum Reprod.* 2004;10(2):77-83. <https://doi.org/10.1093/molehr/gah015>
581. Hagen CP, Aksglaede L, Sorensen K, *et al.* Serum levels of anti-müllerian hormone as a marker of ovarian function in 926 healthy females from birth to adulthood and in 172 Turner syndrome patients. *J Clin Endocrinol Metab.* 2010;95(11):5003-5010. <https://doi.org/10.1210/jc.2010-0930>
582. Nadesapillai S, van der Velden J, van der Coelen S, *et al.* TurnerFertility trial: fertility preservation in young girls with Turner syndrome by freezing ovarian cortex tissue—a prospective intervention study. *Fertil Steril.* 2023;120(5):1048-1060. <https://doi.org/10.1016/j.fertnstert.2023.08.004>
583. Moolhuijsen LME, Visser JA. Anti-Müllerian hormone and ovarian reserve: update on assessing ovarian function. *J Clin Endocrinol Metab.* 2020;105(11):3361-3373. <https://doi.org/10.1210/clinem/dgaa513>
584. Tarani L, Lampariello S, Raguso G, *et al.* Pregnancy in patients with Turner's syndrome: six new cases and review of literature. *Gynecol Endocrinol.* 1998;12(2):83-87. <https://doi.org/10.3109/09513599809024955>
585. Quenby S, Gallos ID, Dhillon-Smith RK, *et al.* Miscarriage matters: the epidemiological, physical, psychological, and economic costs of early pregnancy loss. *Lancet.* 2021;397(10285):1658-1667. [https://doi.org/10.1016/S0140-6736\(21\)00682-6](https://doi.org/10.1016/S0140-6736(21)00682-6)
586. Keukens A, van Wely M, van der Meulen C, Mochtar MH. Pre-eclampsia in pregnancies resulting from oocyte donation, natural conception or IVF: a systematic review and meta-analysis. *Hum Reprod.* 2022;37(3):586-599. <https://doi.org/10.1093/humrep/deab267>
587. Liao J, Luo K, Cheng D, *et al.* Reproductive outcomes after preimplantation genetic testing in mosaic Turner syndrome: a retrospective cohort study of 100 cycles. *J Assist Reprod Genet.* 2021;38(5):1247-1253. <https://doi.org/10.1007/s10815-021-02127-y>
588. Portnoi MF, Chantot-Bastarad S, Christin-Maitre S, *et al.* Familial Turner syndrome with an X;Y translocation mosaicism: implications for genetic counseling. *Eur J Med Genet.* 2012;55(11):635-640. <https://doi.org/10.1016/j.ejmg.2012.07.001>
589. Hagman A, Kallen K, Barrenas ML, *et al.* Obstetric outcomes in women with Turner karyotype. *J Clin Endocrinol Metab.* 2011;96(11):3475-3482. <https://doi.org/10.1210/jc.2011-1421>
590. Ramage K, Grabowska K, Silversides C, Quan H, Metcalfe A. Maternal, pregnancy, and neonatal outcomes for women with Turner syndrome. *Birth Defects Res.* 2020;112(14):1067-1073. <https://doi.org/10.1002/bdr2.1739>
591. Strypstein L, Van Moer E, Nekkebroeck J, *et al.* First live birth after fertility preservation using vitrification of oocytes in a woman with mosaic Turner syndrome. *J Assist Reprod Genet.* 2022;39(2):543-549. <https://doi.org/10.1007/s10815-022-02420-4>
592. Dunlop CE, Jack SA, Telfer EE, Zahra S, Anderson RA. Clinical pregnancy in Turner syndrome following re-implantation of cryopreserved ovarian cortex. *J Assist Reprod Genet.* 2023;40(10):2385-2390. <https://doi.org/10.1007/s10815-023-02905-w>
593. Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology. Mature oocyte cryopreservation: a guideline. *Fertil Steril.* 2013;99(1):37-43. <https://doi.org/10.1016/j.fertnstert.2012.09.028>
594. Viuff M, Gravholt CH. Turner syndrome and fertility. *Ann Endocrinol (Paris).* 2022;83(4):244-249. <https://doi.org/10.1016/j.ando.2022.06.001>
595. Anderson RA, Amant F, Braat D, *et al.* ESHRE guideline: female fertility preservation. *Hum Reprod Open.* 2020;2020(4):hoaa052. <https://doi.org/10.1093/hropen/hoaa052>
596. Oktay K, Bedoschi G. Oocyte cryopreservation for fertility preservation in postpubertal female children at risk for premature ovarian failure due to accelerated follicle loss in Turner syndrome or cancer treatments. *J Pediatr Adolesc Gynecol.* 2014;27(6):342-346. <https://doi.org/10.1016/j.jpjg.2014.01.003>
597. Talaulikar VS, Conway GS, Pimblett A, Davies MC. Outcome of ovarian stimulation for oocyte cryopreservation in women with Turner syndrome. *Fertil Steril.* 2019;111(3):505-509. <https://doi.org/10.1016/j.fertnstert.2018.11.010>
598. Vergier J, Bottin P, Saïas J, Reynaud R, Guillemain C, Courbiere B. Fertility preservation in Turner syndrome: karyotype does not predict ovarian response to stimulation. *Clin Endocrinol (Oxf).* 2019;91(5):646-651. <https://doi.org/10.1111/cen.14076>
599. Martel RA, Blakemore JK, Fino ME. The use of oocyte cryopreservation for fertility preservation in patients with sex chromosome disorders: a case series describing outcomes. *J Assist Reprod Genet.* 2022;39(5):1143-1153. <https://doi.org/10.1007/s10815-022-02469-1>
600. Balen AH, Harris SE, Chambers EL, Picton HM. Conservation of fertility and oocyte genetics in a young woman with mosaic Turner syndrome. *BJOG.* 2010;117(2):238-242. <https://doi.org/10.1111/j.1471-0528.2009.02423.x>
601. El-Shawarby SA, Sharif F, Conway G, Serhal P, Davies M. Oocyte cryopreservation after controlled ovarian hyperstimulation in mosaic Turner syndrome: another fertility preservation option in a dedicated UK clinic. *BJOG.* 2010;117(2):234-237. <https://doi.org/10.1111/j.1471-0528.2009.02422.x>
602. Azem F, Brenner A, Malinger G, *et al.* Bypassing physiological puberty, a novel procedure of oocyte cryopreservation at age 7: a case

- report and review of the literature. *Fertil Steril.* 2020;114(2):374-378. <https://doi.org/10.1016/j.fertnstert.2020.03.009>
603. Ulrich ND, Raja N, Ellman E, Moravek MB. Outcomes of fertility preservation consults for women at risk for primary ovarian insufficiency due to history of cancer treatment or mosaic Turner syndrome. *J Adolesc Young Adult Oncol.* 2022;11(4):427-432. <https://doi.org/10.1089/jayao.2021.0115>
604. Kavoussi SK, Fisseha S, Smith YR, Smith GD, Christman GM, Gago LA. Oocyte cryopreservation in a woman with mosaic Turner syndrome: a case report. *J Reprod Med.* 2008;53(3):223-226.
605. Lau NM, Huang JY, MacDonald S, et al. Feasibility of fertility preservation in young females with Turner syndrome. *Reprod Biomed Online.* 2009;18(2):290-295. [https://doi.org/10.1016/S1472-6483\(10\)60268-4](https://doi.org/10.1016/S1472-6483(10)60268-4)
606. Ito A, Katagiri Y, Tamaki Y, Fukuda Y, Oji A, Morita M. DuoStim: a new option for fertility preservation for a woman with Turner syndrome. *Gynecol Endocrinol.* 2020;36(12):1144-1148. <https://doi.org/10.1080/09513590.2020.1822805>
607. Brouillet S, Ranisavljevic N, Sonigo C, et al. Should we perform oocyte accumulation to preserve fertility in women with Turner syndrome? A multicenter study and systematic review of the literature. *Hum Reprod.* 2023;38(9):1733-1745. <https://doi.org/10.1093/humrep/dead135>
608. Nadesapillai S, van der Velden J, Braat D, Peek R, Fleischer K. The challenge of defining predictive parameters for fertility preservation counseling in young females with Turner syndrome. *Acta Obstet Gynecol Scand.* 2021;100(6):1155-1156. <https://doi.org/10.1111/aogs.14094>
609. Peek R, Nadesapillai S, Thi Nguyen TY, et al. Assessment of folliculogenesis in ovarian tissue from young patients with Turner syndrome using a murine xenograft model. *Fertil Steril.* 2023;120(2):371-381. <https://doi.org/10.1016/j.fertnstert.2023.04.008>
610. Peek R, Schleedoorn M, Smeets D, et al. Ovarian follicles of young patients with Turner's syndrome contain normal oocytes but monosomic 45,X granulosa cells. *Hum Reprod.* 2019;34(9):1686-1696. <https://doi.org/10.1093/humrep/dez135>
611. Gayete-Lafuente S, Turan V, Oktay KH. Oocyte cryopreservation with in vitro maturation for fertility preservation in girls at risk for ovarian insufficiency. *J Assist Reprod Genet.* 2023;40(12):2777-2785. <https://doi.org/10.1007/s10815-023-02932-7>
612. Cobo A, García-Velasco JA, Remohí J, Pellicer A. Oocyte vitrification for fertility preservation for both medical and nonmedical reasons. *Fertil Steril.* 2021;115(5):1091-1101. <https://doi.org/10.1016/j.fertnstert.2021.02.006>
613. Practice Committee of the American Society for Reproductive Medicine. Electronic address: asrm@asrm.org. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion. *Fertil Steril.* 2019;112(6):1022-1033. <https://doi.org/10.1016/j.fertnstert.2019.09.013>
614. Rodriguez-Wallberg KA, Sergouniotis F, Nilsson HP, Lundberg FE. Trends and outcomes of fertility preservation for girls, adolescents and young adults with Turner syndrome: a prospective cohort study. *Front Endocrinol (Lausanne).* 2023;14:1135249. <https://doi.org/10.3389/fendo.2023.1135249>
615. Huang JY, Tulandi T, Holzer H, et al. Cryopreservation of ovarian tissue and in vitro matured oocytes in a female with mosaic Turner syndrome: case report. *Hum Reprod.* 2008;23(2):336-339. <https://doi.org/10.1093/humrep/dem307>
616. Cheng J, Ruan X, Du J, et al. Ovarian tissue cryopreservation for a 3-year-old girl with mosaic Turner syndrome in China: first case report and literature review. *Front Endocrinol (Lausanne).* 2022;13:959912. <https://doi.org/10.3389/fendo.2022.959912>
617. Joshi VB, Behl S, Pittock ST, et al. Establishment of a pediatric ovarian and testicular cryopreservation program for malignant and non-malignant conditions: the Mayo Clinic experience. *J Pediatr Adolesc Gynecol.* 2021;34(5):673-680. <https://doi.org/10.1016/j.jpag.2021.04.006>
618. Hreinsson JG, Ojala M, Fridstrom M, et al. Follicles are found in the ovaries of adolescent girls with Turner's syndrome. *J Clin Endocrinol Metab.* 2002;87(8):3618-3623. <https://doi.org/10.1210/jcem.87.8.8753>
619. te Velde ER, Pearson PL. The variability of female reproductive ageing. *Hum Reprod Update.* 2002;8(2):141-154. <https://doi.org/10.1093/humupd/8.2.141>
620. Baird DT, Webb R, Campbell BK, Harkness LM, Gosden RG. Long-term ovarian function in sheep after ovariectomy and transplantation of autografts stored at -196 C. *Endocrinology.* 1999;140(1):462-471. <https://doi.org/10.1210/endo.140.1.6453>
621. Cacciottola L, Donnez J, Dolmans MM. Ovarian tissue damage after grafting: systematic review of strategies to improve follicle outcomes. *Reprod Biomed Online.* 2021;43(3):351-369. <https://doi.org/10.1016/j.rbmo.2021.06.019>
622. Schleedoorn MJ, Mulder BH, Braat DDM, et al. International consensus: ovarian tissue cryopreservation in young Turner syndrome patients: outcomes of an ethical Delphi study including 55 experts from 16 different countries. *Hum Reprod.* 2020;35(5):1061-1072. <https://doi.org/10.1093/humrep/deaa007>
623. Nadesapillai S, van der Coelen S, Goebel L, et al. Deciding on future fertility: considerations of girls with Turner syndrome and their parents to opt for or against ovarian tissue cryopreservation. *Reprod Biomed Online.* 2023;46(6):1017-1025. <https://doi.org/10.1016/j.rbmo.2023.02.013>
624. Theroux CI, Elliott V, Davis S, et al. Fertility counseling practices for patients with Turner syndrome in pediatric endocrine clinics: results of a Pediatric Endocrine Society Survey. *Horm Res Paediatr.* 2022;95(4):321-330. <https://doi.org/10.1159/000524573>
625. Morgan TL, Kapa HM, Crerand CE, et al. Fertility counseling and preservation discussions for females with Turner syndrome in pediatric centers: practice patterns and predictors. *Fertil Steril.* 2019;112(4):740-748. <https://doi.org/10.1016/j.fertnstert.2019.05.010>
626. Więcek M, Gawlik J, Nowak Z, Gawlik A. Questions concerning fertility preservation during transition in girls with Turner syndrome: review of the literature. *Endocr Connect.* 2022;11(12):e220344. <https://doi.org/10.1530/EC-22-0344>
627. Oktay K, Bedoschi G, Berkowitz K, et al. Fertility preservation in women with Turner syndrome: a comprehensive review and practical guidelines. *J Pediatr Adolesc Gynecol.* 2016;29(5):409-416. <https://doi.org/10.1016/j.jpag.2015.10.011>
628. Rowell EE, Lautz TB, Lai K, et al. The ethics of offering fertility preservation to pediatric patients: a case-based discussion of barriers for clinicians to consider. *Semin Pediatr Surg.* 2021;30(5):151095. <https://doi.org/10.1016/j.sempedsurg.2021.151095>
629. Blakemore JK, Wei LS, Quinn GP. Addressing practical concerns surrounding fertility preservation in patients with Turner syndrome. *Fertil Steril.* 2019;112(4):651-652. <https://doi.org/10.1016/j.fertnstert.2019.05.033>
630. Fiot E, Zenaty D, Boizeau P, Haignere J, Dos SS, Leger J. X chromosome gene dosage as a determinant of congenital malformations and of age-related comorbidity risk in patients with Turner syndrome, from childhood to early adulthood. *Eur J Endocrinol.* 2019;180(6):397-406. <https://doi.org/10.1530/EJE-18-0878>
631. Sari E, Bereket A, Yeşilkaya E, et al. Anthropometric findings from birth to adulthood and their relation with karyotype distribution in Turkish girls with Turner syndrome. *Am J Med Genet A.* 2016;170A(4):942-948. <https://doi.org/10.1002/ajmg.a.37498>
632. Andersen AR, Urhoj SK, Tan J, et al. The burden of disease for children born alive with Turner syndrome—a European cohort study. *Birth Defects Res.* 2023;115(16):1459-1468. <https://doi.org/10.1002/bdr2.2222>
633. Lara DA, Ethen MK, Canfield MA, Nembhard WN, Morris SA. A population-based analysis of mortality in patients with Turner syndrome and hypoplastic left heart syndrome using the Texas birth defects registry. *Congenit Heart Dis.* 2017;12(1):105-112. <https://doi.org/10.1111/chd.12413>

634. Alam S, Claxton JS, Mortillo M, et al. Thirty-year survival after cardiac surgery for patients with Turner syndrome. *J Pediatr*. 2021;239:187-192.e1. <https://doi.org/10.1016/j.jpeds.2021.08.034>
635. Zakaria D, Tang X, Bhakta R, ElHassan NO, Prodhon P. Chromosomal abnormalities affect the surgical outcome in infants with hypoplastic left heart syndrome: a large cohort analysis. *Pediatr Cardiol*. 2018;39(1):11-18. <https://doi.org/10.1007/s00246-017-1717-3>
636. Martin-Giacalone BA, Lin AE, Rasmussen SA, et al. Prevalence and descriptive epidemiology of Turner syndrome in the United States, 2000–2017: a report from the national birth defects prevention network. *Am J Med Genet A*. 2023;191(5):1339-1349. <https://doi.org/10.1002/ajmg.a.63181>
637. Starke M, Albertsson Wikland K, Möller A. Parents' descriptions of development and problems associated with infants with Turner syndrome: a retrospective study. *J Paediatr Child Health*. 2003;39(4):293-298. <https://doi.org/10.1046/j.1440-1754.2003.00150.x>
638. Alkhayat H, Christesen HB, Steer J, Stewart H, Brusgaard K, Hussain K. Mosaic Turner syndrome and hyperinsulinaemic hypoglycaemia. *J Pediatr Endocrinol Metab*. 2006;19(12):1451-1457. <https://doi.org/10.1515/JPEM.2006.19.12.1451>
639. Cappella M, Graziani V, Pragliola A, et al. Hyperinsulinemic hypoglycaemia in a Turner syndrome with Ring (X). *Case Rep Pediatr*. 2015;2015:561974. <https://doi.org/10.1155/2015/561974>
640. Pietzner V, Weigel JF, Wand D, Merckenschlager A, Bernhard MK. Low-level hyperinsulinism with hypoglycemic spells in an infant with mosaic Turner syndrome and mild kabuki-like phenotype: a case report and review of the literature. *J Pediatr Endocrinol Metab*. 2014;27(1-2):165-170. <https://doi.org/10.1515/jpem-2013-0090>
641. Gibson CE, Boodhansingh KE, Li C, et al. Congenital hyperinsulinism in infants with Turner syndrome: possible association with monosomy X and KDM6A haploinsufficiency. *Horm Res Paediatr*. 2018;89(6):413-422. <https://doi.org/10.1159/000488347>
642. Kostopoulou E, Dastamani A, Güemes M, et al. Syndromic forms of hyperinsulinaemic hypoglycaemia—A 15-year follow-up study. *Clin Endocrinol (Oxf)*. 2021;94(3):399-412. <https://doi.org/10.1111/cen.14393>
643. Thornton PS, Stanley CA, De Leon DD, et al. Recommendations from the Pediatric Endocrine Society for evaluation and management of persistent hypoglycemia in neonates, infants, and children. *J Pediatr*. 2015;167(2):238-245. <https://doi.org/10.1016/j.jpeds.2015.03.057>
644. Denniston AK, Butler L. Ophthalmic features of Turner's syndrome. *Eye*. 2004;18(7):680-684. <https://doi.org/10.1038/sj.eye.6701323>
645. Huang J, Basith SST, Patel S, et al. Ocular findings in pediatric Turner syndrome. *Ophthalmic Genet*. 2022;43(4):450-453. <https://doi.org/10.1080/13816810.2022.2045512>
646. Wikiera B, Mulak M, Koltowska-Haggstrom M, Noczynska A. The presence of eye defects in patients with Turner syndrome is irrespective of their karyotype. *Clin Endocrinol (Oxf)*. 2015;83(6):842-848. <https://doi.org/10.1111/cen.12794>
647. Viuff MH, Stochholm K, Juul S, Gravholt CH. Disorders of the eye, ear, skin, and nervous system in women with Turner syndrome - a nationwide cohort study. *Eur J Hum Genet*. 2021;30(2):229-236. <https://doi.org/10.1038/s41431-021-00989-5>
648. Geerardyn A, Willaert A, Decallonne B, Desloovere C, Verhaert N. Prevalence of otological disease in Turner syndrome: a systematic review. *Otol Neurotol*. 2021;42(7):953-958. <https://doi.org/10.1097/MAO.0000000000003118>
649. Mann L, VanLooy L. The impact of amplification on quality of life in women with Turner syndrome. *Orphanet J Rare Dis*. 2024;19(1):119. <https://doi.org/10.1186/s13023-024-03122-z>
650. Hamberis AO, Mehta CH, Dornhoffer JR, Meyer TA. Characteristics and progression of hearing loss in children with Turner's syndrome. *Laryngoscope*. 2020;130(6):1540-1546. <https://doi.org/10.1002/lary.28264>
651. Bonnard Å, Bark R, Hederstierna C. Clinical update on sensorineural hearing loss in Turner syndrome and the X-chromosome. *Am J Med Genet C Semin Med Genet*. 2019;181(1):18-24. <https://doi.org/10.1002/ajmg.c.31673>
652. Kubba H, McAllister K, Hunter K, Mason A. Annual hearing screening in girls with Turner syndrome: results from the first three years in Glasgow. *Int J Pediatr Otorhinolaryngol*. 2019;120:152-156. <https://doi.org/10.1016/j.ijporl.2019.02.025>
653. Álvarez-Nava F, Racines-Orbe M, Witt J, et al. Metabolic syndrome as a risk factor for sensorineural hearing loss in adult patients with Turner syndrome. *Appl Clin Genet*. 2020;13:25-35. <https://doi.org/10.2147/TACG.S229828>
654. Fukami M, Seki A, Ogata T. SHOX haploinsufficiency as a cause of syndromic and nonsyndromic short stature. *Mol Syndromol*. 2016;7(1):3-11. <https://doi.org/10.1159/000444596>
655. Lim D, Hassani S, Lupton K, et al. Prevalence, risk factors and management strategies for otological problems in girls with Turner syndrome. *Acta Paediatr*. 2020;109(10):2075-2083. <https://doi.org/10.1111/apa.15128>
656. Cook KD, Shpargel KB, Starmer J, et al. T follicular helper cell-dependent clearance of a persistent virus infection requires T cell expression of the histone demethylase UTX. *Immunity*. 2015;43(4):703-714. <https://doi.org/10.1016/j.immuni.2015.09.002>
657. Thrasher BJ, Hong LK, Whitmire JK, Su MA. Epigenetic dysfunction in Turner syndrome immune cells. *Curr Allergy Asthma Rep*. 2016;16(5):36. <https://doi.org/10.1007/s11882-016-0612-y>
658. Alvarez-Nava F, Lanes R. Epigenetics in Turner syndrome. *Clin Epigenetics*. 2018;10(1):45. <https://doi.org/10.1186/s13148-018-0477-0>
659. Simonoska R, Stenberg AE, Duan M, et al. Inner ear pathology and loss of hearing in estrogen receptor-beta deficient mice. *J Endocrinol*. 2009;201(3):397-406. <https://doi.org/10.1677/JOE-09-0060>
660. Ostberg JE, Beckman A, Cadge B, Conway GS. Oestrogen deficiency and growth hormone treatment in childhood are not associated with hearing in adults with Turner syndrome. *Horm Res*. 2004;62(4):182-186. <https://doi.org/10.1159/000080888>
661. Lieu JEC, Kenna M, Anne S, Davidson L. Hearing loss in children: a review. *JAMA*. 2020;324(21):2195-2205. <https://doi.org/10.1001/jama.2020.17647>
662. El-Mansoury M, Barrenas ML, Bryman I, Hanson C, Landin-Wilhelmsen K. Impaired body balance, fine motor function and hearing in women with Turner syndrome. *Clin Endocrinol (Oxf)*. 2009;71(2):273-278. <https://doi.org/10.1111/j.1365-2265.2008.03473.x>
663. Maier C, Dumančić J, Brkić H, et al. Tooth crown morphology in Turner and Klinefelter syndrome individuals from a Croatian sample. *Acta Stomatol Croat*. 2019;53(2):106-118. <https://doi.org/10.15644/asc53/2/2>
664. Preda SA, Predescu AM, Stoica LE, et al. Histopathological and immunohistochemical changes of the marginal periodontium in patients with Turner syndrome. *Rom J Morphol Embryol*. 2021;62(1):239-247. <https://doi.org/10.47162/RJME.62.1.24>
665. Kjellberg H, Lundgren T, Barrenäs ML, Rizell S. Apical root resorptions in girls with Turner syndrome: a controlled longitudinal study. *Eur J Orthod*. 2022;44(6):705-710. <https://doi.org/10.1093/ejo/cjac024>
666. Ahiko N, Baba Y, Tsuji M, Horikawa R, Moriyama K. Investigation of maxillofacial morphology and oral characteristics with Turner syndrome and early mixed dentition. *Congenit Anom (Kyoto)*. 2019;59(1):11-17. <https://doi.org/10.1111/cga.12284>
667. Cazzolla AP, Lo Muzio L, Di Fede O, et al. Orthopedic-orthodontic treatment of the patient with Turner's syndrome: review of the literature and case report. *Spec Care Dentist*. 2018;38(4):239-248. <https://doi.org/10.1111/scd.12295>
668. Wójcik D, Beń-Skowronek I. Craniofacial morphology in children with growth hormone deficiency and Turner syndrome. *Diagnostics (Basel)*. 2020;10(2):88. <https://doi.org/10.3390/diagnostics10020088>

669. Eklund M, Kotilainen J, Evälahti M, Waltimo-Sirén J. Cephalometric analysis of pharyngeal airway space dimensions in Turner syndrome. *Eur J Orthod.* 2012;34(2):219-225. <https://doi.org/10.1093/ejo/cjs001>
670. Pham TT, Davis SM, Tong S, Campa KA, Friedman NR, Gitomer SA. High prevalence of obstructive sleep-disordered breathing in pediatric patients with Turner syndrome. *Otolaryngol Head Neck Surg.* 2024;170(3):905-912. <https://doi.org/10.1002/ohn.576>
671. Wu CR, Tu YK, Chuang LP, et al. Diagnostic meta-analysis of the pediatric sleep questionnaire, OSA-18, and pulse oximetry in detecting pediatric obstructive sleep apnea syndrome. *Sleep Med Rev.* 2020;54:101355. <https://doi.org/10.1016/j.smrv.2020.101355>
672. da Silva Gusmão Cardoso T, Pompéia S, Miranda MC. Cognitive and behavioral effects of obstructive sleep apnea syndrome in children: a systematic literature review. *Sleep Med.* 2018;46:46-55. <https://doi.org/10.1016/j.sleep.2017.12.020>
673. Said JT, Pithadia DJ, Snyder E, Elsharkawi I, Lin A, Lilly E. Dermatologic findings in individuals with Turner syndrome: a cross-sectional study across the lifespan. *J Am Acad Dermatol.* 2022;87(2):476-479. <https://doi.org/10.1016/j.jaad.2021.10.023>
674. Bellini C, Di BE, Boccardo F, et al. The role of lymphoscintigraphy in the diagnosis of lymphedema in Turner syndrome. *Lymphology.* 2009;42(3):123-129.
675. Atton G, Gordon K, Brice G, et al. The lymphatic phenotype in Turner syndrome: an evaluation of nineteen patients and literature review. *Eur J Hum Genet.* 2015;23(12):1634-1639. <https://doi.org/10.1038/ejhg.2015.41>
676. Lee YL, Wu LL. Clinical features of girls with Turner syndrome in a single centre in Malaysia. *J ASEAN Fed Endocr Soc.* 2019;34(1):22-28. <https://doi.org/10.15605/jafes.034.01.05>
677. Wonkam A, Veigne SW, Abass A, et al. Features of Turner syndrome among a group of Cameroonian patients. *Int J Gynaecol Obstet.* 2015;129(3):264-266. <https://doi.org/10.1016/j.ijgo.2014.11.025>
678. Jungbauer WN, Jr., Rich MD, Barta RJ, Lacey MS. Surgical techniques for the repair of webbed neck: a scoping review. *J Craniofac Surg.* 2022;33(8):2644-2649. <https://doi.org/10.1097/SCS.00000000000008821>
679. Mehri Turki I. Surgical correction of the webbed neck: an alternative lateral approach. *GMS Interdiscip Plast Reconstr Surg DGPW.* 2017;6:Doc04. <https://doi.org/10.3205/iplrs000106>
680. Nunes MR, Pereira TG, Correira HVD, et al. Clinical and cytogenetic characteristics of patients diagnosed with Turner syndrome in a clinical genetics service: cross-sectional retrospective study. *Sao Paulo Med J.* 2021;139(5):435-442. <https://doi.org/10.1590/1516-3180.2020.0470.r2.110321>
681. Zelinska N, Shevchenko I, Globa E. Nationwide study of Turner syndrome in Ukrainian children: prevalence, genetic variants and phenotypic features. *J Clin Res Pediatr Endocrinol.* 2018;10(3):256-263. <https://doi.org/10.4274/jcrpe.5119>
682. Ji J, Zöller B, Sundquist J, Sundquist K. Risk of solid tumors and hematological malignancy in persons with Turner and klinefelter syndromes: a national cohort study. *Int J Cancer.* 2016;139(4):754-758. <https://doi.org/10.1002/ijc.30126>
683. Lippe B, Geffner ME, Dietrich RB, Boechat MI, Kangarloo H. Renal malformations in patients with Turner syndrome: imaging in 141 patients. *Pediatrics.* 1988;82(6):852-856. <https://doi.org/10.1542/peds.82.6.852>
684. Hamza RT, Shalaby MH, Hamed LS, Abdulla DBA, Elfekky SM, Sultan OM. Renal anomalies in patients with Turner syndrome: is scintigraphy superior to ultrasound? *Am J Med Genet A.* 2016;170A(2):355-362. <https://doi.org/10.1002/ajmg.a.37425>
685. Akalın A, Ertuğrul İ, Şimşek-Kiper P, Utine GE, Boduroğlu K. Main physical features, echocardiographic and renal ultrasonographic findings of Turner syndrome in 107 pediatric patients. *Mol Syndromol.* 2021;12(6):335-341. <https://doi.org/10.1159/000516816>
686. Ogawa T, Takizawa F, Mukoyama Y, Ogawa A, Ito J. Renal morphology and function from childhood to adulthood in Turner syndrome. *Clin Exp Nephrol.* 2021;25(6):633-640. <https://doi.org/10.1007/s10157-021-02031-w>
687. Nicolaou N, Renkema KY, Bongers EM, Giles RH, Knoers NV. Genetic, environmental, and epigenetic factors involved in CAKUT. *Nat Rev Nephrol.* 2015;11(12):720-731. <https://doi.org/10.1038/nrneph.2015.140>
688. Bilge I, Kayserili H, Emre S, et al. Frequency of renal malformations in Turner syndrome: analysis of 82 Turkish children. *Pediatr Nephrol.* 2000;14(12):1111-1114. <https://doi.org/10.1007/s004670000315>
689. Seikaly MG, Ho PL, Emmett L, Fine RN, Tejani A. Chronic renal insufficiency in children: the 2001 annual report of the NAPRTCS. *Pediatr Nephrol.* 2003;18(8):796-804. <https://doi.org/10.1007/s00467-003-1158-5>
690. Pasquali L, d'Annunzio G, Gastaldi R, et al. Collectrin gene screening in Turner syndrome patients with kidney malformation. *J Genet.* 2009;88(1):105-108. <https://doi.org/10.1007/s12041-009-0015-0>
691. Izumita Y, Nishigaki S, Satoh M, et al. Retrospective study of the renal function using estimated glomerular filtration rate and congenital anomalies of the kidney-urinary tract in pediatric Turner syndrome. *Congenit Anom (Kyoto).* 2020;60(6):175-179. <https://doi.org/10.1111/cga.12384>
692. Chang P, Tsau YK, Tsai WY, et al. Renal malformations in children with Turner's syndrome. *J Formos Med Assoc.* 2000;99(10):796-798.
693. Álvarez-Nava F, Racines M, Witt J, Guarderas J, Estévez M, Lanes R. Anthropometric variables as cardiovascular risk predictors in a cohort of adult subjects with Turner syndrome. *Diabetes Metab Syndr Obes.* 2019;12:1795-1809. <https://doi.org/10.2147/DMSO.S214787>
694. Salem NA, Batouty NM, Tawfik AM, et al. Epicardial and perihepatic fat as cardiometabolic risk predictors in girls with Turner syndrome: a cardiac magnetic resonance study. *J Clin Res Pediatr Endocrinol.* 2021;13(4):408-417. <https://doi.org/10.4274/jcrpe.galenos.2021.2021.0030>
695. Hanew K, Tanaka T, Horikawa R, Hasegawa T, Fujita K, Yokoya S. Women with Turner syndrome are at high risk of lifestyle-related disease -from questionnaire surveys by the Foundation for Growth Science in Japan. *Endocr J.* 2016;63(5):449-456. <https://doi.org/10.1507/endocrj.EJ15-0288>
696. Kelley JC, Gutmark-Little I, Backeljauw P, Bamba V. Increased non-high-density lipoprotein cholesterol in children and young adults with Turner syndrome is not explained by BMI alone. *Horm Res Paediatr.* 2017;88(3-4):208-214. <https://doi.org/10.1159/000477761>
697. Malhotra R, Shukla R, Rastogi V, Khadgawat R. Isochromosome Xq and the risk of metabolic comorbidities in Turner syndrome. *Diabetes Metab Syndr.* 2023;17(2):102708. <https://doi.org/10.1016/j.dsx.2023.102708>
698. Baldin AD, Siviero-Miachon AA, Fabbri T, et al. Turner syndrome and metabolic derangements: another example of fetal programming. *Early Hum Dev.* 2011;88(2):99-102. <https://doi.org/10.1016/j.earlhumdev.2011.07.014>
699. Binder G, Frank L, Ziegler J, Blumenstock G, Schweizer R. Resting energy expenditure in girls with Turner syndrome. *J Pediatr Endocrinol Metab.* 2017;30(3):327-332. <https://doi.org/10.1515/jpem-2016-0295>
700. Gravholt CH, Klausen IC, Weeke J, Christiansen JS. Lp(a) and lipids in adult Turner's syndrome: impact of treatment with 17beta-estradiol and norethisterone. *Atherosclerosis.* 2000;150(1):201-208. [https://doi.org/10.1016/S0021-9150\(99\)00369-X](https://doi.org/10.1016/S0021-9150(99)00369-X)
701. Gravholt CH, Hjerrild BE, Mosekilde L, et al. Body composition is distinctly altered in Turner syndrome: relations to glucose metabolism, circulating adipokines, and endothelial adhesion molecules. *Eur J Endocrinol.* 2006;155(4):583-592. <https://doi.org/10.1530/eje.1.02267>

702. Akyürek N, Atabek ME, Ekliloglu BS, Alp H. The relationship of periaortic fat thickness and cardiovascular risk factors in children with Turner syndrome. *Pediatr Cardiol.* 2015;36(5):925-929. <https://doi.org/10.1007/s00246-015-1098-4>
703. Bakalov VK, Cheng C, Zhou J, Bondy CA. X-chromosome gene dosage and the risk of diabetes in Turner syndrome. *J Clin Endocrinol Metab.* 2009;94(9):3289-3296. <https://doi.org/10.1210/jc.2009-0384>
704. Ibarra-Gasparini D, Altieri P, Scarano E, *et al.* New insights on diabetes in Turner syndrome: results from an observational study in adulthood. *Endocrine.* 2018;59(3):651-660. <https://doi.org/10.1007/s12020-017-1336-z>
705. Sun L, Wang Y, Zhou T, *et al.* Glucose metabolism in Turner syndrome. *Front Endocrinol (Lausanne).* 2019;10:49. <https://doi.org/10.3389/fendo.2019.00049>
706. Jorgensen KT, Rostgaard K, Bache I, *et al.* Autoimmune diseases in women with Turner's syndrome. *Arthritis Rheum.* 2010;62(3):658-666. <https://doi.org/10.1002/art.27270>
707. Álvarez-Nava F, Bastidas D, Racines-Orbe M, Guarderas J. Insulin sensitivity and pancreatic β -cell function in Ecuadorian women with Turner syndrome. *Front Endocrinol (Lausanne).* 2020;11:482. <https://doi.org/10.3389/fendo.2020.00482>
708. Sheanon N, Elder D, Khoury J, *et al.* Increased prevalence of β -cell dysfunction despite normal HbA1c in youth and young adults with Turner syndrome. *Horm Res Paediatr.* 2021;94(7-8):297-306. <https://doi.org/10.1159/000520233>
709. Hjerrild BE, Holst JJ, Juhl CB, Christiansen JS, Schmitz O, Gravholt CH. Delayed beta-cell response and glucose intolerance in young women with Turner syndrome. *BMC Endocr Disord.* 2011;11:6(1):6. <https://doi.org/10.1186/1472-6823-11-6>
710. Sandberg DE, Singer D, Bugajski B, *et al.* Research priorities of people living with Turner syndrome. *Am J Med Genet C Semin Med Genet.* 2019;181(1):43-51. <https://doi.org/10.1002/ajmg.c.31676>
711. Baldin AD, Fabbri T, Siviero-Miachon AA, *et al.* Effects of growth hormone on body proportions in Turner syndrome compared with non-treated patients and normal women. *J Endocrinol Invest.* 2010;33(10):691-695. <https://doi.org/10.1007/BF03346671>
712. Segerer SE, Segerer SG, Partsch CJ, Becker W, Nawroth F. Increased insulin concentrations during growth hormone treatment in girls with Turner syndrome are ameliorated by hormone replacement therapy. *Front Endocrinol (Lausanne).* 2020;11:586055. <https://doi.org/10.3389/fendo.2020.586055>
713. Dyrka K, Rozkiewicz N, Obara-Moszynska M, Niedziela M. The influence of growth hormone therapy on the cardiovascular system in Turner syndrome. *J Pediatr Endocrinol Metab.* 2020;33(11):1363-1372. <https://doi.org/10.1515/jpem-2020-0266>
714. Calanchini M, Moolla A, Tomlinson JW, *et al.* Liver biochemical abnormalities in Turner syndrome: a comprehensive characterization of an adult population. *Clin Endocrinol (Oxf).* 2018;89(5):667-676. <https://doi.org/10.1111/cen.13811>
715. Bourcigaux N, Dubost E, Buzzi JC, *et al.* Focus on liver function abnormalities in patients with Turner syndrome: risk factors and evaluation of fibrosis risk. *J Clin Endocrinol Metab.* 2023;108(9):2255-2261. <https://doi.org/10.1210/clinem/dgad108>
716. Gravholt CH, Juul S, Naeraa RW, Hansen J. Morbidity in Turner syndrome. *J Clin Epidemiol.* 1998;51(2):147-158. [https://doi.org/10.1016/S0895-4356\(97\)00237-0](https://doi.org/10.1016/S0895-4356(97)00237-0)
717. Yamamura S, Eslam M, Kawaguchi T, *et al.* MAFLD identifies patients with significant hepatic fibrosis better than NAFLD. *Liver Int.* 2020;40(12):3018-3030. <https://doi.org/10.1111/liv.14675>
718. Cusi K, Isaacs S, Barb D, *et al.* American Association of Clinical Endocrinology clinical practice guideline for the diagnosis and management of nonalcoholic fatty liver disease in primary care and endocrinology clinical settings: co-sponsored by the American Association for the Study of Liver Diseases (AASLD). *Endocr Pract.* 2022;28(5):528-562. <https://doi.org/10.1016/j.eprac.2022.03.010>
719. Fedor I, Zold E, Barta Z. Liver abnormalities in Turner syndrome: the importance of estrogen replacement. *J Endocr Soc.* 2022;6(10):bvac124. <https://doi.org/10.1210/jendso/bvac124>
720. Ching AS, Zhang X, Furuya KN, Benoy ME, Bartlett HL. Turner syndrome may be associated with hepatic adenoma. *Am J Med Genet A.* 2023;191(10):2578-2584. <https://doi.org/10.1002/ajmg.a.63341>
721. Lazarus JV, Mark HE, Anstee QM, *et al.* Advancing the global public health agenda for NAFLD: a consensus statement. *Nat Rev Gastroenterol Hepatol.* 2022;19(1):60-78. <https://doi.org/10.1038/s41575-021-00523-4>
722. Bischoff SC, Barazzoni R, Busetto L, *et al.* European guideline on obesity care in patients with gastrointestinal and liver diseases—joint European Society for Clinical Nutrition and Metabolism / United European Gastroenterology Guideline. *United European Gastroenterol J.* 2022;10(7):663-720. <https://doi.org/10.1002/ueg2.12280>
723. Villanueva-Ortega E, Ahedo B, Fonseca-Sánchez MA, *et al.* Analysis of PTPN22, ZFAT and MYO9B polymorphisms in Turner syndrome and risk of autoimmune disease. *Int J Immunogenet.* 2017;44(4):153-157. <https://doi.org/10.1111/iji.12323>
724. Al-Bluwi GSM, AlNababteh AH, Östlundh L, Al-Shamsi S, Al-Rifai RH. Prevalence of celiac disease in patients with Turner syndrome: systematic review and meta-analysis. *Front Med (Lausanne).* 2021;8:674896. <https://doi.org/10.3389/fmed.2021.674896>
725. Marild K, Stordal K, Hagman A, Ludvigsson JF. Turner syndrome and celiac disease: a case-control study. *Pediatrics.* 2016;137(2):e20152232. <https://doi.org/10.1542/peds.2015-2232>
726. Naessén S, Eliasson M, Berntorp K, *et al.* Autoimmune disease in Turner syndrome in Sweden: an up to 25 years' controlled follow-up study. *J Clin Endocrinol Metab.* 2024;109(2):e602-e612. <https://doi.org/10.1210/clinem/dgad566>
727. Al-Toma A, Volta U, Auricchio R, *et al.* European society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders. *United European Gastroenterol J.* 2019;7(5):583-613. <https://doi.org/10.1177/2050640619844125>
728. Dirvanskyte P, Gurram B, Bolton C, *et al.* Chromosomal numerical aberrations and rare copy number variation in patients with inflammatory Bowel disease. *J Crohns Colitis.* 2023;17(1):49-60. <https://doi.org/10.1093/ecco-jcc/fjac103>
729. Gatti S, Gelzoni G, Catassi GN, Catassi C. The clinical spectrum of inflammatory Bowel disease associated with specific genetic syndromes: two novel pediatric cases and a systematic review. *Front Pediatr.* 2021;9:742830. <https://doi.org/10.3389/fped.2021.742830>
730. Elsheikh M, Dunger DB, Conway GS, Wass JA. Turner's syndrome in adulthood. *Endocr Rev.* 2002;23(1):120-140. <https://doi.org/10.1210/edrv.23.1.0457>
731. Hayward PA, Satsangi J, Jewell DP. Inflammatory bowel disease and the X chromosome. *QJM.* 1996;89(9):713-718. <https://doi.org/10.1093/qjmed/89.9.713>
732. Keating E, Kelleher TB, Lahiff C. De novo anti-TNF- α -induced congestive heart failure in a patient with Turner syndrome and Crohn's disease. *Inflamm Bowel Dis.* 2020;26(12):e161-e162. <https://doi.org/10.1093/ibd/izaa176>
733. Kucharska A, Józefczuk P, Książyk M, Labochka D, Banaszkiwicz A. Gastrointestinal vascular malformations in patients with Turner's syndrome: a systematic review of case reports. *Horm Res Paediatr.* 2018;90(1):39-43. <https://doi.org/10.1159/000490425>
734. Witkowska-Krawczak E, Zapolska A, Banaszkiwicz A, Kucharska A. Recurrent gastrointestinal bleeding due to vascular malformations in a girl with Turner syndrome. *Pediatr Endocrinol Diabetes Metab.* 2021;27(3):222-226. <https://doi.org/10.5114/pedm.2021.107722>

735. Bakalov VK, Bondy CA. Fracture risk and bone mineral density in Turner syndrome. *Rev Endocr Metab Disord*. 2008;9(2):145-151. <https://doi.org/10.1007/s11154-008-9076-2>
736. Gravholt CH, Vestergaard P, Hermann AP, Mosekilde L, Brixen K, Christiansen JS. Increased fracture rates in Turner's syndrome: a nationwide questionnaire survey. *Clin Endocrinol (Oxf)*. 2003;59(1):89-96. <https://doi.org/10.1046/j.1365-2265.2003.01807.x>
737. Shi K, Liu L, He YJ, et al. Body composition and bone mineral status in patients with Turner syndrome. *Sci Rep*. 2016;6(1):38026. <https://doi.org/10.1038/srep38026.38026>
738. Soucek O, Lebl J, Snajderova M, et al. Bone geometry and volumetric bone mineral density in girls with Turner syndrome of different pubertal stages. *Clin Endocrinol (Oxf)*. 2011;74(4):445-452. <https://doi.org/10.1111/j.1365-2265.2010.03955.x>
739. Schweizer R, Mayer J, Binder G. Normal bone density but altered geometry in girls with Turner syndrome. *J Pediatr Endocrinol Metab*. 2023;36(3):270-277. <https://doi.org/10.1515/jpem-2022-0516>
740. Aycan Z, Cetinkaya E, Darendeliler F, et al. The effect of growth hormone treatment on bone mineral density in prepubertal girls with Turner syndrome: a multicentre prospective clinical trial. *Clin Endocrinol (Oxf)*. 2008;68(5):769-772. <https://doi.org/10.1111/j.1365-2265.2007.03107.x>
741. Carrascosa A, Gussinye M, Terradas P, Yeste D, Audi L, Vicens-Calvet E. Spontaneous, but not induced, puberty permits adequate bone mass acquisition in adolescent Turner syndrome patients. *J Bone Miner Res*. 2000;15(10):2005-2010. <https://doi.org/10.1359/jbmr.2000.15.10.2005>
742. Nabhan ZM, Feezle LK, Kunselman AR, Johnson NB, Lee PA. Normal adult height among girls treated for central precocious puberty with gonadotropin-releasing hormone analog therapy. *J Pediatr Endocrinol Metab*. 2009;22(4):309-316. <https://doi.org/10.1515/JPEM.2009.22.4.309>
743. Landin-Wilhelmsen K, Bryman I, Windh M, Wilhelmsen L. Osteoporosis and fractures in Turner syndrome—importance of growth promoting and oestrogen therapy. *Clin Endocrinol (Oxf)*. 1999;51(4):497-502. <https://doi.org/10.1046/j.1365-2265.1999.00841.x>
744. Augoulea A, Zachou G, Lambrinouadaki I. Turner syndrome and osteoporosis. *Maturitas*. 2019;130:41-49. <https://doi.org/10.1016/j.maturitas.2019.09.010>
745. Nordenström A, Ahmed SF, van den Akker E, et al. Pubertal induction and transition to adult sex hormone replacement in patients with congenital pituitary or gonadal reproductive hormone deficiency: an Endo-ERN clinical practice guideline. *Eur J Endocrinol*. 2022;186(6):G9-G49. <https://doi.org/10.1530/EJE-22-0073>
746. Herrick KA, Storandt RJ, Afful J, et al. Vitamin D status in the United States, 2011–2014. *Am J Clin Nutr*. 2019;110(1):150-157. <https://doi.org/10.1093/ajcn/nqz037>
747. Kondapalli AV, Walker MD. Celiac disease and bone. *Arch Endocrinol Metab*. 2022;66(5):756-764. <https://doi.org/10.20945/2359-3997000000561>
748. Chedid VG, Kane SV. Bone health in patients with inflammatory Bowel diseases. *J Clin Densitom*. 2020;23(2):182-189. <https://doi.org/10.1016/j.jocd.2019.07.009>
749. Brunetti G, D'Amato G, De Santis S, Grano M, Faienza MF. Mechanisms of altered bone remodeling in children with type 1 diabetes. *World J Diabetes*. 2021;12(7):997-1009. <https://doi.org/10.4239/wjd.v12.i7.997>
750. Zhu X, Li M, Dong X, Liu F, Li S, Hu Y. A systematic review of the relationship between normal range of serum thyroid-stimulating hormone and bone mineral density in the postmenopausal women. *BMC Womens Health*. 2023;23(1):358. <https://doi.org/10.1186/s12905-023-02488-9>
751. Hansen S, Brixen K, Gravholt CH. Compromised trabecular microarchitecture and lower finite element estimates of radius and tibia bone strength in adults with Turner syndrome: a cross-sectional study using high-resolution-pQCT. *J Bone Miner Res*. 2012;27(8):1794-1803. <https://doi.org/10.1002/jbmr.1624>
752. Ikegawa K, Hasegawa Y. Fracture risk, underlying pathophysiology, and bone quality assessment in patients with Turner syndrome. *Front Endocrinol (Lausanne)*. 2022;13:967857. <https://doi.org/10.3389/fendo.2022.967857>
753. Zemel BS, Leonard MB, Kelly A, et al. Height adjustment in assessing dual energy x-ray absorptiometry measurements of bone mass and density in children. *J Clin Endocrinol Metab*. 2010;95(3):1265-1273. <https://doi.org/10.1210/jc.2009-2057>
754. Kindler JM, Lappe JM, Gilsanz V, et al. Lumbar spine bone mineral apparent density in children: results from the bone mineral density in childhood study. *J Clin Endocrinol Metab*. 2019;104(4):1283-1292. <https://doi.org/10.1210/jc.2018-01693>
755. Crabtree NJ, Shaw NJ, Bishop NJ, et al. Amalgamated reference data for size-adjusted bone densitometry measurements in 3598 children and young adults—the ALPHABET study. *J Bone Miner Res*. 2017;32(1):172-180. <https://doi.org/10.1002/jbmr.2935>
756. Faienza MF, Ventura A, Colucci S, Cavallo L, Grano M, Brunetti G. Bone fragility in Turner syndrome: mechanisms and prevention strategies. *Front Endocrinol (Lausanne)*. 2016;7:34. <https://doi.org/10.3389/fendo.2016.00034>
757. Han TS, Cadge B, Conway GS. Hearing impairment and low bone mineral density increase the risk of bone fractures in women with Turner's syndrome. *Clin Endocrinol (Oxf)*. 2006;65(5):643-647. <https://doi.org/10.1111/j.1365-2265.2006.02643.x>
758. Cardona Attard C, Cameron-Pimblett A, Puri D, et al. Fracture rate in women with oestrogen deficiency—comparison of Turner syndrome and premature ovarian insufficiency. *Clin Endocrinol (Oxf)*. 2019;91(6):743-749. <https://doi.org/10.1111/cen.14110>
759. Alqahtani FF, Offiah AC. Diagnosis of osteoporotic vertebral fractures in children. *Pediatr Radiol*. 2019;49(3):283-296. <https://doi.org/10.1007/s00247-018-4279-5>
760. Bachrach LK, Gordon CM; SECTION ON ENDOCRINOLOGY. Bone densitometry in children and adolescents. *Pediatrics*. 2016;138(4):e20162398. <https://doi.org/10.1542/peds.2016-2398>
761. Acosta AM, Steinman SE, White KK. Orthopaedic manifestations in Turner syndrome. *J Am Acad Orthop Surg*. 2019;27(23):e1021-e1028. <https://doi.org/10.5435/JAAOS-D-17-00796>
762. Mondal S, Bhattacharjee R, Chowdhury S, Mukhopadhyay S. Karyotype-phenotype correlation in Turner syndrome at a single center in Eastern India. *Indian Pediatr*. 2021;58(1):34-37. <https://doi.org/10.1007/s13312-021-2093-x>
763. Wu HH, Li H. Karyotype classification, clinical manifestations and outcome in 124 Turner syndrome patients in China. *Ann Endocrinol (Paris)*. 2019;80(1):10-15. <https://doi.org/10.1016/j.ando.2017.10.011>
764. Bucerzan S, Miclea D, Popp R, et al. Clinical and genetic characteristics in a group of 45 patients with Turner syndrome (monocentric study). *Ther Clin Risk Manag*. 2017;13:613-622. <https://doi.org/10.2147/TCRM.S126301>
765. Frelich J, Irzyniec T, Lepska K, Jeż W. New insights into clinical features, karyotypes, and age at diagnosis in women with Turner syndrome. *Endokrynol Pol*. 2019;70(4):342-349. <https://doi.org/10.5603/EP.a2019.0016>
766. Kilinc S, Yildiz M, Guven A. Associated clinical abnormalities among patients with Turner syndrome. *North Clin Istanbul*. 2020;7(3):226-230. <https://doi.org/10.14744/nci.2019.84758>
767. Miguel-Neto J, Carvalho AB, Marques-de-Faria AP, Guerra-Júnior G, Maciel-Guerra AT. New approach to phenotypic variability and karyotype-phenotype correlation in Turner syndrome. *J Pediatr Endocrinol Metab*. 2016;29(4):475-479. <https://doi.org/10.1515/jpem-2015-0346>
768. Trzcinska D, Olszewska E, Wisniewski A, Milde K, Madej M. The knee alignment and the foot arch in patients with Turner syndrome. *Pediatr Endocrinol Diabetes Metab*. 2011;17(3):138-144.
769. Clement-Jones M, Schiller S, Rao E, et al. The short stature homeobox gene SHOX is involved in skeletal abnormalities in

- Turner syndrome. *Hum Mol Genet.* 2000;9(5):695-702. <https://doi.org/10.1093/hmg/9.5.695>
770. Day G, Szvetko A, Griffiths L, et al. SHOX gene is expressed in vertebral body growth plates in idiopathic and congenital scoliosis: implications for the etiology of scoliosis in Turner syndrome. *J Orthop Res.* 2009;27(6):807-813. <https://doi.org/10.1002/jor.20801>
771. Ricotti S, Petrucci L, Carenzio G, et al. Prevalence and incidence of scoliosis in Turner syndrome: a study in 49 girls followed-up for 4 years. *Eur J Phys Rehabil Med.* 2011;47(3):447-453.
772. Kim SE, Park SH, Han K, Cho WK, Suh BK, Park YG. Population prevalence, cancer risk, and mortality risk of Turner syndrome in south Korean women based on national health insurance service data. *Yonsei Med J.* 2022;63(11):991-998. <https://doi.org/10.3349/ymj.2022.0143>
773. Karila D, Donadille B, Léger J, et al. Prevalence and characteristics of gonadoblastoma in a retrospective multi-center study with follow-up investigations of 70 patients with Turner syndrome and a 45,X/46,XY karyotype. *Eur J Endocrinol.* 2022;187(6):873-881. <https://doi.org/10.1530/EJE-22-0593>
774. Dabrowski E, Johnson EK, Patel V, et al. Turner syndrome with Y chromosome: spontaneous thelarche, menarche, and risk of malignancy. *J Pediatr Adolesc Gynecol* 2020;33(1):10-14. <https://doi.org/10.1016/j.jpag.2019.08.011>
775. Mittal S, Weaver J, Aghababian A, et al. Deferring gonadectomy in patients with Turner syndrome with a genetic Y component is not a safe practice. *J Pediatr Urol.* 2023;19(3):294.e1-294.e5. <https://doi.org/10.1016/j.jpuro.2022.12.012>
776. Mortensen KH, Cleemann L, Hjerrild BE, et al. Increased prevalence of autoimmunity in Turner syndrome—influence of age. *Clin Exp Immunol.* 2009;156(2):205-210. <https://doi.org/10.1111/j.1365-2249.2009.03895.x>
777. Lee YL, Zaini AA, Idris AN, et al. Thyroid autoimmunity and autoimmune thyroid disease in Malaysian girls with Turner syndrome: an understudied population. *J Paediatr Child Health.* 2023;59(7):879-884. <https://doi.org/10.1111/jpc.16405>
778. Mohamed SOO, Elkhidir IHE, Abuzied AIH, Noureddin AAMH, Ibrahim GAA, Mahmoud AAA. Prevalence of autoimmune thyroid diseases among the Turner syndrome patients: meta-analysis of cross sectional studies. *BMC Res Notes.* 2018;11(1):842. <https://doi.org/10.1186/s13104-018-3950-0>
779. Chenbhanich J, Ungprasert P, Kroner PT. Inpatient epidemiology, healthcare utilization, and association with comorbidities of Turner syndrome: a national inpatient sample study. *Am J Med Genet A.* 2023;191(7):1870-1877. <https://doi.org/10.1002/ajmg.a.63217>
780. Gawlik AM, Berdej-Szczot E, Blat D, et al. Immunological profile and predisposition to autoimmunity in girls with Turner syndrome. *Front Endocrinol (Lausanne).* 2018;9:307. <https://doi.org/10.3389/fendo.2018.00307>
781. Kanakatti Shankar R. Immunological profile and autoimmunity in Turner syndrome. *Horm Res Paediatr.* 2020;93(7-8):415-422. <https://doi.org/10.1159/000512904>
782. Stoklasova J, Zapletalova J, Frysak Z, et al. An isolated Xp deletion is linked to autoimmune diseases in Turner syndrome. *J Pediatr Endocrinol Metab.* 2019;32(5):479-488. <https://doi.org/10.1515/jpem-2019-0067>
783. Hanew K, Tanaka T, Horikawa R, Hasegawa T, Yokoya S. Prevalence of diverse complications and its association with karyotypes in Japanese adult women with Turner syndrome—a questionnaire survey by the Foundation for Growth Science. *Endocr J.* 2018;65(5):509-519. <https://doi.org/10.1507/endocrj.EJ17-0401>
784. Vrtel P, Vrtel R, Klaskova E, et al. Haplotype analysis of the X chromosome in patients with Turner syndrome in order to verify the possible effect of imprinting on selected symptoms. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub.* 2022;166(1):63-67. <https://doi.org/10.5507/bp.2020.060>
785. Malhotra R, Shukla R, Kabra M, Gupta Y, Jyotsna VP, Khadgawat R. Impact of parental origin of X-chromosome on clinical and biochemical profile in Turner syndrome. *J Pediatr Endocrinol Metab.* 2020;33(9):1155-1163. <https://doi.org/10.1515/jpem-2020-0104>
786. Pereira AM, Hiort O. Introduction to Endo-ERN-scope and mission. *Endocrine.* 2021;71(3):537-538. <https://doi.org/10.1007/s12020-020-02602-z>
787. Osei-Twum JA, Wiles B, Killackey T, Mahood Q, Lalloo C, Stinson JN. Impact of project ECHO on patient and community health outcomes: a scoping review. *Acad Med.* 2022;97(9):1393-1402. <https://doi.org/10.1097/ACM.0000000000004749>
788. Fiot E, Alauze B, Donadille B, et al. Turner syndrome: French national diagnosis and care protocol (NDCP; National Diagnosis and Care Protocol). *Orphanet J Rare Dis.* 2022;17(Suppl 1):261. <https://doi.org/10.1186/s13023-022-02423-5>
789. Duis J, van Wattum PJ, Scheimann A, et al. A multidisciplinary approach to the clinical management of Prader-Willi syndrome. *Mol Genet Genomic Med.* 2019;7(3):e514. <https://doi.org/10.1002/mgg3.514>
790. Grosse SD, Schechter MS, Kulkarni R, Lloyd-Puryear MA, Strickland B, Trevathan E. Models of comprehensive multidisciplinary care for individuals in the United States with genetic disorders. *Pediatrics.* 2009;123(1):407-412. <https://doi.org/10.1542/peds.2007-2875>
791. Kremen J, Davis SM, Nahata L, et al. Neuropsychological and mental health concerns in a multicenter clinical sample of youth with Turner syndrome. *Am J Med Genet A.* 2023;191(4):962-976. <https://doi.org/10.1002/ajmg.a.63103>
792. Garcia JF, Faye E, Reid MW, et al. Greater telehealth use results in increased visit frequency and lower physician related-distress in adolescents and young adults with type 1 diabetes. *J Diabetes Sci Technol.* 2023;17(4):878-886. <https://doi.org/10.1177/19322968221146806>
793. Vagg T, Shanthikumar S, Morrissy D, Chapman WW, Plant BJ, Ranganathan S. Telehealth and virtual health monitoring in cystic fibrosis. *Curr Opin Pulm Med.* 2021;27(6):544-553. <https://doi.org/10.1097/MCP.0000000000000821>
794. Raymond JK, Reid MW, Fox S, et al. Adapting home telehealth group appointment model (CoYoT1 clinic) for a low SES, publicly insured, minority young adult population with type 1 diabetes. *Contemp Clin Trials.* 2020;88:105896. <https://doi.org/10.1016/j.cct.2019.105896>
795. Curfman A, McSwain SD, Chuo J, et al. Pediatric telehealth in the COVID-19 pandemic era and beyond. *Pediatrics.* 2021;148(3):e2020047795. <https://doi.org/10.1542/peds.2020-047795>
796. Berkanish P, Pan S, Viola A, Rademaker Q, Devine KA. Technology-based peer support interventions for adolescents with chronic illness: a systematic review. *J Clin Psychol Med Settings.* 2022;29(4):911-942. <https://doi.org/10.1007/s10880-022-09853-0>
797. Prakash SK, Lugo-Ruiz S, Rivera-Davila M, et al. The Turner syndrome research registry: creating equipoise between investigators and participants. *Am J Med Genet C Semin Med Genet.* 2019;181(1):135-140. <https://doi.org/10.1002/ajmg.c.31689>
798. Purwar N, Tiwari P, Mathur N, et al. Higher CNV frequencies in chromosome 14 of girls with Turner syndrome phenotype. *J Clin Endocrinol Metab.* 2021;106(12):e4935-e4955. <https://doi.org/10.1210/clinem/dgab572>
799. Berglund A, Viuff MH, Skakkebaek A, Chang S, Stochholm K, Gravholt CH. Changes in the cohort composition of Turner syndrome and severe non-diagnosis of Klinefelter, 47,XXX and 47, XYY syndrome: a nationwide cohort study. *Orphanet J Rare Dis.* 2019;14(1):16-0976. <https://doi.org/10.1186/s13023-018-0976-2>
800. Tuke MA, Ruth KS, Wood AR, et al. Mosaic Turner syndrome shows reduced penetrance in an adult population study. *Genet Med.* 2019;21(4):877-886. <https://doi.org/10.1038/s41436-018-0271-6>
801. Prakash SK, Crenshaw ML, Backeljauw PF, et al. 45,X mosaicism in a population-based biobank: implications for Turner syndrome.

- Genet Med.* 2019;21(8):1882-1883. <https://doi.org/10.1038/s41436-018-0411-z>
802. Kuntsi J, Skuse D, Elgar K, Morris E, Turner C. Ring-X chromosomes: their cognitive and behavioural phenotype. *Am Hum Genet.* 2000;64(4):295-305. <https://doi.org/10.1046/j.1469-1809.2000.6440295.x>
803. Fryns JP, Kleczkowska A, Van den Berghe H. High incidence of mental retardation in Turner syndrome patients with ring chromosome X formation. *Genet Couns.* 1990;1(2):161-165.
804. Leppig KA, Sybert VP, Ross JL, et al. Phenotype and X inactivation in 45,X/46,X,r(X) cases. *Am J Med Genet.* 2004;128A(3):276-284. <https://doi.org/10.1002/ajmg.a.30002>
805. Turner C, Dennis NR, Skuse DH, Jacobs PA. Seven ring (X) chromosomes lacking the XIST locus, six with an unexpectedly mild phenotype. *Hum Genet.* 2000;106(1):93-100. <https://doi.org/10.1007/s004399900221>
806. Viuff M, Skakkebaek A, Nielsen MM, Chang S, Gravholt CH. Epigenetics and genomics in Turner syndrome. *Am J Med Genet C Semin Med Genet.* 2019;181(1):68-75. <https://doi.org/10.1002/ajmg.c.31683>
807. Nielsen MM, Trolle C, Vang S, et al. Epigenetic and transcriptomic consequences of excess X-chromosome material in 47,XXX syndrome-A comparison with Turner syndrome and 46,XX females. *Am J Med Genet C Semin Med Genet.* 2020;184(2):279-293. <https://doi.org/10.1002/ajmg.c.31799>
808. Barr M, Jr., Oman-Ganes L. Turner syndrome morphology and morphometrics: cardiac hypoplasia as a cause of midgestation death. *Teratology.* 2002;66(2):65-72. <https://doi.org/10.1002/tera.10064>
809. De Asis-Cruz J, Limperopoulos C. Harnessing the power of advanced fetal neuroimaging to understand in utero footprints for later neuropsychiatric disorders. *Biol Psychiatry.* 2023;93(10):867-879. <https://doi.org/10.1016/j.biopsych.2022.11.019>
810. Sadhwani A, Wypij D, Rofeberg V, et al. Fetal brain volume predicts neurodevelopment in congenital heart disease. *Circulation.* 2022;145(15):1108-1119. <https://doi.org/10.1161/CIRCULATIONAHA.121.056305>
811. Mathisen B, Reilly S, Skuse D. Oral-motor dysfunction and feeding disorders of infants with Turner syndrome. *Dev Med Child Neurol.* 1992;34(2):141-149. <https://doi.org/10.1111/j.1469-8749.1992.tb14980.x>
812. Van Borsel J, Dhooge I, Verhoye K, Derde K, Curfs L. Communication problems in Turner syndrome: a sample survey. *J Commun Disord.* 1999;32(6):435-444. quiz 444-436. [https://doi.org/10.1016/S0021-9924\(99\)00020-9](https://doi.org/10.1016/S0021-9924(99)00020-9)
813. Pretzel RE, Knickmeyer RC, DeRamus M, et al. Early development of infants with Turner syndrome. *J Dev Behav Pediatr.* 2020;41(6):470-479. <https://doi.org/10.1097/DBP.0000000000000788>
814. Wolstencroft J, Mandy W, Skuse D. Mental health and neurodevelopment in children and adolescents with Turner syndrome. *Womens Health (Lond).* 2022;18:17455057221133635. <https://doi.org/10.1177/17455057221133635>
815. Sánchez XC, Montalbano S, Vaez M, et al. Associations of psychiatric disorders with sex chromosome aneuploidies in the Danish iPSYCH2015 dataset: a case-cohort study. *Lancet Psychiatry.* 2023;10(2):129-138. [https://doi.org/10.1016/S2215-0366\(23\)00004-4](https://doi.org/10.1016/S2215-0366(23)00004-4)
816. Reinhartsen DB, Cornea E, DeRamus M, et al. Turner syndrome: language profile of young girls at 12 and 24 months of age. *J Neurodev Disord.* 2021;13(1):52. <https://doi.org/10.1186/s11689-021-09401-1>
817. Davenport ML, Cornea E, Xia K, et al. Altered brain structure in infants with Turner syndrome. *Cereb Cortex.* 2020;30(2):587-596. <https://doi.org/10.1093/cercor/bhz109>
818. Cook J, Hull L, Crane L, Mandy W. Camouflaging in autism: a systematic review. *Clin Psychol Rev.* 2021;89:102080. <https://doi.org/10.1016/j.cpr.2021.102080>
819. Pennington BF, Heaton RK, Karzmark P, Pendleton MG, Lehman R, Shucard DW. The neuropsychological phenotype in Turner syndrome. *Cortex.* 1985;21(3):391-404. [https://doi.org/10.1016/S0010-9452\(85\)80004-6](https://doi.org/10.1016/S0010-9452(85)80004-6)
820. Baker JM, Klabunde M, Jo B, Green T, Reiss AL. On the relationship between mathematics and visuospatial processing in Turner syndrome. *J Psychiatr Res.* 2020;121:135-142. <https://doi.org/10.1016/j.jpsychires.2019.11.004>
821. Pennington BF, Bender B, Puck M, Salbenblatt J, Robinson A. Learning disabilities in children with sex chromosome anomalies. *Child Dev.* 1982;53(5):1182-1192. <https://doi.org/10.2307/1129006>
822. Rovet JF. The psychoeducational characteristics of children with Turner syndrome. *J Learn Disabil.* 1993;26(5):333-341. <https://doi.org/10.1177/002221949302600506>
823. Mazzocco MM. Math learning disability and math LD subtypes: evidence from studies of Turner syndrome, fragile X syndrome, and neurofibromatosis type 1. *J Learn Disabil.* 2001;34(6):520-533. <https://doi.org/10.1177/002221940103400605>
824. Murphy MM, Mazzocco MM, Gerner G, Henry AE. Mathematics learning disability in girls with Turner syndrome or fragile X syndrome. *Brain Cogn.* 2006;61(2):195-210. <https://doi.org/10.1016/j.bandc.2005.12.014>
825. Baker JM, Reiss AL. A meta-analysis of math performance in Turner syndrome. *Dev Med Child Neurol.* 2016;58(2):123-130. <https://doi.org/10.1111/dmcn.12961>
826. Karipidis II, Hong DS. Specific learning disorders in sex chromosome aneuploidies: neural circuits of literacy and mathematics. *Am J Med Genet C Semin Med Genet.* 2020;184(2):518-530. <https://doi.org/10.1002/ajmg.c.31801>
827. Green T, Naylor PE, Davies W. Attention deficit hyperactivity disorder (ADHD) in phenotypically similar neurogenetic conditions: Turner syndrome and the RASopathies. *J Neurodev Disord.* 2017;9(1):25. <https://doi.org/10.1186/s11689-017-9205-x>
828. Russell HF, Wallis D, Mazzocco MM, et al. Increased prevalence of ADHD in Turner syndrome with no evidence of imprinting effects. *J Pediatr Psychol.* 2006;31(9):945-955. <https://doi.org/10.1093/jpepsy/psj106>
829. Björln Avidic H, Kleberg JL, van der Poll M, et al. Cognitive profile in adult women with Turner syndrome: IQ split and associations with ADHD and ASD. *Cogn Neuropsychiatry.* 2023;28(3):207-225. <https://doi.org/10.1080/13546805.2023.2209312>
830. Saad K, Abdelrahman AA, Abdel-Raheem YF, et al. Turner syndrome: review of clinical, neuropsychiatric, and EEG status: an experience of tertiary center. *Acta Neurol Belg.* 2014;114(1):1-9. <https://doi.org/10.1007/s13760-013-0264-9>
831. Temple CM. Oral fluency and narrative production in children with Turner's syndrome. *Neuropsychologia.* 2002;40(8):1419-1427. [https://doi.org/10.1016/S0028-3932\(01\)00201-9](https://doi.org/10.1016/S0028-3932(01)00201-9)
832. Carl A, Good M, Haag E, et al. Anxiety in Turner syndrome: engaging community to address barriers and facilitators to diagnosis and care [published online ahead of print March 25, 2024]. *Am J Med Genet A.* <https://doi.org/10.1002/ajmg.a.63564>
833. Lozano Wun V, Foland-Ross LC, Jo B, et al. Adolescent brain development in girls with Turner syndrome. *Hum Brain Mapp.* 2023;44(10):4028-4039. <https://doi.org/10.1002/hbm.26327>
834. Xie S, Yang J, Zhang Z, et al. The effects of the X chromosome on intrinsic functional connectivity in the human brain: evidence from Turner syndrome patients. *Cereb Cortex.* 2017;27(1):474-484. <https://doi.org/10.1093/cercor/bhv240>
835. Alexandrou E, Corathers S, Gutmark-Little I, et al. Improving anxiety screening in patients with Turner syndrome. *Horm Res Paediatr.* 2022;95(1):68-75. <https://doi.org/10.1159/000524169>
836. Morris LA, Tishelman AC, Kremen J, Ross RA. Depression in Turner syndrome: a systematic review. *Arch Sex Behav.* 2020;49(2):769-786. <https://doi.org/10.1007/s10508-019-01549-1>
837. Björln Avidic H, Butwicka A, Nordenström A, et al. Neurodevelopmental and psychiatric disorders in females with Turner syndrome: a population-based study. *J Neurodev Disord.* 2021;13(1):51. <https://doi.org/10.1186/s11689-021-09399-6>

838. Knickmeyer RC, Hooper SR. The deep biology of cognition: moving toward a comprehensive neurodevelopmental model of Turner syndrome. *Am J Med Genet C Semin Med Genet.* 2019;181(1):91-99. <https://doi.org/10.1002/ajmg.c.31679>
839. Green T, Bade SS, Chromik LC, et al. Elucidating X chromosome influences on attention deficit hyperactivity disorder and executive function. *J Psychiatr Res.* 2015;68:217-225. <https://doi.org/10.1016/j.jpsychires.2015.06.021>
840. Knouse LE, Hu X, Sachs G, Isaacs S. Usability and feasibility of a cognitive-behavioral mobile app for ADHD in adults. *PLOS Digit Health.* 2022;1(8):e0000083. <https://doi.org/10.1371/journal.pdig.0000083>
841. Andersen AC, Sund AM, Thomsen PH, Lydersen S, Young S, Nøvik TS. Cognitive behavioural group therapy for adolescents with ADHD: a study of satisfaction and feasibility. *Nord J Psychiatry.* 2022;76(4):280-286. <https://doi.org/10.1080/08039488.2021.1965212>
842. Pan MR, Zhang SY, Qiu SW, et al. Efficacy of cognitive behavioural therapy in medicated adults with attention-deficit/hyperactivity disorder in multiple dimensions: a randomised controlled trial. *Eur Arch Psychiatry Clin Neurosci.* 2022;272(2):235-255. <https://doi.org/10.1007/s00406-021-01236-0>
843. Jensen CM, Amdisen BL, Jørgensen KJ, Arnfred SM. Cognitive behavioural therapy for ADHD in adults: systematic review and meta-analyses. *Atten Defic Hyperact Disord.* 2016;8(1):3-11. <https://doi.org/10.1007/s12402-016-0188-3>
844. Hutaff-Lee C, Bennett E, Howell S, Tartaglia N. Clinical developmental, neuropsychological, and social-emotional features of Turner syndrome. *Am J Med Genet C Semin Med Genet.* 2019;181(1):126-134. <https://doi.org/10.1002/ajmg.c.31687>
845. Jez W, Tobiasz-Adamczyk B, Brzyski P, Majkiewicz M, Pankiewicz P, Irzyniec TJ. Social and medical determinants of quality of life and life satisfaction in women with Turner syndrome. *Adv Clin Exp Med.* 2018;27(2):229-236. <https://doi.org/10.17219/acem/66986>
846. Lagrou K, Froidecoeur C, Verlinde F, et al. Psychosocial functioning, self-perception and body image and their auxologic correlates in growth hormone and oestrogen treated young adult women with Turner syndrome. *Horm Res.* 2006;66(6):277-284. <https://doi.org/10.1159/000095547>
847. Verlinde F, Massa G, Lagrou K, et al. Health and psychosocial status of patients with Turner syndrome after transition to adulthood: the Belgian experience. *Horm Res.* 2004;62(4):161-167. <https://doi.org/10.1159/000080099>
848. Noordman ID, van der Velden JA, Timmers HJ, et al. Socioeconomic status in patients with Turner syndrome. *Compr Psychoneuroendocrinol.* 2021;5:100030. <https://doi.org/10.1016/j.cpnec.2021.100030>
849. Fjermestad KW, Naess EE, Bahr D, Gravholt CH. A 6-year follow-up survey of health status in middle-aged women with Turner syndrome. *Clin Endocrinol (Oxf).* 2016;85(3):423-429. <https://doi.org/10.1111/cen.13068>
850. Wolstencroft J, Skuse D. Social skills and relationships in Turner syndrome. *Curr Opin Psychiatry.* 2016;32(2):85-91. <https://doi.org/10.1097/YCO.0000000000000472>
851. Wolstencroft J, Mandy W, Skuse D. Experiences of social interaction in young women with Turner syndrome: a qualitative study. *Child Care Health Dev.* 2020;46(1):46-55. <https://doi.org/10.1111/cch.12710>
852. Savas M, Wester VL, Dykgraaf RHM, et al. Long-term cortisol exposure and associations with height and comorbidities in Turner syndrome. *J Clin Endocrinol Metab.* 2019;104(9):3859-3867. <https://doi.org/10.1210/je.2019-00148>
853. van den Hoven AT, Bons LR, Dykgraaf RHM, et al. A value-based healthcare approach: health-related quality of life and psychosocial functioning in women with Turner syndrome. *Clin Endocrinol (Oxf).* 2020;92(5):434-442. <https://doi.org/10.1111/cen.14166>
854. Rosenberg AGW, Dingemans VDA, Bos-Roubos AG, et al. Associations between fatigue and endocrine and non-endocrine health problems in Turner syndrome: cohort study and review. *J Clin Endocrinol Metab.* 2023;108(12):e1649-e1659. <https://doi.org/10.1210/clinem/dgad337>
855. Hardy KK, Olson K, Cox SM, Kennedy T, Walsh KS. Systematic review: a prevention-based model of neuropsychological assessment for children with medical illness. *J Pediatr Psychol.* 2017;42(8):815-822. <https://doi.org/10.1093/jpepsy/jsx060>
856. Baum KT, Powell SK, Jacobson LA, et al. Implementing guidelines: proposed definitions of neuropsychology services in pediatric oncology. *Pediatr Blood Cancer.* 2017;64(8):e26446. <https://doi.org/10.1002/pbc.26446>
857. Wolfe KR, Hutaff-Lee C, Wilkening G. Neuropsychological screening in pediatric multidisciplinary clinics: group characteristics and predictive utility. *Arch Clin Neuropsychol.* 2022;37(4):789-797. <https://doi.org/10.1093/arclin/acab090>
858. Stein RE, Jessop DJ. A noncategorical approach to chronic childhood illness. *Public Health Rep.* 1982;97(4):354-362.
859. Claahsen-van der Grinten HL, Speiser PW, Ahmed SF, et al. Congenital adrenal hyperplasia-current insights in pathophysiology, diagnostics, and management. *Endocr Rev.* 2022;43(1):91-159. <https://doi.org/10.1210/endrev/bnab016>
860. Houtzager BA, Möller EL, Maurice-Stam H, Last BF, Grootenhuus MA. Parental perceptions of child vulnerability in a community-based sample: association with chronic illness and health-related quality of life. *J Child Health Care.* 2015;19(4):454-465. <https://doi.org/10.1177/1367493514530954>
861. Cousino MK, Hazen RA. Parenting stress among caregivers of children with chronic illness: a systematic review. *J Pediatr Psychol.* 2013;38(8):809-828. <https://doi.org/10.1093/jpepsy/jst049>
862. Lindström C, Aman J, Norberg AL. Increased prevalence of burn-out symptoms in parents of chronically ill children. *Acta Paediatr.* 2010;99(3):427-432. <https://doi.org/10.1111/j.1651-2227.2009.01586.x>
863. Zan H, Scharff RL. The heterogeneity in financial and time burden of caregiving to children with chronic conditions. *Matern Child Health J.* 2015;19(3):615-625. <https://doi.org/10.1007/s10995-014-1547-3>
864. Sentenac M, Arnaud C, Gavin A, Molcho M, Gabhainn SN, Godeau E. Peer victimization among school-aged children with chronic conditions. *Epidemiol Rev.* 2012;34(1):120-128. <https://doi.org/10.1093/epirev/mxr024>
865. Pinquart M. Self-esteem of children and adolescents with chronic illness: a meta-analysis. *Child Care Health Dev.* 2013;39(2):153-161. <https://doi.org/10.1111/j.1365-2214.2012.01397.x>
866. Sorokin DL, Gates-Ulanet P, Mellon NK. Psychosocial aspects of hearing loss in children. *Otolaryngol Clin North Am.* 2015;48(6):1073-1080. <https://doi.org/10.1016/j.otc.2015.07.008>
867. Stevenson J, Kreppner J, Pimperton H, Worsfold S, Kennedy C. Emotional and behavioural difficulties in children and adolescents with hearing impairment: a systematic review and meta-analysis. *Eur Child Adolesc Psychiatry.* 2015;24(5):477-496. <https://doi.org/10.1007/s00787-015-0697-1>
868. Pinquart M. Body image of children and adolescents with chronic illness: a meta-analytic comparison with healthy peers. *Body Image.* 2013;10(2):141-148. <https://doi.org/10.1016/j.bodyim.2012.10.008>
869. Pozo J, Argente J. Delayed puberty in chronic illness. *Best Pract Res Clin Endocrinol Metab.* 2002;16(1):73-90. <https://doi.org/10.1053/beem.2002.0182>
870. Jordan A, Carter B, Forgeron P, Fournier K, Sanders K. Romantic relationships in young people with long-term health conditions: a scoping review. *J Pediatr Psychol.* 2021;46(3):264-279. <https://doi.org/10.1093/jpepsy/jsaa106>
871. Maurice-Stam H, Nijhof SL, Monnikhof AS, Heymans HSA, Grootenhuus MA. Review about the impact of growing up with a chronic disease showed delays achieving psychosocial

- milestones. *Acta Paediatr.* 2019;108(12):2157-2169. <https://doi.org/10.1111/apa.14918>
872. McGonagle AK, Barnes-Farrell JL. Chronic illness in the workplace: stigma, identity threat and strain. *Stress Health.* 2014;30(4):310-321. <https://doi.org/10.1002/smi.2518>
873. Kazak AE, Schneider S, Didonato S, Pai AL. Family psychosocial risk screening guided by the pediatric psychosocial preventative health model (PPPHM) using the psychosocial assessment tool (PAT). *Acta Oncol.* 2015;54(5):574-580. <https://doi.org/10.3109/0284186X.2014.995774>
874. Boman UW, Bryman I, Halling K, Moller A. Women with Turner syndrome: psychological well-being, self-rated health and social life. *J Psychosom Obstet Gynaecol.* 2001;22(2):113-122. <https://doi.org/10.3109/01674820109049961>
875. Platos M, Wojczek K, Laugeson EA. Effects of social skills training for adolescents on the autism spectrum: a randomized controlled trial of the Polish adaptation of the PEERS® intervention via hybrid and in-person delivery. *J Autism Dev Disord.* 2023;53(11):4132-4146. <https://doi.org/10.1007/s10803-022-05714-9>
876. Rabin SJ, Laugeson EA, Mor-Snir I, Golan O. An Israeli RCT of PEERS®: intervention effectiveness and the predictive value of parental sensitivity. *J Clin Child Adolesc Psychol.* 2021;50(6):933-949. <https://doi.org/10.1080/15374416.2020.1796681>
877. Yoo HJ, Bahn G, Cho IH, et al. A randomized controlled trial of the Korean version of the PEERS(®) parent-assisted social skills training program for teens with ASD. *Autism Res.* 2014;7(1):145-161. <https://doi.org/10.1002/aur.1354>
878. Laugeson EA, Gantman A, Kapp SK, Orenski K, Ellingsen R. A randomized controlled trial to improve social skills in young adults with autism spectrum disorder: the UCLA PEERS(®) program. *J Autism Dev Disord.* 2015;45(12):3978-3989. <https://doi.org/10.1007/s10803-015-2504-8>
879. Laugeson EA, Frankel F, Gantman A, Dillon AR, Mogil C. Evidence-based social skills training for adolescents with autism spectrum disorders: the UCLA PEERS program. *J Autism Dev Disord.* 2012;42(6):1025-1036. <https://doi.org/10.1007/s10803-011-1339-1>
880. Greenhill LL, Swanson JM, Hechtman L, et al. Trajectories of growth associated with long-term stimulant medication in the multimodal treatment study of attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry.* 2020;59(8):978-989. <https://doi.org/10.1016/j.jaac.2019.06.019>
881. Last BF, Stam H, Onland-van Nieuwenhuizen AM, Grootenhuis MA. Positive effects of a psycho-educational group intervention for children with a chronic disease: first results. *Patient Educ Couns.* 2007;65(1):101-112. <https://doi.org/10.1016/j.pec.2006.06.017>
882. Nisbet M, O'Connor R, Mason A, Hunter E. A qualitative study utilizing interpretative phenomenological analysis to explore disclosure in adolescents with Turner syndrome. *Br J Health Psychol.* 2022;27(3):990-1010. <https://doi.org/10.1111/bjhp.12586>
883. Sutton EJ, Young J, McInerney-Leo A, Bondy CA, Gollust SE, Biesecker BB. Truth-telling and Turner syndrome: the importance of diagnostic disclosure. *J Pediatr.* 2006;148(1):102-107. <https://doi.org/10.1016/j.jpeds.2005.08.022>
884. Cooley WC, Sagerman PJ. Supporting the health care transition from adolescence to adulthood in the medical home. *Pediatrics.* 2011;128(1):182-200. <https://doi.org/10.1542/peds.2011-0969>
885. Willis ER, McDonagh JE. Transition from children's to adults' services for young people using health or social care services (NICE guideline NG43). *Arch Dis Child Educ Pract Ed.* 2018;103(5):253-256. <https://doi.org/10.1136/archdischild-2017-313208>
886. Sowislo JF, Orth U. Does low self-esteem predict depression and anxiety? A meta-analysis of longitudinal studies. *Psychol Bull.* 2013;139(1):213-240. <https://doi.org/10.1037/a0028931>
887. Steca P, Abela JR, Monzani D, Greco A, Hazel NA, Hankin BL. Cognitive vulnerability to depressive symptoms in children: the protective role of self-efficacy beliefs in a multi-wave longitudinal study. *J Abnorm Child Psychol.* 2014;42(1):137-148. <https://doi.org/10.1007/s10802-013-9765-5>
888. Diehl M, Hay EL. Self-concept differentiation and self-concept clarity across adulthood: associations with age and psychological well-being. *Int J Aging Hum Dev.* 2011;73(2):125-152. <https://doi.org/10.2190/AG.73.2.b>
889. Campbell JD. Self-esteem and clarity of the self-concept. *J Pers Soc Psychol.* 1990;59(3):538-549. <https://doi.org/10.1037/0022-3514.59.3.538>
890. Weidler EM, Suorsa-Johnson KI, Baskin AS, et al. "It became easier once I knew": stakeholder perspectives for educating children and teenagers about their difference of sex development. *Patient Educ Couns.* 2023;113:107763. <https://doi.org/10.1016/j.pec.2023.107763>
891. Pathmalingham T, Moola FJ, Woodgate RL. Illness conversations: self-disclosure among children and youth with chronic illnesses. *Chronic Illn.* 2023;19(3):475-494. <https://doi.org/10.1177/17423953221110152>
892. Moyer DN, Suorsa-Johnson KI, Weidler EM, Ernst MM. Information sharing in differences of sex development: the creation of a caregiver-support tool. *Fam Syst Health.* 2023;41(2):256-264. <https://doi.org/10.1037/fsh0000724>
893. Rolstad SG, Moller A, Bryman I, Boman UW. Sexual functioning and partner relationships in women with Turner syndrome: some empirical data and theoretical considerations regarding sexual desire. *J Sex Marital Ther.* 2007;33(3):231-247. <https://doi.org/10.1080/00926230701267886>
894. Pavlidis K, McCauley E, Sybert VP. Psychosocial and sexual functioning in women with Turner syndrome. *Clin Genet.* 1995;47(2):85-89. <https://doi.org/10.1111/j.1399-0004.1995.tb03929.x>
895. Vijayakanthi N, Marcus DJ, Fritz SP, Xiang Y, Fadoju D. Body image, self-perception, and satisfaction among girls with Turner syndrome: a prospective cross-sectional study. *J Clin Endocrinol Metab.* 2022;107(4):e1382-e1389. <https://doi.org/10.1210/clinem/dgab889>
896. van de Grift TC, Kreukels BPC. Breast development and satisfaction in women with disorders/differences of sex development. *Hum Reprod.* 2019;34(12):2410-2417. <https://doi.org/10.1093/humrep/dez230>
897. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Gynecology. Female sexual dysfunction: ACOG practice bulletin clinical management guidelines for obstetrician-gynecologists, number 213. *Obstet Gynecol.* 2019;134(1):e1-e18. <https://doi.org/10.1097/AOG.0000000000003324>
898. Meston CM, Bradford A. Sexual dysfunctions in women. *Annu Rev Clin Psychol.* 2007;3(1):233-256. <https://doi.org/10.1146/annurev.clinpsy.3.022806.091507>
899. Clayton AH, Valladares Juarez EM. Female sexual dysfunction. *Med Clin North Am.* 2019;103(4):681-698. <https://doi.org/10.1016/j.mcna.2019.02.008>
900. Thompson DM, Booth L, Moore D, Mathers J. Peer support for people with chronic conditions: a systematic review of reviews. *BMC Health Serv Res.* 2022;22(1):427. <https://doi.org/10.1186/s12913-022-07816-7>
901. Sartore GM, Pourliakas A, Lagioia V. Peer support interventions for parents and carers of children with complex needs. *Cochrane Database Syst Rev.* 2021;12(12):Cd010618. <https://doi.org/10.1002/14651858.CD010618.pub2>
902. Institute of Medicine Committee on Quality of Health Care in A. *Crossing the Quality Chasm: A New Health System for the 21st Century.* National Academies Press (US) Copyright 2001 by the National Academy of Sciences; 2001. All rights reserved.
903. Légaré F, Witteman HO. Shared decision making: examining key elements and barriers to adoption into routine clinical practice. *Health Aff (Millwood).* 2013;32(2):276-284. <https://doi.org/10.1377/hlthaff.2012.1078>
904. Elwyn G, Laitner S, Coulter A, Walker E, Watson P, Thomson R. Implementing shared decision making in the NHS. *BMJ.* 2010;341:c5146. <https://doi.org/10.1136/bmj.c5146>

905. Stacey D, Suwalska V, Boland L, Lewis KB, Presseau J, Thomson R. Are patient decision aids used in clinical practice after rigorous evaluation? A survey of trial authors. *Med Decis Making*. 2019; 39(7):805-815. <https://doi.org/10.1177/0272989X19868193>
906. Elwyn G, Rix A, Holt T, Jones D. Why do clinicians not refer patients to online decision support tools? Interviews with front line clinics in the NHS. *BMJ Open*. 2012;2(6):e001530. <https://doi.org/10.1136/bmjopen-2012-001530>
907. Stacey D, Légaré F, Lewis K, *et al.* Decision aids for people facing health treatment or screening decisions. *Cochrane Database Syst Rev*. 2017;4(4):Cd001431. <https://doi.org/10.1002/14651858.CD001431.pub5>