

# Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting

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On behalf of the International Turner Syndrome Consensus Group\*

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\*(Details of the International Turner Syndrome Consensus Group is presented in the Summary section)

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## Abstract

Turner syndrome affects 25–50 per 100,000 females and can involve multiple organs through all stages of life, necessitating multidisciplinary approach to care. Previous guidelines have highlighted this, but numerous important advances have been noted recently. 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 meetings in 2014 in both Europe and the USA, and culminated with a Consensus Meeting held in Cincinnati, Ohio, USA in July 2016. Prior to this meeting, five groups each addressed important areas in TS care: 1) diagnostic and genetic issues, 2) growth and development during childhood and adolescence, 3) congenital and acquired cardiovascular disease, 4) transition and adult care, and 5) other comorbidities and neurocognitive issues. 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. These four questions related to the efficacy and most optimal treatment of short stature, infertility, hypertension, and hormonal replacement therapy. The guidelines project was initiated by the European Society for Endocrinology and the Pediatric Endocrine Society, in collaboration with The European Society for Pediatric Endocrinology, The Endocrine Society, European Society of Human Reproduction and Embryology, The American Heart Association, The Society for Endocrinology, and the European Society of Cardiology. The guideline has been formally endorsed by the European Society for Endocrinology, the Pediatric Endocrine Society, the European Society for Pediatric Endocrinology, the European Society of Human Reproduction and Embryology and the

Endocrine Society. Advocacy groups appointed representatives who participated in pre-meeting discussions and in the consensus meeting.

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## 1. 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'.

### 1.1. Diagnosis and genetics

**R 1.1.** We recommend considering a diagnosis of TS in phenotypic females 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 females 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 suggest that the new general surveillance management guideline applies to TS patients with any karyotype (⊕⊕○○).

**R 1.4.** We recommend to consider testing for Turner syndrome (TS) in a female with typical signs (Table 2) (⊕⊕⊕⊕).

**R 1.5.** We recommend gonadectomy in all female individuals with Y chromosome material identified on standard karyotyping (⊕⊕○○).

### 2. Growth and puberty

**R 2.1.** We recommend initiating growth hormone (GH) treatment early (around 4–6 years of age, and preferably before 12–13 years) in the following circumstances: the child already has evidence of growth failure (e.g., below 50th percentile height velocity (HV) observed over 6 months in the absence of other treatable cause of poor growth), the child is already short or has a strong likelihood of short stature (e.g., short parents and short

predicted adult height or already pubertal at the time of diagnosis) (⊕⊕⊕○).

**R 2.2.** We recommend using a GH dose of 45–50 µg/kg/day or 1.3–1.5 mg/m<sup>2</sup>/day (4.0–4.5 IU/m<sup>2</sup>/day) in most instances, increasing to 68 µg/kg/day (2.0 mg/m<sup>2</sup>/day) if adult height potential is substantially compromised (⊕⊕⊕⊕).

**R 2.3.** We recommend monitoring growth-promoting treatment by measurement of height at least every 4–6 months during the first year of treatment and at least every 6 months thereafter (⊕⊕⊕○).

**R 2.4.** We recommend monitoring the safety of growth-promoting therapy by measurement of IGF-I at least annually (⊕⊕○○).

**R 2.5.** We suggest that for TS patients treated with GH the measured IGF-I should ideally be no greater than 2 SDS above the mean for age. If an IGF-I value is measured above +3 SDS, a GH dose decrease is warranted. For an IGF-I value between +2 SDS and +3 SDS, clinical judgment should guide further GH dose selection (⊕○○○).

**R 2.6.** We suggest concomitant treatment with oxandrolone from the age of 10 years or older at 0.03 mg/kg/day and maintained below 0.05 mg/kg/day, if the diagnosis of TS (and therefore GH treatment initiation) is delayed, and/or adult height outcome is likely to be unsatisfactory with the standard GH dose alone (⊕⊕⊕⊕).

**R 2.7.** We suggest to not routinely add very-low-dose estrogen supplementation in the prepubertal years to further promote growth (⊕⊕○○).

**R 2.8.** We recommend that estrogen replacement should start between 11 and 12 years of age increasing to adult dosing over 2–3 years (⊕⊕⊕○).

**R 2.9.** We suggest that low-dose estradiol (E2) is the preferred estrogen and that it be administered by a systemic route and that the transdermal route is preferred (⊕○○○).

**R 2.10.** We recommend adding progesterone once breakthrough bleeding occurs, or after 2 years of estrogen treatment (⊕⊕⊕⊕).

### 3. Fertility, assisted reproductive technologies and pregnancy

**R 3.1.** We recommend counseling females with TS that their probability to conceive spontaneously decrease

rapidly with age, if at all present, and consideration should be given to offering fertility treatment at a young age (⊕⊕⊕⊕).

**R 3.2.** We suggest that young mosaic TS women with persistent ovarian function should be counseled that oocyte cryopreservation after controlled ovarian hyperstimulation is a possible fertility preservation option (⊕○○○).

**R 3.3.** We recommend against routine oocyte retrieval for fertility preservation of young TS girls before the age of 12 years (⊕○○○).

**R 3.4.** We recommend considering oocyte donation for fertility, only after thorough screening and appropriate counseling (⊕⊕⊕⊕).

**R 3.5.** We recommend that management of pregnant women with TS should be undertaken by a multidisciplinary team including maternal–fetal medicine specialists and cardiologists with expertise in managing women with TS (⊕⊕⊕○).

**R 3.6.** We suggest that other options for motherhood such as adoption or using a gestational carrier should be mentioned during preconception counseling (⊕○○○).

**R 3.7.** We suggest that all women with TS should be counseled about the increased cardiovascular risk of pregnancy (⊕○○○).

**R 3.8.** We recommend imaging of the thoracic aorta and heart with a transthoracic echocardiography (TTE) and CT/cardiac magnetic resonance scan (CMR) within 2 years before planned pregnancy or assisted reproductive therapy (ART) in all women with TS (⊕○○○).

**R 3.9.** We suggest that ART or spontaneous conception should be avoided in case of an ascending aortic size index (ASI) of  $>2.5$  cm/m<sup>2</sup> or an ascending ASI 2.0–2.5 cm/m<sup>2</sup> with associated risk factors for aortic dissection (AoD), which include bicuspid aortic valve, elongation of the transverse aorta, coarctation of the aorta and hypertension (⊕○○○).

**R 3.10.** We suggest that women with a history of AoD should be advised against pregnancy. If already pregnant these women should be followed very closely at a specialist center and deliver by cesarean section (⊕○○○).

**R 3.11.** We suggest performing TTE in women with TS without aortic dilatation or other risk factors (hypertension, bicuspid aortic valve, coarctation, previous aortic surgery) at least once during pregnancy, at approximately 20 weeks of gestation (⊕○○○).

**R 3.12.** We suggest that women with TS with an ascending ASI  $>2.0$  cm/m<sup>2</sup> or any risk factor (hypertension,

bicuspid aortic valve, coarctation, previous AoD or surgery) should be monitored frequently, including TTE at 4- to 8-week intervals during pregnancy and during the first 6 months postpartum (⊕○○○).

**R 3.13.** We suggest that CMR imaging (without gadolinium) should be performed during pregnancy when there is suspicion of disease of the distal ascending aorta, aortic arch or descending aorta (⊕○○○).

**R 3.14.** We recommend that blood pressure control is strict (135/85 mmHg) in all pregnant women with TS (⊕○○○).

**R 3.15.** We suggest that during pregnancy, prophylactic surgery is reasonable in case of a dilated aorta with rapid increase in diameter (⊕○○○).

**R 3.16.** We suggest that in case of an acute ascending AoD before the fetus is viable, to perform emergency aortic surgery understanding that fetal viability may be at risk. If the fetus is viable, it is reasonable to perform cesarean section first, followed by aortic surgery, which should be performed under near-normothermia, pulsatile perfusion, high pump flow and avoidance of vasoconstrictors (⊕○○○).

**R 3.17.** We suggest that exercise testing before pregnancy can be useful to reveal exercise induced hypertension, especially in women with coarctation (⊕○○○).

**R 3.18.** We suggest that women with aortic dilatation, bicuspid aortic valve, elongation of the transverse aorta, coarctation of the aorta and/or hypertension should be advised that pregnancy would carry a high risk of AoD (⊕○○○).

**R 3.19.** We suggest that vaginal delivery is reasonable in women with TS with an ascending ASI below 2.0 cm/m<sup>2</sup> (⊕○○○).

**R 3.20.** We suggest that in women with TS with an ascending ASI of 2.0–2.5 cm/m<sup>2</sup>, a vaginal delivery with epidural anesthesia and expedited second stage is preferred or a cesarean section may be considered. In women with TS with an ascending ASI  $>2.5$  cm/m<sup>2</sup>, a cesarean section is reasonable or a vaginal delivery with epidural anesthesia and expedited second stage may be considered (⊕○○○).

**R 3.21.** We recommend that in women with TS with a history of AoD, a cesarean section should be performed (⊕○○○).

#### 4. Cardiovascular health issues in Turner syndrome

**R 4.1.** We recommend that an infant or child is examined with transthoracic echocardiography (TTE) at

the time of diagnosis, even if the fetal echocardiogram or postnatal cardiac examination was normal (⊕⊕○○).

**R 4.2.** We recommend that girls or women with aortic dilatation and/or bicuspid aortic valve be counseled to seek prompt evaluation if they are experiencing acute symptoms consistent with AoD, such as chest, neck, shoulder, back or flank discomfort, particularly if it is sudden in onset and severe (⊕⊕○○).

**R 4.3.** We recommend that women with TS demonstrating an increase in TS-specific Z-score of 1 in aortic diameter or an increase of >0.5 cm over a one-year period, need an optimization of medical treatment and surgical consultation (⊕⊕○○).

**R 4.4.** We suggest that elective operations for aneurysm of the aortic root and/or ascending aorta are reasonable for women with TS who are ≥16 years of age with an ascending ASI ≥2.5 cm/m<sup>2</sup> and associated risk factors for AoD, including bicuspid aortic valve, elongation of the transverse aorta, coarctation of the aorta and/or hypertension according to standard definitions (⊕○○○).

**R 4.5.** We suggest that elective operations for aneurysm of the aortic root and/or ascending aorta may be considered for women with TS who are ≥16 years of age with an ascending ASI ≥2.5 cm/m<sup>2</sup>, and no associated risk factors for AoD (⊕○○○).

**R 4.6.** We suggest that elective operations for aneurysm of the aortic root and/or ascending aorta may be considered for women with TS, who are <16 years of age, and for whom their ascending aorta TS-specific Z-score is ≥4.0, with or without associated risk factors for AoD (i.e., bicuspid aortic valve, elongation of the transverse aorta, coarctation of the aorta and/or hypertension) (⊕○○○).

**R 4.7.** We recommend that in adolescents and adults TS cardiovascular screening with TTE and CMR at the time of diagnosis is the preferred approach (⊕⊕○○).

**R 4.8.** We recommend that a CMR scan is performed as soon as it is feasible without needing general anesthesia. If an adult or child cannot tolerate a CMR study, a CT scan is a reasonable option (⊕⊕○○).

**R 4.9.** We recommend, in the absence of a bicuspid aortic valve or other significant disease at the initial screening, TTE or CMR surveillance studies should be performed every 5 years in children, every 10 years in adults, or prior to anticipated pregnancy (see **R 3.8**) to evaluate the aorta based on published guidelines (⊕⊕○○).

**R 4.10.** We recommend that, if TS is highly suspected or has been confirmed prenatally, a fetal echocardiogram should be performed (⊕⊕○○).

**R 4.11.** We recommend that diagnosis of a bicuspid aortic valve or a left-sided obstructive lesion in a female fetus or child should prompt a genetic evaluation for TS (⊕⊕○○).

**R 4.12.** We recommend referral to a pediatric cardiologist when congenital heart disease is detected prenatally in a fetus with TS to provide counseling regarding the anatomy and physiology of the specific defect, recommended site and mode of delivery and postnatal multidisciplinary management plan (⊕⊕○○).

**R 4.13.** We suggest that a resting electrocardiogram (ECG) with QTc measurement should be done in every individual with TS at the time of diagnosis and that Hodge's may be preferred over Bazett's formula to estimate QTc (⊕⊕○○).

**R 4.14.** We suggest that 24-h Holter monitoring and exercise testing be considered for risk estimation in women with TS with QTc interval prolongation (QTc >460 ms) (⊕○○○).

**R 4.15.** We suggest that, in individuals with prolonged QTc, drugs that prolong the QTc should be avoided. If they are deemed necessary, ECG should be performed 1–2 weeks after initiation of QT-prolonging drugs (⊕○○○).

**R 4.16.** We recommend that the function of the aortic valve and the presence of any other congenital heart disease and/or hypertension should be considered in determining participation recommendations for the athlete with TS and aortic dilation (⊕○○○).

**R 4.17.** We suggest that, for girls and women with TS ≥16 years with a moderately dilated aorta (ascending ASI ≥2.0 cm/m<sup>2</sup>), avoidance of intense weight-training should be advised (⊕○○○).

**R 4.18.** We suggest that, for girls and women with normal aortic size (age <16 years; TS-specific Z-score of <2.5 or age ≥16 years and ASI <2.0 cm/m<sup>2</sup>), it is reasonable to participate in all sports (⊕○○○).

**R 4.19.** We suggest that, for girls and women with a mild to moderately dilated aorta (age <16 years old (TS-specific Z-score of 2.5–3), or age ≥16 years (ASI 2.0–2.3 cm/m<sup>2</sup>)), participation in low and moderate static and dynamic competitive sports may be advised (⊕○○○).

**R 4.20.** We suggest that girls and women with a moderately to severely dilated aorta, age <16 years (TS-specific Z-score of >3) or age ≥16 years (ASI >2.3 cm/m<sup>2</sup>) should be advised not to participate in any competitive sports (⊕○○○).

**R 4.21.** We recommend that in individuals without structural heart disease, annual assessment of blood pressure should be performed and medical treatment

thereof should be considered if hypertension is present. We suggest medical treatment to include a beta-blocker, an angiotensin receptor blocker or both to reduce the risk for AoD in women with TS who are  $\geq 16$  years of age for whom their ascending ASI is  $\geq 2.3$  cm/m<sup>2</sup> ( $\oplus\oplus\circ\circ$ ).

**R 4.22.** We suggest that medical treatment, including a beta-blocker, an angiotensin receptor blocker or both, to reduce dilatation of an enlarged aortic root and/or ascending aorta may be considered for girls with TS who are  $\leq 16$  years of age for whom their ascending aorta TS-specific Z-score is  $\geq 3.0$  ( $\oplus\circ\circ\circ$ ).

## 5. Transition from pediatric to adult care

**R 5.1.** We recommend that the pediatric endocrinologist (or any other TS care provider/coordinator) implements a planned and staged transition process in early adolescence for their patients with TS ( $\oplus\oplus\circ\circ$ ).

**R 5.2.** We suggest that the pediatric endocrinology team uses or adapts available transition tools to track and document the core elements of transition ( $\oplus\oplus\circ\circ$ ).

**R 5.3.** We suggest that, irrespective of the health care delivery system, the pediatric and adult health care teams establish a workflow to support a coordinated transition process ( $\oplus\oplus\circ\circ$ ).

**R 5.4.** We suggest that pediatric endocrinologists and their care teams encourage peer-to-peer (and parent-to-parent) contact with TS support and advocacy organizations to enhance knowledge and confidence, reduce stress and distress and promote the reciprocal sharing of experiences ( $\oplus\oplus\circ\circ$ ).

## 6. Health surveillance for comorbidities throughout the lifespan

**R 6.1.** We recommend a formal audiometric evaluation every 5 years regardless of the initial age at diagnosis, initial hearing threshold levels, karyotype and/or presence of a mid-frequency sensorineural hearing loss, to assure early and adequate technical and other rehabilitative measures ( $\oplus\oplus\circ\circ$ ).

**R 6.2.** We recommend aggressive treatment of middle-ear disease and otitis media (OM) with antibiotics and placement of myringotomy tubes as indicated ( $\oplus\oplus\circ\circ$ ).

**R 6.3.** We recommend screening for hypothyroidism at diagnosis and then annually with (free) T4 and TSH measurements beginning in early childhood and throughout the lifespan ( $\oplus\oplus\circ\circ$ ).

**R 6.4.** We suggest counseling on healthy nutrition and physical activity starting in early childhood ( $\oplus\oplus\circ\circ$ ).

**R 6.5.** We recommend lifelong annual measurement of HbA1c with or without fasting plasma glucose starting at age of 10 years ( $\oplus\oplus\circ\circ$ ).

**R 6.6.** We recommend that a lipid profile be performed in individuals who have at least one risk factor for cardiovascular disease starting at age 18 years ( $\oplus\oplus\circ\circ$ ).

**R 6.7.** We recommend that, while peripheral edema mostly resolves by 2 years of age without therapy, any serious compromise of fingernails, toenails or extremity skin at any age be assessed and treated by a professional edema therapist ( $\oplus\circ\circ\circ$ ).

**R 6.8.** We recommend dental/orthodontic evaluation at diagnosis if no previous dental/orthodontic care was established. Future management and follow-up should be based on the standard of dental/orthodontic care, individual clinical findings and patient needs ( $\oplus\circ\circ\circ$ ).

**R 6.9.** We recommend a comprehensive ophthalmological examination between 12 and 18 months of age or at the time of diagnosis, if at an older age, with emphasis on early correction of refractive errors ( $\oplus\circ\circ\circ$ ).

**R 6.10.** We recommend clinical evaluation for scoliosis every 6 months during GH therapy or otherwise annually until growth is completed ( $\oplus\circ\circ\circ$ ).

**R 6.11.** We suggest treatment with GH be coordinated with orthopedic care if spine abnormalities are present at the start of therapy or if they develop during therapy ( $\oplus\circ\circ\circ$ ).

**R 6.12.** We recommend that all patients should be counseled on healthy lifestyle measures, and on the role of estrogen replacement in bone health ( $\oplus\oplus\circ\circ$ ).

**R 6.13.** We recommend that dietary intake of calcium and vitamin D follow region-specific recommendations ( $\oplus\oplus\circ\circ$ ).

**R 6.14.** We suggest screening for vitamin D deficiency with a serum 25-hydroxyvitamin D measurement between 9 and 11 years of age and every 2–3 years thereafter throughout the lifespan and treating with inactive vitamin D (ergocalciferol) as necessary ( $\oplus\circ\circ\circ$ ).

**R 6.15.** We suggest using dual energy X-ray absorptiometry (DXA) scans to monitor bone mineral density after adult hormone replacement therapy has been instituted ( $\oplus\oplus\circ\circ$ ).

**R 6.16.** We recommend using DXA scans to monitor bone mineral density in all women when considering discontinuation of estrogen therapy (simulating menopause) ( $\oplus\oplus\circ\circ$ ).



**R 6.17.** We recommend screening for celiac disease by measurement of transglutaminase antibodies beginning at 2–3 years of age at a frequency of every 2 years throughout childhood and with suggestive symptoms in adulthood (⊕○○○).

**R 6.18.** We recommend monitoring liver function tests (including AST, ALT, GGT and alkaline phosphatase) yearly throughout the lifespan starting at age 10 years (⊕⊕○○).

**R 6.19.** We recommend appropriate timing (see **R 2.8**) for the initiation of female hormone replacement therapy for improvement of liver function (⊕⊕○○).

**R 6.20.** We recommend a renal ultrasound at the time of diagnosis (⊕⊕⊕⊕).

**R 6.21.** We recommend that girls and women with TS attend specialist interdisciplinary or multidisciplinary clinics for health surveillance (⊕⊕○○).

## 7. Neurocognitive and behavioral aspects

**R 7.1.** We recommend that neuropsychology and allied behavioral health services is integrated into the care for girls and women with TS (⊕⊕⊕○).

**R 7.2.** We recommend annual developmental and behavioral screenings until adulthood with referrals as indicated (⊕⊕⊕○).

**R 7.3.** We suggest conducting neuropsychological assessments at key transitional stages in schooling (⊕⊕○○).

**R 7.4.** We recommend academic and occupational adjustments if indicated, to accommodate learning/performance issues (⊕⊕⊕○).

**R 7.5.** We recommend aiming for on-time puberty and aggressive management of predictors of hearing impairment to facilitate positive psychosocial and psychosexual adaptation (⊕⊕○○).

**R 7.6.** We suggest that evidence-based interventions for cognitive or psychosocial problems in other populations may be adapted to meet the needs of girls/women with TS (⊕○○○).

## Introduction

Turner syndrome (TS) affects 25–50 per 100 000 females and can involve multiple organs through all stages of life, necessitating a multidisciplinary approach to care. Previous guidelines have highlighted this, but numerous important advances have been noted since their publication (1, 2). 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 meetings in 2014 in both Europe and the USA and culminated with a consensus meeting held in Cincinnati, Ohio, USA in July 2016. Prior to this meeting, five groups each addressed important areas in TS care: (1) diagnostic and genetic issues, (2) growth and development during childhood and adolescence, (3) congenital and acquired cardiovascular disease, (4) transition and adult care and (5) other comorbidities and neurocognitive issues. 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 (2). These four questions related to the efficacy and most optimal treatment of short stature, infertility, hypertension and hormonal replacement therapy. These guidelines were initiated and developed by the European Society of Endocrinology (ESE) in Europe, and by the Pediatric Endocrine Society (PES) in USA, with important contributions from the European Society of Human Reproduction and Embryology (ESHRE), the Endocrine Society (ES), the European Society for Cardiology (ESC), the American Heart Association (AHA), the Society for Endocrinology (SfE) and the European Society for Pediatric Endocrinology (ESPE). Several delegates from other societies also participated. Advocacy groups appointed representatives who participated in pre-meeting discussions and in the consensus meeting.

## Methods

### Guideline development consensus working group

The guidelines project was initiated by the European Society for Endocrinology and the Pediatric Endocrine Society, in collaboration with The European Society for Pediatric Endocrinology, The Endocrine Society, European Society of Human Reproduction and Embryology, The American Heart Association, The Society for Endocrinology, and the European Society of Cardiology. The guideline has been formally endorsed by the European Society for Endocrinology, the Pediatric Endocrine Society, the European Society for Pediatric Endocrinology, the European Society of Human Reproduction and Embryology and the Endocrine Society.

These guidelines were sponsored primarily by ESE, and co-sponsored by PES, ESPE and ES. Furthermore, ESHRE, SfE, and ESC supported their own delegates

for the meeting, and additional support was obtained from the AHA, the National Institute of Child Health and Human Development (NICHD), the National Center for Advancing Translational Sciences, Cincinnati Children's Hospital Medical Center's TS Foundation, as well as several advocacy groups (TS Society of the United States, the TS Global Alliance and the Turner Resource Network). The chairs of the consensus working group, Claus H Gravholt and Philippe F Backeljauw, were appointed by the ESE Clinical Committee and PES respectively. Other members of the working and writing group are Niels H Andersen (adult cardiologist), Gerard S Conway (adult endocrinologist), Olaf M Dekkers (epidemiologist), Mitchell E Geffner (pediatric endocrinologist), Angela E Lin (clinical geneticist), Nelly Mauras (pediatric endocrinologist), Karen O Klein (pediatric endocrinologist), Charmian A Quigley (pediatric endocrinologist), Karen Rubin (pediatric endocrinologist), David E Sandberg (clinical psychologist), Theo C J Sas (pediatric endocrinologist), Michael Silberbach (pediatric cardiologist), Viveca Soderstrom-Anttila (fertility specialist), Kirstine Stochholm (adult endocrinologist), Janielle A van Alfen-van der Velden (pediatric endocrinologist) and Joachim Woelfle (pediatric endocrinologist). The working group had two in-person meetings (September 2015, with some of the participants present, and July 2016, where all members were present). Consensus was reached upon discussion; minority positions were taken into account in the rationale behind the recommendations. Each working group included at least one member from Turner syndrome advocacy community. These individuals provided a valuable and nuanced perspective. All participants completed conflict-of-interest forms ([Appendix 1](#), see section on [supplementary data](#) given at the end of this article).

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 2](#).

### Target group

This guideline document was developed for health care providers of patients with TS, i.e., both primary-care providers (pediatricians, family doctors, internal medicine specialists), as well as specialists, such as specialist

pediatricians, geneticists, endocrinologists, cardiologists, fertility doctors and specialists in internal medicine.

### Aims

The overall purpose of the guidelines is to provide a practical clinical guideline, with focus on operational recommendations for daily management. We also aimed to address those health care issues not addressed in the previous guidelines.

### Summary of methods used for guideline development

The methods used have been described in more detail previously (3). In short, the guidelines used GRADE as a methodological base for four clinical questions. The first step was to define these question(s), 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 took into account: (1) quality of the evidence, (2) balance of desirable and undesirable outcomes, (3) values and preferences (patient preferences, goals for health, costs, management inconvenience, feasibility of implementation, etc.) (4). Additional recommendations based on good practice were graded based on expert opinion (5). Evidence tables are provided in [Appendix 2](#) and [Supplementary Fig. 1](#).

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 (⊕⊕⊕⊕) (6). 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 the working group, and as such represent good clinical practice based on the limited available evidence.

## 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, is treated with GH, with/without oxandrolone (a non-aromatizable androgen), with the goals of increasing 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, quality of life (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 crossover trials.

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

Usually, TS is 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 abortion and complications (e.g., 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 effects of blood pressure treatment on clinical outcomes in TS? (GRADE question 3)

Turner syndrome is often accompanied by primary hypertension, which has been linked to the development of aortic dilation or even AoD – 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 and (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.

### Estrogen replacement in TS (GRADE question 4)

Turner syndrome is usually accompanied by hypergonadotropic hypogonadism and primary or secondary amenorrhea. Most TS individuals will therefore need hormonal replacement therapy (HRT) – first for induction of puberty and later for maintaining secondary sex characteristics, attaining peak bone mass, normalizing uterine growth (for possible pregnancy later) and can today be offered oocyte donation. 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 all four clinical questions. The following databases were searched: PubMed, EMBASE (OVID version), Web of Science, COCHRANE Library, CINAHL, Academic Search Premier and ScienceDirect. The number of articles retrieved, exclusion of articles and final inclusion of eligible articles are shown in the flowchart (Supplementary Fig. 1).

## 1. Recommendations and their rationale

### 1.1. Diagnosis and genetics of Turner syndrome

**R 1.1.** We recommend considering a diagnosis of TS in phenotypic females 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 females 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 (⊕⊕○○).



**Table 1** Type and frequency of chromosome abnormalities in Turner syndrome.

Karyotype	%	Description
45,X	40–50	Monosomy X
45,X/46,XX	15–25	
45,X/47,XXX; 45,X/46,XX/47,XXX	3	Mosaicism with 'Triple X'
45,X/46,XY	10–12	Mixed gonadal dysgenesis
46,XX, del(p22.3); 46,X,r(X)/46,XX		Deletion Xp22.3
		Ring X chromosome
46,X i(Xq); 46,X, idic(Xp)	(10%)	Isochromosome Xq; isodicentric Xp
X-autosome translocation, unbalanced	Rare	Various
46,XX, del(q24)		Not TS; premature ovarian failure
46,X, idic(X)(q24)		Not TS; isodicentric Xq24

**R 1.3.** We suggest that the new general surveillance management guideline apply to TS patients with any karyotype (⊕⊕○○).

### 1.1.1. Definition

Turner syndrome is a chromosomal disorder that affects phenotypic *females* who have one intact X chromosome and complete or partial absence of the second sex chromosome in association with one or more clinical manifestations (Table 1). Although the traditional definition of TS implies the presence of physical features such as the characteristic facial appearance, with neck webbing and lymphedema (7, 8), we suggest that the clinical manifestations of TS should be broadened to include other features, such as linear growth failure, ovarian insufficiency (pubertal delay), early sensorineural hearing loss, distinctive congenital cardiovascular, skeletal, digital and renal anomalies, a particular neurodevelopmental profile, and a constellation of other disorders that are more common in TS, including hypothyroidism and celiac disease (2, 9, 10).

Smaller X chromosome deletions cause distinct features and are not included in the definition of TS. Females 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 (11, 12). They do not appear to be at higher risk for cardiac anomalies, neuropsychiatric issues or ovarian failure, which are often present in women with TS and a 45,X karyotype (13). In contrast, neurocognitive deficits typical of 45,X TS are common in girls with cytogenetically visible deletions of Xp22.3 (14), although this may not be the case for girls with submicroscopic Xp22.3 deletions detected only by molecular cytogenetic or microarray studies.

Females 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 failure (POF). Phenotypic males with 45,X/46,XY (or other variant) are excluded from the diagnosis of TS (15, 16). Women over the age of 50 years with less than 5% 45,X cells are also excluded, because 45,X mosaicism may develop in older women as part of the aging process (17). In women less than 50 years of age, there is no specific lower limit for 45,X that defines TS, although many have used 5% (18, 19, 20).

### 1.1.2. Karyotype–phenotype analysis

The broad clinical spectrum of TS ranges from a classic appearance with many physical differences to individuals who have no apparent or minimal observable features; short stature is also not ubiquitous (10). Because of this TS may be diagnosed across the lifespan. The karyotype in TS ranges from complete 45,X to forms of mosaicism in which there is a normal (46,XX or 46,XY) cell line or an abnormal second (or third) cell line in a female. Comparative analysis of the karyotypes and phenotypes in TS is difficult, even in the largest studies, due to differences in patient ages, variability in the definition of the clinical features, and general uncertainty regarding the extent of mosaicism in different tissues (9, 19, 21, 22, 23). It has been hypothesized that all 45,X individuals who survive to birth have some degree of 'cryptic mosaicism' for a normal cell line somewhere in the body, although this has not been proven conclusively (24, 25, 26).

There are sufficient case series and anecdotal experience showing that, in an individual patient, the specific karyotype does not always predict the phenotype. Nevertheless, several generalizations can be made about

the different karyotype subgroups. Compared to patients with a 45,X karyotype:

- 45,X/46,XX mosaicism is associated with a milder phenotype, including less prevalent and less severe congenital heart disease and lymphatic abnormalities. Mosaicism varies with tissue type and patient age (19, 27).
- 45,X/46,XX and various other forms of mosaicism are more likely to have spontaneous pregnancies. Although more fertile, they experience frequent early miscarriage (18, 28).
- 45,X/46,XX mosaicism diagnosed postnatally has a more severe presentation than when identified prenatally, as many of these are found incidentally due to karyotyping for other indications, such as for advanced maternal age (22, 29, 30).
- 45,X/47,XXX mosaicism has a milder phenotype (31).
- The presence of a Y chromosome detected by standard karyotype or FISH (fluorescent *in situ* hybridization) is associated with an increased risk of gonadoblastoma (32).
- A ring X chromosome is sometimes associated with variable intellectual disability, and when intellectual disability is present, it does not always correlate to the presence of a small ring X or to the absence of *XIST* (X-inactive specific transcript) (33).

We suggest that these general surveillance management guidelines apply to TS patients with any karyotype, although long-term echocardiographic surveillance can be omitted for those with the lowest levels of 45,X (20). Collaborative studies involving large TS registries with consistent data enrollment are needed to provide a more evidence-based analysis of the genotype–phenotype associations.

### 1.1.3. Indications for testing

**R 1.4.** We recommend to consider testing for TS in a female with typical signs (Table 2) (⊕⊕⊕⊕).

The diagnosis of TS should be a foremost consideration in any female with unexplained growth failure or pubertal delay, with or without the constellation of the lymphedema sequence (edema of the hands or feet, nuchal fold, neck webbing, low hairline and hyperconvex or hypoplastic nails); characteristic facial features such as epicanthal folds, downslanting palpebral fissures, low-set ears and micrognathia; left-sided cardiac anomalies, especially coarctation of the aorta, bicuspid aortic valve and aortic stenosis; markedly elevated follicle-stimulating

hormone (FSH); cubitus valgus; multiple pigmented nevi; bone anomalies including short fourth metacarpal/metatarsal, Madelung deformity and scoliosis; chronic OM and conductive or sensorineural hearing loss or learning disabilities, especially affecting visuospatial or nonverbal skills and other traits (Table 2) (2, 9, 10). We suggest a new approach to guide clinicians in ordering a karyotype for suspected TS (Table 3).

Turner syndrome is often diagnosed in distinct age groups, with peaks during fetal life, infancy, late prepubescence (8–12 years) and during late adolescence/early adulthood (34, 35, 36, 37, 38). We recommend that care be coordinated and performed in the setting of a multidisciplinary clinic dedicated to TS, or at the least by a team of specialists with such expertise.

### 1.2. Prenatal diagnosis

Sex chromosome abnormalities, in general, can be detected prenatally by chorionic villous sampling or amniocentesis, whether performed for advanced maternal age, abnormal serum markers or the presence of multiple anomalies. Regardless of the indication, test procedure or specific result, genetic counseling by a geneticist or genetic counselor should be provided *before and after* any prenatal diagnostic procedure. Ultrasonography can play an important role that suggests an increased likelihood of TS. In the first trimester, increased nuchal translucency is common in fetuses with TS, but is also observed in the autosomal trisomy syndromes. The presence of a frank cystic hygroma, however, makes the diagnosis of TS more likely (39). Other ultrasound findings suggestive of TS are coarctation of the aorta and/or left-sided cardiac defects (which should be further imaged by fetal echocardiography), brachycephaly, renal anomalies, polyhydramnios, oligohydramnios and growth retardation (40). Abnormal triple or quadruple maternal serum screening (alpha-fetoprotein, human chorionic gonadotropin, inhibin A and unconjugated estriol) may also suggest the diagnosis of TS (41), but these tests may be perfectly normal together with normal nuchal fold thickness (42). Ultrasound and maternal serum screening are not diagnostic, and karyotype confirmation of TS is obligatory.

Because an amniocentesis karyotype reflects fibroblast analysis, the postnatal outcome and *constitutional* karyotype of individuals with prenatally diagnosed 45,X are uncertain, especially in patients with mosaicism. Therefore, chromosome analysis should be repeated

**Table 2** Detailed list of more common abnormalities associated with Turner syndrome and their approximate prevalence (see also Table 7).

Feature	Frequency (%)
Growth failure and reduced adult height	95–100
Failure to thrive during first year of life	50
Endocrinopathies	
Glucose intolerance	15–50
Type 2 diabetes	10
Type 1 diabetes	?
Thyreoiditis and hypothyreosis	15–30, ann. incidence ~3%
Hypertension	50
Android body composition	?
Gastrointestinal and hepatic disorders	
Elevated hepatic enzymes	50–80
Celiac disease	8
Inflammatory bowel disease	2–3
Phenotypic characteristics	
Eyes	
Epicanthus	20
Nearsightedness	20
Strabismus	15
Ptosis	10
Ears	
Infection of middle ear	60
Hearing defects	30
Deformity of external ear	15
Mouth	
Micrognathia (small mandibular bone)	60
High-arched palate	35
Abnormal dental development	?
Neck	
Low posterior hairline	40
Broad short-appearing neck	40
Pterygium colli (webbed neck)	25
Thorax	
Broad chest (shield chest)	30
Inverted nipples	5
Skin, nails, and hair	
Increased skin ridge count	30
Lymphedema of hands and feet	25
Multiple pigmented naevi	25
Nail hypoplasia/dystrophy	10
Vitiligo	5
Alopecia	5
Skeleton	
Bone age delay	85
Decreased bone mineral content	50–80
Cubitus valgus	50
Short fourth metacarpal	35
Genu valgum	35
Congenital hip luxation	20
Scoliosis	10
Madelung deformity	5
Heart	
Bicuspid aortic valve	14–34
Coarctatio aorta	7–14
Aortic dilation/aneurysm	3–42
Kidneys	
Horseshoe kidney	10
Abnormal positioning or duplication of renal pelvis, ureters or vessels	15
Renal aplasia	3
Neurocognitive and psychosocial issues <sup>a</sup>	
Emotional immaturity	~40
Specific (nonverbal) learning disorder	~40
Psychological and behavioral problems	~25

<sup>a</sup>The data are inconsistent, and the given percentages should be viewed with caution.

**Table 3** Indications for chromosome analysis to diagnose Turner syndrome.

As the only clinical feature:

- Fetal cystic hygroma, or hydrops, especially when severe
- Idiopathic short stature
- Obstructive left-sided congenital heart defect<sup>a</sup>
- Unexplained delayed puberty/menarche
- Couple with infertility
- Characteristic facial features in a female<sup>b</sup>

At 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<sup>c</sup>
- Hearing impairment <40 years of age together with short stature

<sup>a</sup>Typically bicuspid aortic valve, coarctation, aortic stenosis (with/without bicuspid aortic valve), mitral valve anomalies, and hypoplastic left heart syndrome. <sup>b</sup>Down-slanted palpebral fissures, epicanthal folds, low-set anomalous pinnae, micrognathia, narrow palate, short broad neck, and webbing. <sup>c</sup>Partial anomalous pulmonary venous return; atrial septal defect, secundum type; and ventricular septal defects, muscular or membranous.

postnatally *in all patients*. In general, any of the features of TS may be seen with virtually any of the common chromosome constitutions (2, 10). Although non-mosaic 45,X fetuses with pleural effusion or cystic hygroma often spontaneously abort, these findings are also compatible with delivery of a viable newborn (43).

The recent developments in non-invasive prenatal testing (NIPT) have had implications for diagnosing TS (44). When TS is suspected, the possible interpretations may include TS in the fetus or TS in the mother. Additional testing is offered such as maternal karyotype, amniocentesis, fetal echocardiography and genetic counseling. There is insufficient evidence to recommend NIPT for TS by sequencing or SNP (single-nucleotide polymorphism) array analysis of cell-free fetal DNA (cfDNA) in maternal blood. A recent meta-analysis of 37 studies showed that the detection rate (90%) and positive predictive value (23%) of cfDNA analysis were relatively low (45, 46). In such cases, the investigation of choice continues to be invasive testing for fetal karyotype evaluation.

Pre-implantation genetic screening (PGS) is being used with increased frequency in *in vitro* fertilization (IVF) programs, and pregnancy rates continue to be studied (47, 48). Such PGS is currently offered to women with recurrent pregnancy loss or repetitive implantation failure. It is also being used as a method of embryo selection to increase pregnancy rates in all women undergoing IVF. Embryos now are being diagnosed with TS, which means that pre-

implantation has become an additional time for diagnosis and counseling. If used more extensively in the future, this could have a significant impact on the prevalence of TS.

Decisions regarding pregnancy termination are 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 QoL of individuals affected with TS, as well as of recent advances in management (49). The input of a physician with experience in the long-term follow-up of TS patients will be valuable to put management of the different comorbidities in perspective. The discussion should include variability of features, the possibility of short stature and ovarian failure and their management. It should be emphasized that most individuals with TS have intelligence scores in the normal range, although many specific types of learning disabilities and psychological challenges are common. Of course, the discussion should be tailored to the specific findings of that fetus, because decisions regarding termination are often influenced by the presence and severity of an abnormal phenotype (50, 51). Discussion with families of girls and women with TS can be very helpful. This is often accomplished through contact with TS support organizations.

### 1.3. Postnatal diagnosis

All individuals with suspected TS should have a standard 20-cell karyotype as recommended by the American College of Medical Genetics, as this will identify at least 10% mosaicism with 95% confidence in the blood (52, 53, 54). If mosaicism is strongly suspected, but not demonstrated with standard karyotype, additional metaphases may be counted or FISH studies performed (26, 52). Although a peripheral blood karyotype is usually adequate, a second tissue, such as skin fibroblasts, buccal mucosa cells or possibly urine for bladder epithelial cells, may be examined if there is a strong clinical suspicion of TS despite a normal blood karyotype or low-level mosaicism.

There are several situations in which a formal karyotype should be repeated: (1) all infants diagnosed prenatally should have a postnatal karyotype to confirm the findings, (2) those diagnosed by a buccal swab only, (3) individuals with a karyotype performed in the distant past or (4) when no original report is available for review.

**R 1.5.** We recommend gonadectomy in all female individuals with Y chromosome material identified on standard karyotyping (⊕⊕○○).



An increased prevalence of germ cell tumors has been noted in TS individuals with Y chromosome sequences. The risk of malignancy is determined by the presence of Y chromosome material and mosaicism (genotype), and the degree of masculinization (phenotype). At least 10% of females with TS harbor Y chromosome sequences. With the availability of newer molecular methods, the detection rate of Y-chromosomal material has increased. Real-time polymerase chain reaction (PCR) with multiple Y-specific probes is more sensitive than FISH and can detect Y mosaicism in up to 12% of TS cases (55, 56, 57, 58). FISH with X and Y centromere probes are recommended to determine the origin of ring or small marker chromosomes. We propose that it is no longer clinically indicated to use FISH with SRY probes to exclude cryptic Y material. The gonadoblastoma locus was mapped adjacent to the centromere to a region that does not include the SRY gene; therefore, SRY probes are not required (59, 60). When virilization is present, it remains essential to test at least two to three tissues to search for cryptic Y material; FISH of buccal cells may detect Y mosaicism that is not detectable in peripheral blood (61, 62).

The rate of gonadoblastoma among TS patients with Y chromosome sequences that were detected by PCR or FISH varied from 4 to 60% in 14 studies, and data on the long-term outcome of this cohort are incomplete. Putting all data together, approximately 10% may develop a gonadoblastoma, although there is considerable variation in risk estimates, possibly related to methodology, sample size and potential selection bias (56, 63). The rate of gonadoblastoma among all TS patients, including those without Y chromosome sequences, is low (approximately 1%). For these reasons, molecular screening to detect Y-chromosomal sequences is currently recommended *only* in TS individuals with masculine features who are negative for Y material by conventional cytogenetic and FISH analyses. In these individuals, multiple sequences adjacent to the Y centromere should be amplified using PCR.

Chromosomal microarray analysis has revolutionized the study of people with growth disorders, unusual appearance, multiple anomalies and/or neuropsychological differences, but its role in TS is currently considered to be supplemental. X chromosome structural classifications of 187 TS patients using SNP microarray genotypes were comparable to conventional cytogenetics in more than 90% of the cases, and identified two derivative Y chromosomes and 13 large copy-number variants that were not identified by karyotyping (64). Long-term

studies are needed to determine the prognostic utility of microarray data before these methods are incorporated into routine clinical practice.

Based on the observation that phenotypical features in TS subjects vary greatly, even when focusing on women with monosomy X, an imprinting effect has been proposed as a potential explanation for the observed variance (65). Most of the studies analyzing parent-of-origin effects in TS, report a predominance of the maternal X, largely due to the non-viability of the karyotype 45,Y and a slight preferential loss of paternal sex chromosomes (66, 67, 68, 69, 70, 71). Several studies analyzed whether X-linked imprinting effects might be associated with distinct phenotypical features, with conflicting results (72, 73, 74). Lack of statistical power to detect subtle differences explains part of the observed heterogeneity (Table 4).

Based on the currently available data, it seems premature to conclude whether the paternal origin of the remaining X might exert an impact on height, growth (response) or the frequency of organ anomalies in TS. Regarding central nervous system (CNS) morphology and function, including certain neuropsychological features, most studies described the differences between individuals who inherited a maternal or paternal X. Some studies described a more severe phenotype in subjects with a maternally derived X chromosome (75), although another study found no convincing effect of genomic imprinting on neurocognitive/socialization function, but rather reported a subtle difference in visual perceptual reasoning with lower scores in subjects with a paternal X chromosome (76).

From a clinical perspective, a genetic work-up to detect the parental origin of the remaining X is currently not indicated in routine care of women with TS.

#### 1.4. Newborn screening

Missed and delayed diagnoses of TS remain a major problem. For girls with TS who are not identified in infancy with lymphedema and webbed neck, diagnosis is often made years after growth failure is apparent, and sometimes when little or no growth potential remains (34, 35, 36, 37, 77). In general, the later GH therapy is initiated, the greater the height deficit and the lower the likelihood of normal adult stature and age-appropriate initiation of therapies for pubertal development. Early diagnosis allows for timely screening and intervention for problems such as strabismus, hearing loss, renal and cardiac abnormalities, hypothyroidism, celiac disease and learning disabilities, thus improving QoL. It may also

**Table 4** Influence of the parental origin of the remaining X chromosome on phenotype.

Author, year	n	Mat X	Pat X	Phenotype parameter(s)	Specific parameter(s)	Stat. analysis (Xm vs Xp)
Chu <i>et al.</i> , 1994 (65)	63	43	20	Clinical phenotype	Cardiac	ns
					Webbed neck	ns
				Pooled data on clinical phenotype	Renal	ns
					Cardiac	$P < 0.01$
Devernay <i>et al.</i> , 2012 (546)	180	128	52	Growth	Webbed neck	$P < 0.05$
					Renal	ns
					Birth length SDS	ns
					Birth weight SDS	ns
					Height before GH	ns
					Height gain	ns
					Adult height SDS	ns
Gould <i>et al.</i> , 2013 (518)	161	116	45	Education	Baccalaureate degree	ns
				Employment	ns	
Hamelin <i>et al.</i> , 2006 (351)	54	35	19	Marital status		ns
				Growth	Birth weight (kg)	ns
Sagi <i>et al.</i> , 2007 (449)	80	60	20	Clinical phenotype	Birth length (cm)	ns
					Cardiac	ns
					Hypertension	ns
				Growth	Renal	$P < 0.05$
					Birth weight (kg)	ns
					Height SDS	ns
					BMI SDS	$P < 0.05$
				Biochemistry	Height velocity SDS (with GH)	ns
					Cholesterol	$P < 0.005$
					Triglycerides	ns
Skuse <i>et al.</i> , 1997 (75)	80	55	25	Cognitive function	Fasting glucose	ns
					Verbal IQ	$P < 0.05$
				Special educational needs Executive function tasks	Nonverbal IQ	ns
					Behavioral inhibition	$P < 0.05$
					Planning ability	ns

Excludes studies with 50 or fewer subjects.

ADHD, attention-deficit hyperactivity disorder; GH, growth hormone; IQ, intelligence quotient; Mat, maternal; ns, not significant; Pat, paternal; SDS, standard deviation score.

improve fertility in some individuals with TS by allowing for oocyte or ovarian tissue harvesting before the death of too many follicles. Earlier diagnosis of TS will require greater recognition of the disorder through education and/or population screening.

Ideally, screening for TS would be part of existing newborn screening programs. Karyotyping, considered to be the gold-standard technique for diagnosing TS, has major limitations as a screening tool given its long processing time, high cost and requirement for specialized personnel. However, several molecular methods have been proposed for neonatal screening of TS, of which pyrosequencing and real-time PCR appear to hold the greatest promise (78). Advances in pyrosequencing technology have been rapid, but it remains expensive. In contrast, a recent study estimated that each real-time

PCR test for TS detection costs \$15 US. 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 (79). Most recently, whole-exome sequencing was shown to accurately diagnose TS, including cases with low-level mosaicism, isochromosome Xq and cryptic Y material (80).

If molecular screening for TS is offered, positive findings will need karyotype confirmation. Like all other disorders diagnosed on newborn screening, infrastructure for follow-up, treatment and support of the newborns diagnosed will need to be developed.

Possible drawbacks to screening include the likelihood that some girls identified with TS will be phenotypically normal, experience minor or no clinical consequences,

and, thus, may be needlessly concerned. Other sex chromosome abnormalities, such as Klinefelter syndrome (if both phenotypic males and females are tested), may also be diagnosed and will 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 (81). Studies are needed to quantitate the benefits of newborn diagnoses of TS and the feasibility of molecular techniques for diagnosis needs to be established. We conclude that newborn screening for TS should be considered after additional improvements in methodology.

## 2. Growth and puberty

**R 2.1.** We recommend initiating growth hormone (GH) treatment early (around 4–6 years of age, and preferably before 12–13 years) in the following circumstances: the child already has evidence of growth failure (e.g., below 50th percentile HV observed over 6 months in the absence of other treatable cause of poor growth), the child is already short or has a strong likelihood of short stature (e.g., short parents and short predicted adult height or already pubertal at the time of diagnosis) (⊕⊕⊕○).

**R 2.2.** We recommend using a GH dose of 45–50 μg/kg/day or 1.3–1.5 mg/m<sup>2</sup>/day (4.0–4.5 IU/m<sup>2</sup>/day) in most instances, increasing to 68 μg/kg/day (2.0 mg/m<sup>2</sup>/day) if adult height potential is substantially compromised (⊕⊕⊕⊕).

**R 2.3.** We recommend monitoring growth-promoting treatment by measurement of height at least every 4–6 months during the first year of treatment and at least every 6 months thereafter (⊕⊕⊕○).

**R 2.4.** We recommend monitoring the safety of growth-promoting therapy by measurement of IGF-I at least annually (⊕⊕○○).

**R 2.5.** We suggest that for TS patients treated with GH the measured IGF-I should ideally be no greater than 2 SDS above the mean for age. If an IGF-I value is measured above +3 SDS, a GH dose decrease is warranted. For an IGF-I value between +2 SDS and +3 SDS, clinical judgment should guide further GH dose selection (⊕○○○).

### 2.1. Growth-promoting therapies

The goals of growth-promoting therapies are to facilitate attainment of heights during childhood and adulthood

that minimize physical restrictions and allow puberty to begin at an age similar to peers. The centerpiece of growth-promoting therapy is GH, which increases HV and results in modest increases in adult stature for most patients (82). However, as most girls will require estrogen replacement to either initiate or complete puberty prior to completion of linear growth, the estrogen route, dosage and escalation tempo will have an impact on pubertal growth (see section on estrogen supplementation) and, therefore, on adult height (AH). AH within the lower range for female population standards is the likely outcome for most women at completion of growth-promoting therapy.

### 2.2. Efficacy of GH treatment

Despite the plethora of studies of GH treatment in TS, a 2007 Cochrane Center review (82) identified only four trials in which GH treatment was compared in a randomized fashion with a concurrent non-treatment or placebo control for at least 1 year (83, 84, 85, 86), and only a single RCT that followed participants to AH (83). More recently, a 2-year RCT evaluating the impact of GH initiation before age 4 years, and a double-blind, placebo-controlled trial to AH have been published (87, 88). Patients with TS in the North American GH registration trials treated to (near-) AH had average gains vs concurrent control (83), baseline predicted/projected height or historical controls ranging from about 5 to 8 cm over periods ranging from 5.5 to 7.6 years (89, 90, 91); similar results were observed in the more recent placebo-controlled trial (87). These data indicate that height gain of about 1 cm per year of GH therapy is a reasonable expectation. Two European studies using high GH doses at young ages have demonstrated much more dramatic gains of 15–17 cm (mean) vs baseline projected AH (92, 93, 94). A formal GRADE evaluation for the present guideline included 14 randomized studies on the effect of growth-promoting therapies in TS (both GH and oxandrolone) (Appendix 2). Studies were published between 1991 and 2011. Studies displayed large heterogeneity with respect to design, included patients, treatment schedules (dose and duration), follow-up duration and reported endpoints. There is a considerable risk of bias in the included studies. Only five studies were adequately blinded, while the remaining were not. Long-term data were often characterized by considerable loss to follow-up. For example, long-term effects were only studied in approximately 62% of the original study population (95). Such post-randomization loss to follow-up may introduce selection bias – even in a RCT. In addition, the use of a run-in period to exclude

non-compliance (96) may hamper the generalizability of the results. In almost all studies, the primary endpoint was not well defined. Finally, many small studies were underpowered (97), and no study reported on mortality.

Most studies reported on HV, expressed as either cm/year or change in height SDS. In studies that enabled a comparison of GH to no treatment or placebo (83, 87, 88, 89), the GH-treated group had a greater growth rates. Additionally, in studies comparing the added value of oxandrolone therapy to GH, this addition of oxandrolone resulted in a greater growth rate (95, 96, 97, 98, 99). AH was taller in GH-treated compared to non-GH-treated patients, with reported differences ranging from 0.5 to 1.5 SDS (83, 87, 88).

If catch-up growth to within the normal range occurred within the first two years of treatment, HV was maintained close to the mean for age, and there was adequate pubertal growth, and then AH within the lower normal range (above about 152 cm or 60 inches) was observed. However, comparison with published ranges for HV and height SD score may be unreliable during the pubertal age range because girls with TS lack the pubertal growth spurt resulting from the synergistic actions of endogenous GH and estrogen. During this period, GH-treated girls with TS may lose ground when height SD score is calculated according to general standards, but height SD score should still continue to increase compared with TS standards.

### 2.2.1. Factors influencing the efficacy of GH treatment

Factors predictive of *taller adult stature* include a relatively tall height at initiation of therapy, tall parental heights (i.e., mid-parental height (MPH)), young age at initiation of therapy, longer period of treatment before induction of puberty, long duration of therapy and higher GH dose (85, 93, 94, 100, 101, 102, 103, 104). Factors predictive of the magnitude of short- or long-term height gain from baseline include young baseline age; difference between baseline height SD score and MPH SD score; maternal height SD score (105); weight SD score and dose, frequency and duration of GH treatment (88, 94, 100).

Factors such as the patient's baseline height and difference from MPH, while not modifiable, may provide useful information to facilitate realistic expectations of treatment outcomes. Factors that can be influenced such as age at the initiation of GH treatment, GH dosing strategies and addition of supplemental oxandrolone or low-dose estrogen are discussed in the following sections.

### 2.2.2. Age at GH initiation

The optimal age for initiation of GH treatment has not been firmly established, but various lines of evidence indicate that younger age at treatment initiation (83, 85, 104, 106, 107), including at least 4 years of treatment prior to puberty (101, 105, 108, 109), is associated with greater treatment effect. Analyses of large cohort studies followed in national or pharmaceutical company-sponsored registries report a similar positive effect of younger age at treatment initiation (100, 103, 104, 106, 110, 111).

Relatively early GH initiation, around 4–6 years of age, is likely to result in greater height gains during childhood and allow for age-appropriate induction of feminization, such that the goals for both optimal adult stature and timing of puberty can be achieved. Therapy may be continued until the girl is satisfied with her height or until little growth potential remains (bone age  $\geq 14$  years and HV  $< 2$  cm/year). There is no physiological rationale for continuing GH treatment into the transition period after the completion of puberty.

### 2.2.3. GH dose and frequency of administration

GH therapy for TS in North America is generally initiated at a dose of 0.350–0.375 mg/kg/week (equivalent to 50–54  $\mu\text{g}/\text{kg}/\text{day}$ ), in Europe at 1.3–1.4 mg/m<sup>2</sup>/day (4.0–4.3 IU/m<sup>2</sup>/day; 45–50  $\mu\text{g}/\text{kg}/\text{day}$ ) and in Australasia at 4.5–9.5 mg/m<sup>2</sup>/week (0.6–1.4 mg/m<sup>2</sup>/day), administered in divided doses 7 days/week. Higher GH doses are not routinely recommended, but an increase in the GH dose may be considered in girls with very poor height prognosis, within the authority-approved dose range and following careful discussion of potential risks and benefits.

### 2.2.4. Safety of GH treatment

Safety of GH treatment in TS in long-term clinical trials has generally been reassuring with respect to blood pressure and risk factors for cardiovascular disease (112, 113, 114, 115), carbohydrate and lipid metabolism (113, 116, 117, 118), body composition (113, 117), bone mineralization (119), body proportions (112, 120) and prevalence of OM and hearing loss (121). However, it is important to recognize that clinical trials are not powered for these safety endpoints and absence of evidence of a safety signal is not equivalent to evidence of its absence. Large observational studies that have adequate patient numbers to detect rare adverse outcomes (122, 123, 124) provide more robust assessment of the longer-term safety of GH. Observational data indicate that girls with TS appear to be at increased



risk of intracranial hypertension and slipped capital femoral epiphysis during GH treatment compared with children with idiopathic GH deficiency or idiopathic short stature (123). In analyses of another large observational study, development or progression of scoliosis was more common in girls with TS than children with other growth disorders (122). Both problems may be exacerbated by the rapid increase in linear growth stimulated by GH (125). In this same study, 3 of 10 reported cases of pancreatitis were in girls with TS, with the total number of patients with TS in this registry about 10% of the overall subjects, suggesting that girls with TS may be at greater risk of this specific adverse event than GH-treated children with other growth disorders. Although there have been rare case reports of neoplasia in GH-treated patients with TS (126, 127), data from GH registries provide no evidence of an increase in risk of neoplasia in GH-treated patients with TS (122, 128, 129).

Patients with TS are inherently at increased risk of disorders of carbohydrate metabolism (130, 131, 132) and have a specific defect in glucose-stimulated insulin secretion (131, 133). Although most long-term data regarding exacerbation of such problems by GH treatment in patients with TS have been reassuring (113, 116, 118, 134, 135, 136, 137), persistently reduced insulin sensitivity 5 years after discontinuation of GH in one study (116) underscores the need for careful follow-up of carbohydrate metabolism. In contrast, another study found reduced abdominal adiposity and significantly better glucose tolerance in GH-treated vs -untreated girls with TS, suggesting that beneficial effects on body composition and regional fat deposition may outweigh GH-induced insulin antagonism (117). Whether the risk of type 2 diabetes (T2DM) is increased by GH treatment in TS remains an open question, as analysis from one observational study reported an increase vs general population rates (138), while no increases were reported in analyses from two other observational databases (122, 124).

### 2.3. Concomitant treatment with the anabolic steroid oxandrolone

**R 2.6.** We suggest concomitant treatment with oxandrolone from the age of 10 years or older at 0.03 mg/kg/day and maintained below 0.05 mg/kg/day, if the diagnosis of TS (and therefore GH treatment initiation) is delayed, and/or AH outcome is likely to be unsatisfactory with the standard GH dose alone (⊕⊕⊕⊕).

Although well-controlled studies have demonstrated modest synergistic increases in growth response by

addition of oxandrolone during treatment with GH (95, 97, 139, 140, 141, 142), the potential for the unwanted effects of delayed breast development and dose-dependent virilization (e.g., clitoromegaly, voice deepening, hirsutism and acne) prompts the need for caution in the use of this therapy. If the decision is made to add oxandrolone, this should not be done until around age 10 years, initiated at a dose of 0.03 mg/kg/day and maintained at no greater than 0.05 mg/kg/day. The GRADE evaluation showed further that AH was approximately 2–5 cm higher in oxandrolone- and GH-treated patients compared to GH-treated only (95, 139, 140). Thus, existing literature show a growth effect of addition of oxandrolone to GH. In one study, virilization was more often reported in the oxandrolone and GH group compared to the GH only group (16 vs 5%) (139). Heterogeneity between studies prevents performing a formal meta-analysis and prohibits a final evidence-based verdict on the optimal growth-promoting treatment schedule in TS.

### 2.4. Concomitant treatment with childhood ultra-low-dose estrogen

**R 2.7.** We suggest to not 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 ethinylestradiol as a growth-promoting agent during the prepubertal period combined with GH demonstrated a modest synergistic increase in AH, normalization of the timing of thelarche for about one-quarter of the girls, and modest improvements in cognition and memory within specific developmental windows (87, 143, 144, 145).

However, no other independent trials have evaluated this approach, the dosing and administration of childhood estrogen have not been optimized, and long-term safety has not been assessed. The addition of very-low-dose estrogen replacement as a growth-promoting therapy is currently not recommended.

### 2.5. Sex hormone replacement

**R 2.8.** We recommend that estrogen replacement should start between 11 and 12 years of age increasing to adult dosing over 2–3 years (⊕⊕⊕○).

**R 2.9.** We suggest that low-dose estradiol (E2) is the preferred estrogen and that it be administered by a

systemic route and that the transdermal route is preferred (⊕○○○).

**R 2.10.** We recommend adding progesterone once breakthrough bleeding occurs or after 2 years of estrogen treatment (⊕⊕⊕⊕).

Turner syndrome is usually accompanied by hypergonadotropic hypogonadism and primary or secondary amenorrhea due to gonadal dysgenesis. Approximately one-third of girls with TS have spontaneous thelarche, occurring most often in girls with mosaicism (146, 147, 148). Regular menstrual cycles occur in at most 6% of these subjects (148).

Most patients with TS will therefore need HRT – for induction of puberty and for maintaining female secondary sex characteristics, attaining peak bone mass and normalizing uterine growth.

The optimal estrogen replacement therapy regimen to induce pubertal development is still being evaluated, but, since the previous guidelines (2), studies suggest use of transdermal (TD) preparations as the preferred choice. However, there is no study to date of TD use from initiation of puberty until adulthood. Therefore, we present data in support of TD use based on available studies and theoretical considerations. Theoretical reasons include: a more physiologic route of delivery without the first-pass effect through the liver, thereby avoiding the accumulation of non-physiologic estrogens observed after the oral route (149). The latter route is associated with a pro-coagulable state (150) and increased risk of stroke in the postmenopausal setting (151).

Estradiol (E2) is normally secreted into the systemic circulation; thus, the liver receives the same concentration as other somatic tissues, and a systemic route of replacement estrogen delivery is physiologic (152). In contrast, estrogen given orally reaches the systemic circulation only after absorption into the portal venous system and after metabolism by the liver, thus exposing the liver to a greater amount of estrogen than the rest of the body. Orally administered estrogens are metabolized by the liver to estrone and other metabolites before reaching the systemic circulation. Thus, delivery of E2 into

the systemic circulation by TD, transvaginal or parenteral administration more closely mimics normal physiology. A transvaginal route is not recommended for prepubertal girls, and parenteral administration (injection) is not preferred by most patients when a TD option is available.

Timing, route and dose of some recommended estrogen replacement options are depicted in Table 5. The goals of replacement are to mimic the progression of puberty in an average girl and minimize risks. The initiation dose is based on an average progression of puberty and protection of growth potential. Delaying estrogen replacement may be deleterious to bone and uterine health, as observed in anorexia nervosa. It is important to remember that the recommendation is for estrogen replacement of a deficient state, not supplementation of endogenous hormones. Adult dosing is also based on uterine and bone health, as well as symptoms of hypogonadism.

To mimic normal physical and social development, treatment should begin at 11–12 years, as long as gonadotropins are elevated. Luteinizing hormone (LH) and FSH may be measured annually starting at age 11 years or earlier. If gonadotropins are normal for age, observation for spontaneous puberty is appropriate, with future replacement therapy if gonadal failure occurs. Low anti-Müllerian hormone (AMH) and undetectable inhibin B can also be used to predict ovarian failure in TS (153, 154, 155). Using low doses of estrogen is crucial to preserve height potential whether or not GH treatment has already been initiated, because very-low-dose ethinylestradiol (EE), TD E2, oral E2 and systemic (depot) E2 do not interfere with the growth response to GH therapy (87, 94, 152, 156, 157). It should be noted that EE doses  $\geq 3 \mu\text{g}/\text{day}$  administered prior to 14 years may decrease the growth response (140, 158). Therefore, the lower-dose E2 preparations are preferable for initiation of puberty.

Incremental dose increases can occur approximately every 6 months to mimic the normal pubertal tempo until adult dosing is reached over a 2- to 3-year period. This theoretically translates into a 25–100% increase in dose every 6 months using 4–6 dose changes between

**Table 5** Recommended estrogen replacement options for feminization in adolescent TS.

Preparation	Pubertal initiation dose	Adult dosing
Transdermal E2	3–7 $\mu\text{g}/\text{day}$ *	25–100 $\mu\text{g}/\text{day}$
Micronized 17 $\beta$ oral E2 (E2)	0.25 mg/day	1–4 mg/day
Ethinyl estradiol (EE)**	2 $\mu\text{g}/\text{day}$	10–20 $\mu\text{g}/\text{day}$
Depot E2***	0.2 mg/month	2 mg/month

\*See discussion of how to apply patches below; \*\*not available in the US as monotherapy; \*\*\*not available in Europe. E2, 17 $\beta$ -estradiol.

the initiation and adult doses portrayed in [Table 5](#). However, no studies to date have rigorously studied outcomes in relation to the rate of dose increase for the different preparations. Routine monitoring of serum LH or FSH is not recommended during estrogen treatment as concentrations remain elevated in hypergonadotropic hypogonadal women until higher doses of estrogen are given. Estradiol measurement using an ultrasensitive assay allows titrating dosage, if desired, though E2 concentrations for optimal growth remain to be determined ([149](#)). Clinical assessment, patient satisfaction, patient age and often residual growth potential are the primary determinants for a dose increase. If potential for taller stature is still possible, girls may remain on lower estrogen doses longer. If girls are already older at initiation, the duration of time until adult dosing may be shortened.

Studies of the regimens report onset of breast buds within 6 months in most girls ([94](#), [159](#), [160](#), [161](#), [162](#)). The starting doses for depot E2 lead to slightly slower onset and for oral E2 slightly faster onset ([156](#), [159](#), [160](#)). Each of these regimens results in Tanner stage 4 breasts in approximately 2.25 year, which is similar to the tempo seen in TS girls with spontaneous puberty (1.9 year) ([158](#)) and in girls in general ([161](#)).

Girls with TS typically have a normal uterus, and progestin must be added once breakthrough bleeding occurs, or after 2 years of treatment, due to the risk of endometrial cancer associated with prolonged unopposed estrogen ([163](#)). In adult women, micronized crystalline progesterone, e.g. Prometrium (100–200 mg) or medroxyprogesterone, is preferred based on decreased breast cancer risk, but the data for this are relatively weak ([164](#), [165](#)). However, the risk of breast cancer is low in TS ([166](#), [167](#), [168](#)), and long-term treatment with HRT does not seem to induce breast cancer ([169](#)). Progestin can be added for 10 days each month for withdrawal bleeding, and adult women with TS should preferably continue treatment with 17 $\beta$ -estradiol in combination with a sequential progestational agent. A recent publication showed no increased risk of stroke with progesterone and pregnane- or nortestosterone-derived progestins. However, norpregnane derivatives were found to increase this risk ([151](#)). Studies have not been done in TS comparing various progestin options.

Once adult replacement doses are reached, treatment should persist until the risk of continuation outweighs the benefits, around the average age of menopause. Assessment of risk must be individualized for each woman ([164](#), [170](#)). Screening for thromboembolic risk should

be performed in girls with a personal or family history. However, routine screening is not recommended, and screening is done only to educate the family on risks, not to postpone estrogen therapy ([171](#)).

A randomized controlled trial showed that early, very low-dose, depot E2 monthly injections initiated normal pubertal growth and development in conjunction with GH treatment ([156](#)). Transdermal E2 is likely to be preferred by girls over depot injections, although these two modalities have not been directly compared. A fractionated patch dose (one-quarter of a 25- $\mu$ g patch or about 6.25  $\mu$ g) applied overnight mimics the normal early morning serum E2 peak ([162](#)). Although not recommended by the product labels, two studies report pubertal E2 concentrations and/or breast development with use of a fractionated patch, and include practical guidelines for cutting the patch and application ([162](#), [172](#)). There is also a published opinion that cyclical administration of patches, commencing with the application of a 14–25- $\mu$ g patch, the lowest doses commercially available, for 1 week monthly, may achieve similar results ([156](#)). Because the effect of the weeks without estrogen exposure is unknown, further data are needed before recommendations can be made regarding the best approach for patch application.

The GRADE evaluation of HRT found seven randomized studies on the differences between oral and TD hormone replacement therapies in TS. Studies were published between 1995 and 2013. Two studies ([173](#), [174](#)) were excluded because they did not report sufficient data on differences between routes of administration. Included studies displayed large heterogeneity with respect to design, included patients, choice of treatment (only 3 studies compared oral vs TD E2), treatment schedules (dose and duration), follow-up duration and reported endpoints. Overall, there is a considerable risk of bias in included studies. All studies were non-blinded and several studies included a small number of subjects. Details of the included studies are shown in [Supplementary Fig. 1](#), the GRADE scoring per outcome and evidence synthesis is provided in [Appendix 3](#).

Five studies reported data on HDL cholesterol concentrations ([149](#), [160](#), [172](#), [175](#), [176](#)). TD E2 showed a decrease in HDL plasma concentrations compared to oral estrogen as shown in [Appendix 4](#) (weighted mean difference  $-8.09$ ; 95% CI  $-12.7$ ,  $-3.5$ ). The plasma concentrations of total cholesterol, LDL cholesterol and TG were not different across routes of administration.

In two studies, bone mineral density was studied ([149](#), [160](#)). Both studies showed a somewhat better lumbar

Z-score after TD use compared with oral administration (weighted mean difference 0.93; 95% CI 0.68, 1.19). However, sample sizes were too small and follow-up was too short to draw meaningful conclusions regarding bone density.

The type and route of estrogen administration did not affect glucose or insulin concentrations in any study.

Additionally, we included one randomized study that compared low-dose estrogen replacement therapy with high-dose therapy, one study on the effect of timing of administration (morning or evening administration) and one randomized study on the difference between fixed and individualized dose of estrogen therapy (177, 178, 179).

With regard to the dose of estrogen administration, one study compared conjugated and ethinylestradiol and found that some parameters were affected by either low or high dose (hypotrophic endometria, insulin, PTH, 1,25-dihydroxyvitamin D, liver enzymes), some were unaffected by either of them (urinary deoxyypyridinoline cross-links) and some required high-dose preparation (FSH, alkaline phosphatase, osteocalcin) (177). A RCT study on the effect of dose of administration of E2 on bone mineral density or anthropometric markers did not find differences during 5 years, although bone-specific alkaline phosphatase was significantly higher in the high dose compared with the low-dose estrogen group (180). A RCT concluded that a low fixed dose of estrogen produces a satisfactory pubertal development not inferior to an individualized dose (178).

Very little evidence is available on the timing of administration. Based only on one RCT, evening administration of oral estrogen together with evening injections of GH may be preferable compared with morning administration (179).

Only one study has directly compared the route of administration in adolescence, oral vs TD, using E2 in 40 girls with TS followed for 1 year (149). The study found no differences in body composition, bone mineralization or plasma lipids when the plasma E2 concentrations were titrated to those of normally menstruating adolescents in both groups. However, oral estrogen was associated with a marked increase in conjugated estrogen precursors, such as estrone sulfate and serum estrogenic bioactivity. This is concerning in the context of the increased thromboembolic risk observed with oral estrogen in epidemiological studies (181, 182, 183).

Current evidence does not indicate that the hepatic effects on lipids or binding proteins cause an appreciable

clinical difference between low-dose oral estrogens vs low-dose TD E2. There were no significant differences in glucose (149), insulin tolerance (177, 184), fasting insulin concentration, protein turnover, lipolysis (175), osteocalcin, highly sensitive C-reactive protein, BMI or waist-to-hip ratio (184, 185) between groups with TD vs oral estrogen treatment. Glucagon and insulin levels (during an OGTT) as well as insulin resistance tended to be lower following evening oral E2 administration (0.3–0.5 mg/day) (179). With the exception of one study reporting significantly higher HDL cholesterol after oral E2 (172), there were no significant differences in lipids between groups with different routes of estrogen administration (149, 175, 176, 177). There was also no evidence of liver toxicity from estrogen replacement therapy (186). Liver enzymes were elevated in untreated TS (174, 187, 188, 189) and reduced by exogenous estrogen-progestin administered orally or via the TD route (190). Replacement therapy with E2, by either oral or TD routes, lowers blood pressure (191, 192, 193), although E2 causes salt and water retention (194). This contrasts with EE-containing contraceptives, which, unless containing an anti-mineralocorticoid progestin, raise blood pressure significantly (195). Several studies looking at oral conjugated estrogens (CEE) vs TD E2 replacement in the postmenopausal setting have shown increased thromboembolic risk, especially in the first year of treatment in the oral group, and more pronounced in women with existing risk factors such as obesity (181, 182, 183).

EE exerts dose-related suppression of IGF-I in GH-naïve patients (196, 197). However, data concerning the influence of different routes of estrogen therapy on IGF-I concentration in GH-treated subjects are inconsistent, with some suggesting no effect and others suggesting suppression. Dose-response studies are lacking for most forms of estrogen (149, 172, 174, 175, 179).

Transdermal E2 administration (25–37.5 µg/day) has been reported as better than CEE (0.3–0.45 mg/day) for spine bone mineral density (BMD) in one study of TS girls (160), while no differences were observed in another study in which TD and oral E2 doses were titrated to similar concentrations (149).

Data concerning the influence of different routes of estrogen therapy on uterine volume are still inconclusive as route, dose, age at onset of treatment and duration of treatment all influence uterine growth. One study showed that EE treatment regimen gives rise to satisfactory pubertal induction and maintenance, but 20–30 µg daily



failed to induce a fully mature uterus in 50% of the girls (198). Most studies reported that uterine volume was not affected by the type of estrogen used (199, 200), but is related to dose and duration of therapy (201, 202) (see Fertility section for optimal dosing). Although there have been no studies in children, we suggest against CEE in view of thromboembolic and cardiovascular disease risks reported in postmenopausal women (150).

Low-dose oxandrolone (0.03–0.05 mg/kg/day; maximum 2.5 mg/day) may modestly slow pubertal progression in response to estrogen replacement, delay menarche and increase clitoral size slightly, but these effects are minor and/or transient. A reasonable suggestion is that adjunctive treatment with oxandrolone be considered in very short TS girls, as suggested above, and until estrogen therapy is initiated (95, 139, 141, 158, 203).

The young women with TS who reached normal height and had age-appropriate pubertal development reported normal health-related quality of life (HRQoL); satisfaction with breast development (and height) had a positive influence on several HRQoL scales (204). Puberty should be induced at a physiologically appropriate age to optimize self-esteem, social adjustment and initiation of the patient's sex life (205, 206). One study showed that both estrogen use and age of puberty did not influence sexual function in patients with TS (207). Available data indicate that, on average, adult women with TS demonstrate characteristic neurocognitive profiles despite preserved ovarian function or adequate estrogen replacement (208).

### 3. Fertility, reproductive assisted technologies and pregnancy

Due to early ovarian insufficiency, most women with TS are infertile. Women with TS report infertility to be one of the greatest issues affecting their QoL (49).

#### 3.1. Spontaneous pregnancies

**R 3.1.** We recommend counseling females with TS that their probability to conceive spontaneously decrease rapidly with age, if at all present, and consideration should be given to offering fertility treatment at a young age (⊕⊕⊕⊕).

Only few TS women will be able to get pregnant with their own eggs, and the few TS individuals that are fertile often enter menopause earlier than normal women. Spontaneous pregnancies occur in 4.8–7.6%

of women with TS (18, 28, 209), but the frequency of miscarriages after spontaneous pregnancy was reported to be high: 30.8–45.1% (Supplementary Table 1) (18, 28). A study of 160 spontaneous pregnancies in 74 TS women found that, of the 58% resulting in a live birth, 34% were complicated by a fetal malformation. Of these, two-thirds were TS or Down syndrome, and the remaining etiologies were multifactorial (210). The risk rate of early pregnancy loss in the general population is 8–20% (211).

In a retrospective study of 115 women with a TS karyotype, obstetrical outcomes were compared with those of the general population (212). Most of the pregnancies were conceived naturally, and the TS diagnosis was unknown in 52% at the time of pregnancy. The karyotype of 10 women was 45,X. Pre-eclampsia occurred in 6.3% of women with TS compared to 3.0% in the control group, and AoD occurred in one TS woman (213). Compared with the reference group, women with a TS karyotype gave birth to children at an earlier gestational age and with a lower median birth weight. The cesarean section rate was 35.6% in women with TS karyotype vs 11.8% in the control group. The rate of birth defects did not differ between the two groups (212).

#### 3.2. Assisted reproductive technologies (ART) with autologous oocytes

**R 3.2.** We suggest that young mosaic TS women with persistent ovarian function should be counseled that oocyte cryopreservation after controlled ovarian hyperstimulation is a possible fertility preservation option (⊕○○○).

**R 3.3.** We recommend against routine oocyte retrieval for fertility preservation of young TS girls before the age of 12 years (⊕○○○).

In the only published study to date of IVF stimulation in women with TS, Doger *et al.* reported outcomes of standard IVF in a total of 35 cycles in 22 women with mosaic TS. The clinical pregnancy rate was 8.6%, and live birth rate was 5.7% (214). It is well established that decreased ovarian reserve results in lower IVF pregnancy rates (215, 216). Given that TS women have rapidly decreasing ovarian reserve from a very young age, it is vital to counsel that their chance of pregnancy with autologous oocytes decreases rapidly and that consideration should be given to offering fertility treatment (including standard IVF) at a young age and without unnecessary delay.

### 3.3. Assisted reproductive technologies with oocyte donation (OD)

**R 3.4.** We recommend considering OD for fertility, only after thorough screening and appropriate counseling (⊕⊕⊕⊕).

**R 3.5.** We recommend that management of pregnant women with TS should be undertaken by a multidisciplinary team including maternal–fetal medicine specialists and cardiologists with expertise in managing women with TS (⊕⊕⊕○).

For most patients with TS, OD is the only way to achieve a viable pregnancy. There have been reports of clinical pregnancies in oocyte recipients with TS since 1990, but the number of patients treated has been small. After GRADE evaluation, 11 studies were included based on eligibility criteria and endpoint definition. Sample size of TS women per study varied from 3 to 30 subjects, totaling 179 patients with either monosomy (45,X) or other variants such as mosaicism with 45,X in one cell line and X deletions. Studies were published between 1990 and 2011. Risk of bias was moderate, mainly due to small sample sizes and the potential of selection bias (i.e. inclusion of patients because of specifically positive outcomes).

The clinical pregnancy rate varied between 16 and 40% (Supplementary Table 2), like other recipients of donated oocytes (18, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227). The pooled proportion (random effects model) of clinical pregnancy per embryo transfer was 28% (95% CI 23–34%) (Supplementary Fig. 2).

Initial studies found high rates of early pregnancy loss in TS females ranging from 16 to 80% (219, 220, 221, 222, 223, 224), likely related to inadequate HRT (228). A structurally abnormal uterus, autoimmune mechanisms and/or diminished endometrial receptivity due to long-term hypoestrogenism may also increase spontaneous abortion rates in women with TS (229).

Previous studies have found that women with TS treated with oral or TD E2 or CEE may attain a normal mature uterine size and configuration (230). Estradiol-based regimens result in better uterine development than contraceptive-based regimens (199).

Women with TS who conceive with OD are at high risk for obstetrical complications (Supplementary Table 3). In TS, the incidence of hypertensive disorders of pregnancy has been reported to be 35–67% in singleton pregnancies and as high as 100% in multiple pregnancies (222, 224, 225, 226, 231, 232, 233). The reported incidence of pre-eclampsia ranged between 18% and

44% in singleton pregnancies and 75–100% in multiples, while the cesarean section rate is as high as 82–100% (222, 224, 225, 226, 231, 232, 233). In comparison, in oocyte recipients without TS, the rate of hypertensive disorders of pregnancy is 13–39%, and the cesarean section rate is 31–85% in singleton pregnancies (234).

In singleton pregnancies in TS, the risk of prematurity has been reported to be 9–33% and that of low birth weight 12–40% (Supplementary Table 4). In many studies, the outcomes of singleton and multiple pregnancies are not reported separately, which make their interpretation difficult. The perinatal mortality rate has been reported between 0 and 11% in published studies (225, 226, 231, 232, 233).

A large Nordic cohort study of 106 women with TS who gave birth after treatment with OD between 1992 and 2011 (233) reported 122 deliveries and a multiple delivery rate of 7.4%. In this cohort, the 45,X karyotype was observed in 44% of the recipients. Ten women had a known cardiac defect before pregnancy, 49% had a pre-pregnancy cardiac evaluation within two years before pregnancy and only 29% had an echocardiogram or CMR during pregnancy. In total, 35% of pregnancies were associated with a hypertensive disorder of pregnancy, including pre-eclampsia in 20.5%. Potentially life-threatening complications occurred in four patients (3.3%), but no maternal deaths were reported. The mean birth weight of the singletons was 3150g and that of twins is 2200g. These outcome statistics need to be viewed with caution considering the knowledge that with OD in non-TS women, the risk for hypertension during pregnancy is already twofold to threefold higher than observed after conventional IVF/intracytoplasmic sperm injection (ICSI). Rates of cesarean section, premature birth and low birth weight are also increased compared with conventional IVF/ICSI (234, 235). The higher risk of hypertensive disorder with OD pregnancies in TS women is postulated to be related to abnormal placentation due to maternal immunological reactions from a genetically foreign embryo (236).

### 3.4. Fertility preservation in Turner syndrome

Fertility preservation is potentially feasible in women with TS, as many girls with TS have ovarian follicles until their late teens, and some women with mosaic TS have follicles for many years thereafter, even though they tend to experience early menopause (237, 238). Oocyte cryopreservation after controlled ovarian hyperstimulation is a possible fertility preservation option

in young mosaic TS women with persistent ovarian function. Case reports describe cryopreservation of 8–13 mature oocytes after controlled ovarian hyperstimulation in TS women aged 14–28 years (239, 240, 241). So far, there are no pregnancies reported after oocyte freezing and thawing in TS, as these women are still young and have not attempted pregnancy yet. Vitrification of oocytes at an even younger age, perhaps about 12 years, may be feasible, but so far, there are no reliable data in TS (239, 240, 249).

Biopsy of ovarian cortical tissue is feasible at younger ages, but it requires an operation and anesthesia. In a study of follicular density in TS girls, the youngest girl studied was 8 years old, but she had very small ovaries with no follicles (237). Signs of spontaneous puberty, mosaicism, and normal FSH and AMH concentrations for age and pubertal stage were positive and statistically significant, but not exclusive, prognostic factors to find follicles. To date, there is not enough evidence to recommend routine fertility preservation of young TS girls before the age of 12 years (237, 238).

### 3.5. Counseling and ethical considerations about fertility preservation or fertility treatment

**R 3.6.** We suggest that other options for motherhood such as adoption or using a gestational carrier should be mentioned during preconception counseling (⊕○○○).

As women with TS have rapidly decreasing ovarian reserve from a very young age, it is vital to counsel them that their chances to conceive spontaneously decrease rapidly and consideration should be given to offering fertility treatment at a younger age. Counseling regarding fertility aspects should begin at the time of diagnosis to allow the patient and her parent(s)/guardian(s) to have time to consider its implications and the possibility of fertility preservation. Prior to initiating investigation or treatment, it is important for both the physician and patient to consider the ethical implications of proceeding with fertility preservation or fertility treatment. The decision to proceed with treatment should consider many factors, including the apparent increased risk of pregnancy loss or birth defects using autologous oocytes. This may result in grief and hardship, and the patient must be prepared and accepting of this potential outcome. Patients should be counseled about the availability of prenatal genetic diagnosis and pre-implantation genetic diagnosis or screening, although they may not have

adequate embryos available from IVF for these procedures. Mothers of daughters with TS might be willing to freeze their own oocytes for future use by the daughter (250). This is an option only in countries allowing egg vitrification and use of a known oocyte donor. Given that such intrafamilial donation comes with unique practical implications determined by different practice rules in different countries, careful additional ethical counseling seems warranted.

Whether conceiving with autologous or donated oocytes, the patient needs to be fully counseled regarding the increased maternal morbidity and mortality. Intensive cardiac screening is recommended before pregnancy, but normal results do not preclude the possibility of maternal death from AoD or aortic rupture (228, 231, 251, 252, 253). More challenging is the patient who has identifiable risk factors for AoD, but who wishes to proceed with fertility treatment. In this scenario, the physician must consider the safety of the patient as well as her reproductive rights. In preconception counseling, other options for motherhood such as adoption or using a gestational carrier should also be mentioned.

### 3.6. Cardiovascular risks during pregnancy

**R 3.7.** We suggest that all women with TS should be counseled about the increased cardiovascular risk of pregnancy (⊕○○○).

**R 3.8.** We recommend imaging of the thoracic aorta and heart with a transthoracic echocardiography (TTE) and CT/CMR within 2 years before planned pregnancy or ART in all women with TS (⊕○○○).

**R 3.9.** We suggest that ART or spontaneous conception should be avoided in case of an ascending ASI of >2.5 cm/m<sup>2</sup> or an ascending ASI 2.0–2.5 cm/m<sup>2</sup> with associated risk factors for AoD, which include bicuspid aortic valve, elongation of the transverse aorta, coarctation of the aorta and hypertension (⊕○○○).

**R 3.10.** We suggest that women with a history of AoD should be advised against pregnancy. If already pregnant, these women should be followed very closely at a specialist center and deliver by cesarean section (⊕○○○).

**R 3.11.** We suggest performing transthoracic echocardiography (TTE) in women with TS without aortic dilatation or other risk factors (hypertension, bicuspid aortic valve, coarctation, previous aortic surgery) at least once during pregnancy, at approximately 20 weeks of gestation (⊕○○○).

**R 3.12.** We suggest that women with TS with an ascending ASI >2.0 cm/m<sup>2</sup> or any risk factor (hypertension, bicuspid aortic valve, coarctation, previous AoD or surgery) should be monitored frequently, including TTE at 4- to 8-week intervals during pregnancy and during the first 6 months postpartum (⊕○○○).

**R 3.13.** We suggest that CMR (without gadolinium) should be performed during pregnancy when there is suspicion of disease of the distal ascending aorta, aortic arch or descending aorta (⊕○○○).

**R 3.14.** We recommend that blood pressure control is strict (135/85 mmHg) in all pregnant women with TS (⊕○○○).

**R 3.15.** We suggest that during pregnancy prophylactic surgery is reasonable in case of a dilated aorta with rapid increase in diameter (⊕○○○).

In 1997, the first reports of serious cardiac complications and deaths in pregnant women with TS were published (254), followed by additional reports of deaths after AoD related to pregnancy (228, 231, 251, 252, 253). The risk of maternal death from aortic dissection/rupture during pregnancy in women with TS has been estimated to be 2% (231, 255). However, only 38–49% of these women had any cardiac evaluation before embryo transfer. Published studies vary from 0% cardiac evaluation to 100% before fertility treatment (Supplementary Table 3). In the two largest studies to date, including 93 and 106 women, only 38% and 49% respectively had cardiac examinations with echocardiography or CMR imaging before pregnancy (231, 233).

Additional studies have estimated the risk of maternal cardiac complications to be 0–4% in OD pregnancies in women with TS (222, 224, 225, 226, 231, 232, 233). The risk of AoD during a multiple gestation is estimated in the literature to be approximately five times higher than that associated with a singleton pregnancy (232). It is imperative that any woman with TS undergoing treatment with IVF or OD has a mandatory single embryo transfer (233, 255).

### 3.6.1. Pregnancy and aortic disease

Aortopathy and aortic dilation increase the risks of pregnancy (256). Whether pregnancy-induced changes in cardiac output and circulating blood volume (257) also lead to an increased risk of AoD in pregnant women remain undetermined, due to inconsistent evidence. The largest registry of AoD did not reveal pregnancy as a risk factor (258). However, in a study of 278 pregnancies in women with Marfan syndrome, an eightfold increased dissection risk was reported (259). In the international

AoD registry (IRAD) of all those who suffered AoD during pregnancy or post-partum (0.4%), a disproportionate number had connective tissue disorders (73%). The most convincing evidence came from a Swedish birth registry that found a 25-fold increase in non-TS women (260). ART, as opposed to spontaneous pregnancy, is a risk factor for significant complications (232). A comprehensive registry that includes all cases of TS pregnancy will be essential to answer the question of dissection risk in TS pregnancy (261). In TS cases where the aorta is dilated, there are no studies that consider the advisability of elective aortic surgery before pregnancy.

After aortic surgery, women are still considered at high risk for AoD. Apart from the risk of AoD, women with TS may have other cardiovascular abnormalities such as aortic valve stenosis or coarctation of the aorta. The guidelines for care are similar to those for women without TS with cardiovascular disease (262).

### 3.6.2. Cardiovascular risks beyond the aorta

**R 3.16.** We suggest that in case of an acute ascending AoD before the fetus is viable, to perform emergency aortic surgery understanding that fetal viability may be at risk. If the fetus is viable, it is reasonable to perform cesarean section first, followed by aortic surgery, which should be performed under near-normothermia, pulsatile perfusion, high pump flow and avoidance of vasoconstrictors (⊕○○○).

**R 3.17.** We suggest that exercise testing before pregnancy can be useful to reveal exercise-induced hypertension, especially in women with coarctation (⊕○○○).

**R 3.18.** We suggest that women with aortic dilatation, bicuspid aortic valve, elongation of the transverse aorta, coarctation of the aorta and/or hypertension should be advised that pregnancy would carry a high risk of AoD (⊕○○○).

In addition to the potentially increased risk of AoD and congenital heart disease, women with TS are at increased risk of hypertensive disorders of pregnancy, including pre-eclampsia (226, 231, 233). 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, anti-phospholipid antibodies, multiple gestation and pre-existing hypertension (263). Hypertension is more common in women with TS, which may contribute to the higher incidence of hypertensive complications during pregnancy.



### 3.6.3. Medical treatment during pregnancy

Medical treatment, specifically regarding cardiovascular health, comprises anti-hypertensive treatment and prophylactic medication to prevent (further) 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 dilatation. Beta-blockers and angiotensin receptor blockers are advised in women with aortic syndromes (such as Marfan), but angiotensin receptor blockers are contraindicated in pregnancy. Beta-blockers may be considered during pregnancy and do not cause fetal abnormalities; still, some effect on fetal birth weight has been described (264, 265). The National Institute for Health and Care Excellence recommends 75 mg aspirin daily from 12 weeks of gestation until delivery for women at risk of pre-eclampsia. This recommendation is based on the knowledge that having two or more moderate risk factors, such as a first pregnancy, becomes an indication for aspirin use (266). OD is not given as a specific risk factor, but consideration to prescribing aspirin should be given in such pregnancies in a woman with TS (267).

### 3.6.4. Mode of delivery in women with a dilated aorta and TS

**R 3.19.** We suggest that vaginal delivery is reasonable in women with TS with an ascending ASI below 2.0 cm/m<sup>2</sup> (⊕○○○).

**R 3.20.** We suggest that in women with TS with an ascending ASI of 2.0–2.5 cm/m<sup>2</sup>, a vaginal delivery with epidural anesthesia and expedited second stage is preferred or a cesarean section may be considered. In women with TS with an ascending ASI >2.5 cm/m<sup>2</sup>, a cesarean section is reasonable or a vaginal delivery with epidural anesthesia and expedited second stage may be considered (⊕○○○).

**R 3.21.** We recommend that in women with TS with a history of AoD, a cesarean section should be performed (⊕○○○).

A delivery plan should be made by a multidisciplinary team consisting of at least an obstetrician, cardiologist and anesthesiologist, all with expertise in pregnancy in the context of maternal heart disease and/or aortopathy. Vaginal delivery is the preferred mode of delivery in most women, based on the available literature. In the registry of pregnancy and cardiac disease (ROPAC), cesarean section was not superior to a vaginal delivery

for the mother, while an increase of adverse fetal events was seen (265). Based on expert opinion, in women with a dilated aorta, a cesarean section is reasonable, although it also leads to hemodynamic changes. AoD during pregnancy is with very high risk and needs immediate attention on a high specialist level. 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 cesarean section followed by emergency aortic surgery.

## 4. Cardiovascular health issues in Turner syndrome

### 4.1. Background

Girls and women with TS face a lifelong heavy burden of congenital and acquired cardiovascular disease, with increased mortality and morbidity (37, 268). Congenital heart disease occurs in approximately 50% of girls with TS, including a high incidence of bicuspid aortic valve, coarctation of the aorta and an aortopathy that can lead to rare but often fatal dissection or rupture of the thoracic aorta. In addition, a generalized arteriopathy is observed (269), and TS alone is an independent risk factor for thoracic aortic dilation (270). While AoD has received more attention since previous international guidelines were published, it has become increasingly apparent that other cardiovascular conditions such as systemic hypertension, ischemic heart disease and cerebrovascular disease (stroke) are the major factors that reduce the lifespan in TS (268). This consensus statement proposes specific aortic dimensions that (1) may warrant consideration for operative intervention, (2) help in decision-making regarding participation in competitive sports and (3) serve to clarify when more frequent health monitoring may be beneficial. The rapidly evolving field of ART is increasing the potential for childbearing for women with TS. Accordingly, it is imperative that reproductive health practitioners and obstetricians understand who might safely attempt pregnancy.

### 4.2. Medical and operative management of aortic enlargement and aneurysm

**R 4.1.** We recommend that an infant or child is examined with transthoracic echocardiography (TTE) at the time of diagnosis, even if the fetal echocardiogram or postnatal cardiac examination was normal (⊕⊕○○).



**R 4.2.** We recommend that girls or women with aortic dilatation and/or bicuspid aortic valve be counseled to seek prompt evaluation if they are experiencing acute symptoms consistent with AoD, such as chest, neck, shoulder, back or flank discomfort, particularly if it is sudden in onset and severe (⊕⊕○○).

*Aortic dissection in Turner syndrome:* In TS, AoD occurs in approximately 40 per 100 000 person-years compared to 6 per 100 000 person-years in the general population (271). Most AoD originate in the ascending aorta (Type A), while a smaller percentage (around 10%) originate in the descending thoracic aorta (Type B) (271, 272, 273). It is important to note that for women with TS, AoD appears to occur at smaller ascending aortic diameters than in those with other genetically triggered aortopathies (272, 273, 274). In addition, AoD also occurs at an age (median age 29–35, range 4–64 years) like others with genetically triggered aortopathies (273). Furthermore, in women with AoD, a cardiovascular abnormality such as bicuspid aortic valve, elongation of the transverse aorta, coarctation of the aorta and/or hypertension is common (272, 273, 274, 275). Aortic dilatation and enlargement of the brachiocephalic and carotid arteries may be present even in the absence of structural heart disease, suggesting the presence of an underlying vasculopathy (275, 276, 277). Using ascending ASI (ASI = aortic size index or absolute aortic diameter in cm divided by body surface area (BSA)) has been proposed to better predict risk for AoD in TS (270, 271, 272, 273, 278). The ASI decreases with body growth and age until mid-teenage years and remains relatively stable thereafter making it a useful index beyond the age of 15 years. Limited data suggest that AoD usually occurs above 16 years of age and at an ascending ASI  $\geq 2.5$  cm/m<sup>2</sup>. Because the ascending aorta ASI is age dependent, in those patients aged below 16 years, TS-specific Z-scores could be used. In a woman with average BSA for TS, an absolute ascending aortic diameter of >4 cm is equivalent to an ascending ASI of  $>2.5$  cm/m<sup>2</sup> and corresponds to a TS-specific Z-score of >4 (279), as determined by echocardiography. Although BMI is not consistently a predictor of aortic size (279, 280) and because BSA calculations also include body weight, decisions based upon either Z-score or ASI should be made with caution. This is particularly important in short-statured but obese individuals or those who weigh very little relative to their height. In these cases, an absolute ascending aorta diameter of 4 cm

in someone  $\geq 16$  years of age may be preferable to ASI when determining AoD risk.

#### 4.2.1. Medical management

**R 4.3.** We recommend that women with TS demonstrating an increase in TS-specific Z-score of 1 in aortic diameter or an increase of >0.5 cm over a one-year period, need an optimization of medical treatment and surgical consultation (⊕⊕○○).

An approach to managing individuals with TS with aortic dilatation is a pragmatic one, recognizing the absence of clinical trials to guide pharmacological therapy. Cystic medial degeneration like other aortopathies has been documented in resected aortic tissue of women with TS.

Because hypertension is common in TS, maintenance of normal blood pressure may lessen risk of aortic events (281, 282, 283). Since AoD appears to occur at smaller absolute and ASI in TS, it is reasonable to begin prophylactic medical therapies earlier than what has been recommended for other patient groups.

#### 4.2.2. Operative repair of aortic aneurysms and aortic dissection

**R 4.4.** We suggest that elective operations for aneurysm of the aortic root and/or ascending aorta are reasonable for women with TS who are  $\geq 16$  years of age with an ascending ASI  $\geq 2.5$  cm/m<sup>2</sup> and associated risk factors for AoD, including bicuspid aortic valve, elongation of the transverse aorta, coarctation of the aorta and/or hypertension according to standard definitions (⊕○○○).

**R 4.5.** We suggest that elective operations for aneurysm of the aortic root and/or ascending aorta may be considered for women with TS who are  $\geq 16$  years of age with an ascending ASI  $\geq 2.5$  cm/m<sup>2</sup>, and no associated risk factors for AoD (⊕○○○).

**R 4.6.** We suggest that elective operations for aneurysm of the aortic root and/or ascending aorta may be considered for women with TS, who are <16 years of age, and for whom their ascending aorta TS-specific Z-score is  $\geq 4.0$ , with or without associated risk factors for AoD (i.e., bicuspid aortic valve, elongation of the transverse aorta, coarctation of the aorta and/or hypertension) (⊕○○○).

The general technical concept and peri-operative care are not different from those for other patients with thoracic aortic aneurysms and dissections (284, 285).

### 4.3. Cardiac imaging (see monitoring protocols Figs 1 and 2)

**R 4.7.** We recommend that in adolescents and adults TS cardiovascular screening with TTE and CMR at time of diagnosis is the preferred approach (⊕⊕○○).

**R 4.8.** We recommend that a CMR scan is performed as soon as it is feasible without needing general anesthesia. If an adult or child cannot tolerate a CMR study, a CT scan is a reasonable option (⊕⊕○○).

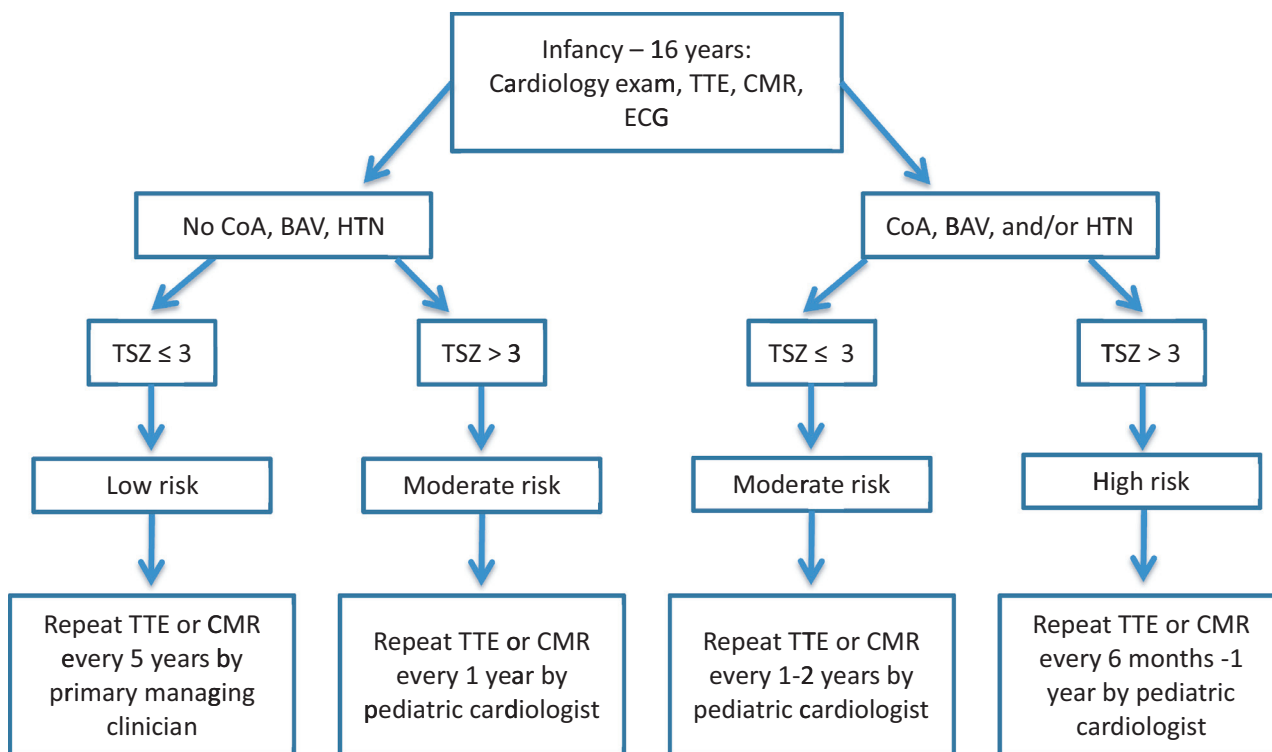
**R 4.9.** We recommend, in the absence of a bicuspid aortic valve or other significant disease at the initial screening, TTE or CMR surveillance studies should be performed every 5 years in children, every 10 years in adults or prior to anticipated pregnancy (see R 3.8) to evaluate the aorta based on published guidelines (⊕⊕○○).

**R 4.10.** We recommend that, if TS is highly suspected or has been confirmed prenatally, a fetal echocardiogram should be performed (⊕⊕○○).

**R 4.11.** We recommend that diagnosis of a bicuspid aortic valve or a left-sided obstructive lesion in a female fetus or child should prompt a genetic evaluation for TS (⊕⊕○○).

**R 4.12.** We recommend referral to a pediatric cardiologist when congenital heart disease is detected prenatally in a fetus with TS to provide counseling regarding the anatomy and physiology of the specific defect, recommended site and mode of delivery and postnatal multidisciplinary management plan (⊕⊕○○).

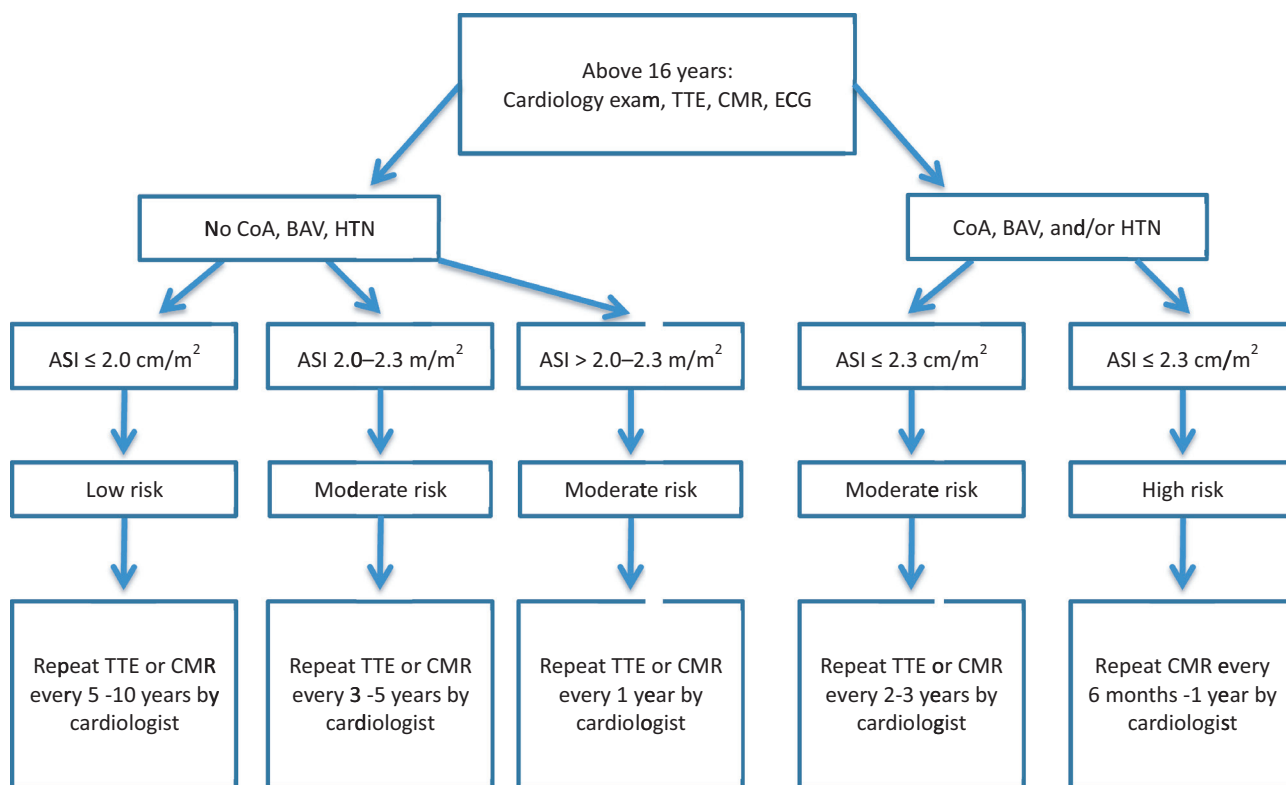
Because of the high prevalence of congenital and acquired cardiovascular disease in TS, non-invasive cardiac imaging is crucial for diagnosis, management and risk assessment (2, 9, 286, 287). The most common modalities include TTE, CMR and CT (275, 288, 289, 290, 291, 292, 293). TTE is useful in the diagnosis of a bicuspid aortic valve (294) and other congenital heart diseases as well as in the surveillance of aortic dilatation (290). However, the high prevalence of undiagnosed



TTE: transthoracic echocardiography. CMR: cardiac magnetic resonance imaging. ECG: electrocardiogram. CoA: coarctation of aorta. BAV: bicuspid aortic valve. HTN: hypertension. TSZ: Turner syndrome specific Z-score of the aorta (see text for explanation).

#### Figure 1

Suggested monitoring protocol for girls with TS from infancy to 16 years of age. TTE, transthoracic echocardiography; CMR, cardiac magnetic resonance imaging; ECG, electrocardiogram; CoA, coarctation of aorta; BAV, bicuspid aortic valve; HTN, hypertension; TSZ, Turner syndrome specific Z-score of the aorta (see text for explanation).



TTE: transthoracic echocardiography. CMR: cardiac magnetic resonance imaging. ECG: electrocardiogram. CoA: coarctation of aorta. BAV: bicuspid aortic valve. HTN: hypertension. ASI: Aortic size index (see text for explanation).

**Figure 2**

Suggested cardiac monitoring protocol for girls and women with TS above 16 years of age. TTE, transthoracic echocardiography; CMR, cardiac magnetic resonance imaging; ECG, electrocardiogram; CoA, coarctation of aorta; BAV, bicuspid aortic valve; HTN, hypertension; ASI, aortic size index (see text for explanation).

abnormalities such as elongation of the transverse aortic arch, aortic coarctation and partial anomalous pulmonary venous return in TS has led to increased utility of CMR as a screening and surveillance tool (275, 289, 291, 293). CMR has also been shown to be better than TTE in adults with TS for the diagnosis of bicuspid aortic valve (288). CT is another option, but serial surveillance (294) will involve radiation exposure. In addition, both CMR and CT are more sensitive than TTE to changes in aortic size, particularly beyond the aortic root and in adults with TS, who often have limited echocardiographic windows (295, 296).

#### 4.4. Congenital heart disease

Congenital heart disease occurs in 23–50% of individuals with TS and is the most frequent cause of early mortality (21, 297, 298). The incidence is higher in individuals with 45,X compared to X mosaicism or

other X structural abnormalities (299, 300). Left-sided obstructive lesions are most common, with a baseline prevalence of 15–30% for bicuspid aortic valve and 7–18% for coarctation (193, 301). Since bicuspid aortic valve is likely to occur 30–60 times more frequently in TS than that in the 46,XX females, it is possible that bicuspid aortic valve in a female may be an independent marker for the TS diagnosis. At least 12.6% of newborn girls with coarctation of the aorta have TS and should be viewed as an independent marker of TS (302). Cross-sectional imaging modalities have unveiled an increased incidence of additional vascular anomalies that might otherwise have gone undetected by TTE, including partial anomalous pulmonary venous connection, left superior vena cava, an elongated transverse arch and dilatation of the brachiocephalic arteries (288, 291). Neck webbing and an increased anterior–posterior thoracic diameter have been shown to be strong predictors of arterial and venous anomalies

in TS (303, 304). Additional less frequently occurring anomalies include hypoplastic left heart syndrome, mitral valve anomalies, interrupted inferior vena cava with azygous continuation, cardiac dextroposition, ventricular septal defect, atrioventricular septal defect, pulmonary valve abnormalities, coronary artery anomalies (305, 306) and patent ductus arteriosus (307). Congenital, morphological coronary artery anomalies appear to be common in TS (306). Whether coronary malformations increase mortality risk is unknown. It is important for the cardiothoracic surgeon to be aware of unusual coronary anatomy because it may necessitate modifications of the operative approach.

#### 4.5. Electrocardiogram

**R 4.13.** We suggest that a resting electrocardiogram (ECG) with QTc measurement should be done in every individual with TS at the time of diagnosis and that Hodge's may be preferred over Bazett's formula to estimate QTc (⊕⊕○○).

**R 4.14.** We suggest that 24-h Holter monitoring and exercise testing be considered for risk estimation in women with TS with QTc interval prolongation (QTc >460ms) (⊕○○○).

**R 4.15.** We suggest that, in individuals with prolonged QTc, drugs that prolong the QTc should be avoided. If they are deemed necessary, ECG should be performed 1–2 weeks after initiation of QT-prolonging drugs (⊕○○○).

Differences between the ECG in TS and in the general population can be roughly categorized into morphological issues (bundle branch block, T-wave changes and P-wave changes) on the one hand, and time intervals (PR-interval and QT-interval) on the other hand. The reported prevalence of these changes in women and girls with TS is about 50%, which is higher than that in non-TS controls (30%) (308). Some changes such as those in P-wave and QTc-dispersion and heart rate variability in women with TS can be attributed to the underlying characteristic autonomic dysfunction (309). Shortening of the PR-interval (due to accelerated atrioventricular conduction) may be a consequence of excessive sympathetic drive. The clinical relevance of these potential abnormalities may be twofold: (1) right-axis deviation in an individual with TS is correlated with the presence of partially abnormal pulmonary venous return (310) and should trigger further diagnostics in those cases that are not already known and (2) QTc prolongation is associated with an increased risk for arrhythmias or even sudden cardiac death in the general population. Yet, it

should be emphasized that there is no published evidence so far for sudden cardiac death related to QTc prolongation in women with TS, although case-based QTc prolongation due to a dose of amiodarone followed by cardiac arrest has been seen (311). Additional uncertainties include the threshold to define QT prolongation, and calculation method to define QTc interval in TS – in view of the increased intrinsic heart rate in many individuals with TS, Hodge's formula may be preferred over Bazett's formula, because it takes the higher heart rate into account (312). Whether QTc prolongation should be considered as an intrinsic feature of TS is unclear; a potential correlation with variants in the LQTS genes deserves further investigation (313). Caution with the use of QT-prolonging drugs may be warranted in this population.

#### 4.6. Sports participation

**R 4.16.** We recommend that the function of the aortic valve and the presence of any other congenital heart disease and/or hypertension should be considered in determining participation recommendations for the athlete with TS and aortic dilation (⊕○○○).

**R 4.17.** We suggest that, for girls and women with TS ≥16 years with a moderately dilated aorta (ascending ASI ≥2.0 cm/m<sup>2</sup>), avoidance of intense weight-training should be advised (⊕○○○).

**R 4.18.** We suggest that, for girls and women with normal aortic size (age <16 years; TS-specific Z-score of <2.5 or age ≥16 years and ASI <2.0 cm/m<sup>2</sup>), it is reasonable to participate in all sports (⊕○○○).

**R 4.19.** We suggest that, for girls and women with a mild to moderately dilated aorta (age <16 years old (TS-specific Z-score of 2.5–3), or age ≥16 years (ASI 2.0–2.3 cm/m<sup>2</sup>)), participation in low and moderate static and dynamic competitive sports may be advised (⊕○○○).

**R 4.20.** We suggest that girls and women with a moderately to severely dilated aorta, age <16 years (TS-specific Z-score of >3) or age ≥16 years (ASI >2.3 cm/m<sup>2</sup>) should be advised not to participate in any competitive sports (⊕○○○).

A safe level of exercise is important for a healthy lifestyle in girls and women with TS. Evidence is lacking regarding cardiovascular and aortic risks for competitive athletics with TS. 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 AoD in absolute terms (about 40:100 000 patient-years (271)) in this population. Therefore, consideration of the

risk for AoD should be tempered by the importance of encouraging individualized levels of physical activity in individuals with TS. In addition, there is no published evidence that collision represents a significant threat for AoD among girls and women with TS without significant aortic enlargement.

#### 4.7. Hypertension

**R 4.21.** We recommend that in individuals without structural heart disease, annual assessment of blood pressure should be performed and medical treatment thereof should be considered if hypertension is present. We suggest medical treatment to include a beta-blocker, an angiotensin receptor blocker, or both to reduce the risk for AoD in women with TS who are  $\geq 16$  years of age for whom their ascending ASI is  $\geq 2.3$  cm/m<sup>2</sup> (⊕⊕○○).

**R 4.22.** We suggest that medical treatment, including a beta-blocker, an angiotensin receptor blocker or both, to reduce dilatation of an enlarged aortic root and/or ascending aorta may be considered for girls with TS who are  $\leq 16$  years of age for whom their ascending aorta TS-specific Z-score is  $\geq 3.0$  (⊕○○○).

Although individuals with TS are frequently found to have systemic hypertension, and even though hypertension is a known risk factor for progressive cardiac dysfunction and aortopathy, little has been documented about definitions and management of systemic hypertension, specifically for women with TS (281). Individuals with TS have been considered to have systemic hypertension in several studies with frequency as high as 20–40% in childhood (282) and in as many as 60% of adults (191, 314, 315, 316). Systemic hypertension may appear at early ages and continue through adulthood. Systemic hypertension may be the result of renal anomalies that are frequently seen in TS or may be idiopathic. Hypertension can persist after coarctation repair even in those without residual descending aortic pressure gradients and possibly the intrinsic shape of the aorta in individuals with TS without coarctation can be a factor in the etiology of hypertension for some (283).

Several guidelines regarding measurement and ascertainment of systemic hypertension in infants, children, adolescents (317) and adults (318) are available, but none specifically addresses individuals with TS. De Groote *et al.* (281) suggest a practical approach to hypertension identification and management for girls and women with TS, including a practical algorithm for blood

pressure evaluation in adult patients. Left ventricular hypertrophy (increased LV mass) has been identified in TS, even in those who are normotensive (319, 320). This could be an end-organ effect of hypertension that is masked during resting blood pressure assessment or is related to loss of diurnal variation (lack of night-time dipping). Ambulatory blood pressure monitoring (ABPM) has been considered useful in demonstrating abnormal diurnal variation in blood pressure values in women with TS (191, 314, 321, 322).

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

The systematic search found 313 articles, of which 12 articles were assessed in full-text. No comparative studies on treatment of hypertension in TS individuals were found based on eligibility criteria and endpoint definition. Similarly, no studies comparing different treatment targets were found. Two different treatment strategies are commonly described in reviews (193, 281). However, these reviews do not refer to original articles on effect of blood pressure treatment or blood pressure treatment strategies. Thus, neither blood pressure threshold nor most effective anti-hypertensive therapeutic intervention could be defined. We conclude that recognition of and definitive treatment for systemic hypertension in TS is like that in other individuals, including encouragement of healthy lifestyle choices and aggressive management of obesity. It is essential to diagnose underlying causes such as renal anomalies, obstructive uropathy and coarctation of the aorta.

#### 4.8. The coagulation system

Cerebrovascular accidents (strokes) occur in excess of the general population (268), but whether this is simply related to the increased risk of systemic hypertension or other TS-specific causes is unknown. Disturbances of thrombosis and fibrinolysis are related to thromboembolic stroke. Clotting factors and clotting times may be normal for cohorts with TS when assessed in total, but, on the individual level, many will have increased procoagulant values of clotting and fibrinolytic factors (323). Fibrinogen has been found to be elevated in 65% of females with TS, and proteins C and S were reduced in a large fraction (323). Conversely, clotting factors, fibrinolytic factors and fibrinogen levels, as well as clotting times have also been reported to be within the normal range in other cohorts



with TS (315, 324), though high-normal values have been reported for some procoagulant factors (325, 326). The most common mutations associated with thrombus formation are more frequently reported in TS (325, 326). One study showed that factor V Leiden G1691A gene polymorphism heterozygosity is more prevalent in TS (13%) than that in the background population (2%) (325).

Even though the clotting system appears to be excessively activated in some women with TS, outcome data are lacking, and the common denominator has not yet been found. Therefore, no general recommendation can be issued concerning the coagulation system, but awareness about thromboembolic disease in TS will help identify the few women with TS women with coagulation disorders.

## 5. Transition from pediatric to adult care

**R 5.1.** We recommend that the pediatric endocrinologist (or any other TS care provider/coordinator) implements a planned and staged transition process in early adolescence for their patients with TS (⊕⊕○○).

In childhood, girls with TS are typically cared for and monitored by a pediatric endocrinologist at routine intervals for initiation of GH therapy, induction of puberty and for screening and referral for associated medical and psycho-behavioral conditions. As girls with TS grow older, visits are often less frequent despite persistence of lifelong health needs. Although the critical importance of pediatric endocrinologists in providing their TS patients with a staged and seamless transition to ensure uninterrupted transition to adult care has been recognized for over a decade (327), widespread adoption of this best practice remains elusive. As a result, many young adult women with TS are lost to follow-up and do not receive recommended age-appropriate screening, leading to reports of under-recognition and treatment of comorbidities and suboptimal health outcomes (328, 329, 330).

Adolescence is a time when many lifelong health habits are established (331) and, for those with chronic conditions, health management tasks move from parent to child during this time (332). For individuals with chronic conditions, transition from parental oversight to patient autonomy and from pediatric to adult care is increasingly recognized as a vulnerable time wherein competing developmental tasks of emerging adulthood, including pursuit of education, employment, social and romantic relationships and financial concerns may take priority over health care (333). Adolescence is an ideal time to promote the development of independent self-

care behaviors and to make the adolescent with TS aware of her own health history and of the evolving impact of TS into adulthood and promote healthy lifestyle behaviors to ameliorate risk. Given the dual aspects of both chronic medical and potential psychosocial needs, purposeful preparation for transition to adult care over time can alleviate some of the challenges for young women with TS during this stage of life.

Transition research and clinical care guidelines across the spectrum of chronic health conditions support that readiness skills that include health navigation, and self-management competencies are predictors of adult health outcomes (334, 335, 336). The Transition Readiness Assessment Questionnaire 5.0 (TRAQ) is a 20-item validated measure that examines knowledge and self-reported health-related skills in areas of appointment-keeping, tracking health issues, managing medications, talking with providers and managing daily activities (337). Development of health literacy skills, which combine 'cognitive and social skills to communicate and articulate health needs and preferences' (338), is an additional component of transition preparation. In a comparative study of transition readiness across chronic conditions, youth with TS had similar health literacy scores, but slightly lower TRAQ scores, compared to peers without a chronic condition (339). We suggest that validated tools such as TRAQ can be a useful way to assess preparedness for adult care, complemented by individualized TS-specific content for personal health history and ongoing adult health care recommendations.

### 5.1. Use of generic and TS-specific tools to meet the transition challenge

**R 5.2.** We suggest that the pediatric endocrinology team uses or adapts available transition tools to track and document the core elements of transition (⊕⊕○○).

**R 5.3.** We suggest that, irrespective of the health care delivery system, the pediatric and adult health care teams establish a workflow to support a coordinated transition process (⊕⊕○○).

**R 5.4.** We suggest that pediatric endocrinologists and their care teams encourage peer-to-peer (and parent-to-parent) contact with TS support and advocacy organizations to enhance knowledge and confidence, reduce stress and distress and promote the reciprocal sharing of experiences (⊕⊕○○).

Many professional societies have endorsed health care transition preparation, planning, and implementation as

a key component of quality health care. Generic tools are available at the American Academy of Pediatrics *Got Transition* Website ([www.gottransition.org](http://www.gottransition.org)). An example of condition-specific tools is the TS Pediatric to Adult Care Transition Toolkit, co-produced by the Endocrine Society, Hormone Health Network, Turner Syndrome Foundation and American College of Physicians (ACP) ([https://www.acponline.org/system/files/documents/clinical\\_information/high\\_value\\_care/clinician\\_resources/pediatric\\_adult\\_care\\_transitions/endo\\_turner/endo\\_ts\\_transition\\_tools.pdf](https://www.acponline.org/system/files/documents/clinical_information/high_value_care/clinician_resources/pediatric_adult_care_transitions/endo_turner/endo_ts_transition_tools.pdf)) to help the young adult in transition to achieve optimal self-care as an emerging adult. Each condition-specific set of tools includes, at a minimum, the following three core transition elements:

*Transition readiness assessment:* An assessment tool to be used by the pediatric care team to begin the conversation about the youth's needed skills to manage their specific condition. The tool is intended to be used for documentation and revisited over time as a teaching and training aid to ensure that each item is mastered by the time a young adult is transferred to adult care.

*Transfer summary:* A summary of key medical record elements or essential information needed for communication between pediatric and adult clinicians, to be completed by pediatric clinician(s), shared with youth and family, and sent to receiving adult care clinician(s).

*Self-care assessment:* An assessment tool to be used by the receiving adult care team to assess any remaining gaps in self-care knowledge, skills or additional issues that need to be addressed.

In addition to the three core elements mentioned previously, the customized set of TS-specific tools includes guiding principles for estrogen therapy, a recommended approach for planning for pediatric practices and a recommended approach for transitioning to an adult practice, which underscores the need for the TS young adult to clarify the roles of each provider on her adult care team.

## 5.2. Key TS-specific content areas to be addressed during transition

*Estrogen therapy and reproductive issues:* The impact of TS on puberty should be discussed in simple terms with TS patient by 9–11 years of age, with further explanations during adolescence. The induction of puberty with more physiological hormonal replacement regimens by age 11–12 years provides most girls with TS with documented ovarian insufficiency the psychological benefit of experiencing an appropriate timing of puberty.

The scope of available and emerging reproductive options is to be reviewed. Serious health risks of spontaneous or assisted pregnancy need to be discussed. The benefits of long-term estrogen therapy to sustain vascular, bone and psychosexual health, as well as to maintain reproductive organ and tissue integrity are to be emphasized.

*Associated needs and lifestyle requirements to ensure optimal health outcomes:* Pediatric providers need to articulate clearly to each young adult with TS how, in addition to the need for continued follow-up care for specific conditions identified during childhood, that there is a risk for conditions not yet detected by the time of their transition to adult care. These conditions need to be specified as well as three key preventive measures that can be taken to stay healthy – (1) live a healthy and active lifestyle, (2) have blood pressure carefully monitored and treated if hypertension develops and (3) continue to take sufficient estrogen well into adulthood. It is essential for each young adult with TS to understand how early prevention or identification and treatment of related comorbidities will determine their future health, QoL and longevity.

*Cardiovascular health care from childhood to adulthood:* Girls with TS are at increased risk of obesity, elevated cholesterol, diabetes, hypertension, stroke and ischemic heart disease. [Table 6](#) is a list of topics that are helpful to discuss. During this transition period, the importance of preparation for adulthood cardiovascular care is emphasized with the aim of ensuring guideline-driven care and a reduction in morbidity and loss to medical follow-up.

*Psychosocial, educational and vocational issues to ensure full potential and high quality of life:* The typical neurocognitive profile, personality type and difficult social adjustment observed in TS pose psychosocial risk that, if not addressed during transition, can impact QoL. It is also important for pediatric providers to ascertain that educational and career goals align with the abilities of the individual TS young woman and to provide appropriate counseling as needed. See also Section 7.

## 5.3. Transition care models from adolescent to adult care and guiding principles

Joint pediatric-adult care multidisciplinary programs offer the advantage of providing a more seamless transition and exchange of health care information from pediatric to adult care by sharing similar members of the health care team, a familiar site of care to the transitioning patient, and the same electronic health records. This vertically integrated care model appears more prevalent in Europe where each center serves large populations of

**Table 6** Recommendations for screening in Turner syndrome at diagnosis and throughout life (excluding those covered elsewhere, i.e. cardiac and neuropsychological).

	At diagnosis	After diagnosis (childhood)	After diagnosis (adults)
Weight/BMI	Yes	Every visit	Every visit
Blood pressure	Yes	Every visit	Every visit
Thyroid function (TSH and (free) T4)	Yes	Annually	Annually
Lipids			Annually if at least one cardiovascular risk factor <sup>a</sup> or regional recommendation
Aminotransferase, GGT and alkaline phosphatase		Annually after 10 years of age	Annually
HbA1c with or without fasting plasma glucose		Annually after 10 years of age	Annually
25-Hydroxyvitamin D		Every 2–3 years after 9–11 years of age	Every 3–5 years
Celiac screen		Starting at 2 years; thereafter every two years	With suggestive symptoms
Renal ultrasound	Yes		
Audiometric evaluation	Yes*	Every 3 years	Every 5 years
Ophthalmological examination	Yes <sup>#</sup>		
Dental evaluation	Yes, if no previous care has been established		
Clinical investigation for congenital hip dysplasia	Yes, in newborns		
Skin examination	At diagnosis	Annually	Annually
Bone mineral density			Every 5 years and when discontinuing estrogen
Skeletal assessment		5–6 years and 12–14 years (see 6.1.10.)	

The recommendations are for screening only. A clinical suspicion of active disease should always lead to relevant investigation. For details, please see text.

\*When 9–12 months old; <sup>#</sup>when 12–18 months old; <sup>a</sup>cardiovascular risk factors: hypertension, overweight, tobacco, diabetes, and physical inactivity.

TS patients and report low rates of loss to follow-up care when young adults leave the pediatric phase of their care. In the United States, similar models exist in few places.

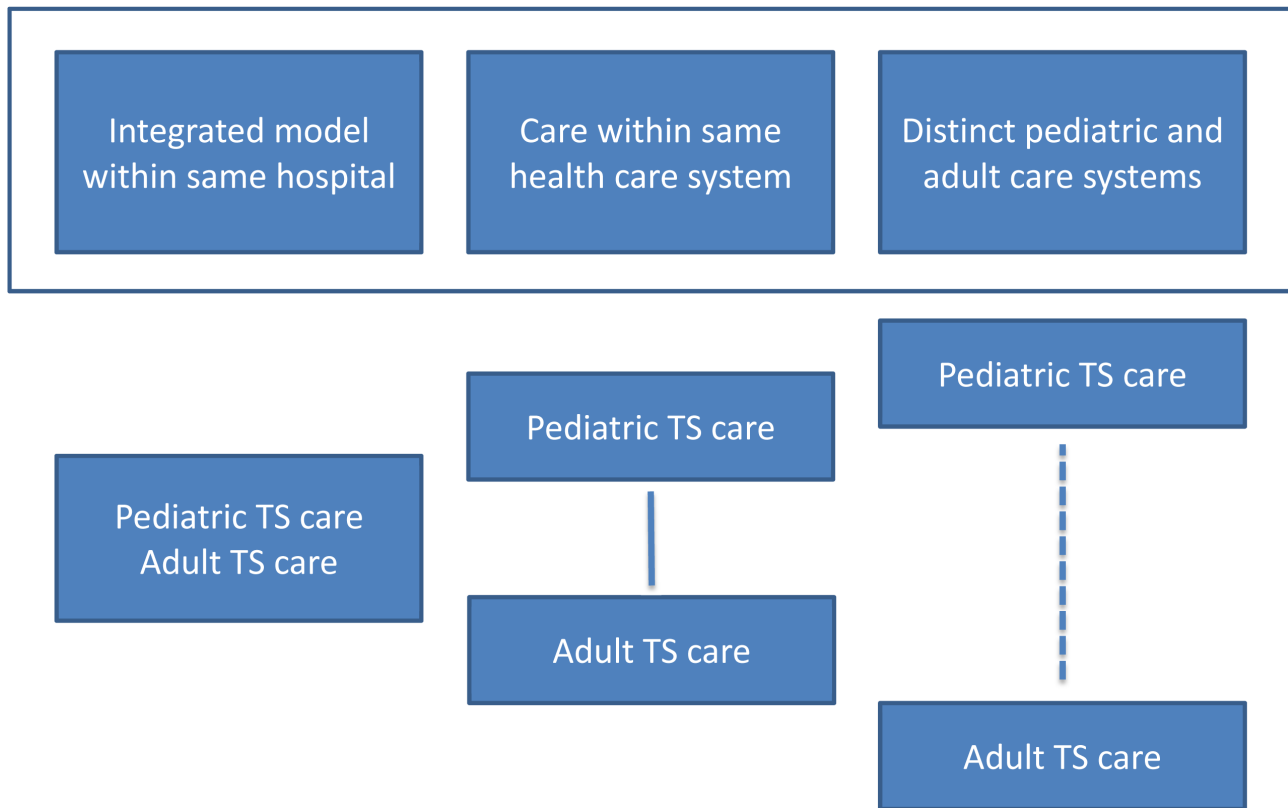
**Structural requirements:** The reality is that many TS young adults do not have access to an integrated pediatric-adult multidisciplinary care program. Some have access to adult care providers within the same health care system using the same electronic health records (EHR), while others need to transition to one or more adult providers outside of their health care system (Fig. 3). Regardless of the care model, it does not preclude a quality transition as long as a staged transition process that includes the core elements of transition as detailed above is followed. Identifying an office and clinical ‘transition champion’ to oversee the implementation of transition activities is recommended. It is essential to define which member(s) of the pediatric care team is(are) responsible for implementing each core element and to design an office workflow to support transition. Helping the individual with TS and her family identify an adult endocrinologist and other adult clinicians to best meet their needs is an essential role for the pediatric endocrinology care team to fulfill. Establishing

a good partnership with the receiving adult providers is encouraged and needed. Overcoming non-interoperability of health information between pediatric and adult providers using different EHRs will assist in a seamless transition and a printed rather than digital health summary document may be required. In some settings, a brief period of shared or co-management between the pediatric and receiving adult endocrinologist may be beneficial to ensure a successful transition and ascertain that the TS patient successfully transferred to her adult provider(s). Leveraging of telemedicine platforms may open the door to yet another transition strategy in the near future.

## 6. Health surveillance for comorbidities throughout the lifespan

### 6.1. Comorbidities in Turner syndrome (from childhood to adulthood)

In this section, management recommendations for comorbidities of TS not covered elsewhere will be made. Attention will be given to: (1) the age of subjects, (2)

**Figure 3**

Transition models from pediatric to adult care.

geographical differences in management of issues such as hyperlipidemia and vitamin D deficiency (as occur in normal populations) and (3) cost–benefit ratios. There exists little evidence for many of the following recommendations beyond expert opinion. For a summary of recommended screenings see [Table 6](#).

#### 6.1.1. Otolaryngology problems

**R 6.1.** We recommend a formal audiometric evaluation every 5 years regardless of initial age at diagnosis, initial hearing threshold levels, karyotype and/or presence of a mid-frequency sensorineural hearing loss, to assure early and adequate technical and other rehabilitative measures (⊕⊕○○).

**R 6.2.** We recommend aggressive treatment of middle-ear disease and OM with antibiotics and placement of myringotomy tubes as indicated (⊕⊕○○).

Early recognition, evaluation and appropriate management of hearing impairment in females with TS are crucial to avoid hearing-related speech pathology and risk of isolation, depression and, possibly, dementia.

The reasons for hearing impairment are multifactorial. Anomalies of the external ear have been described in up to 34% of patients and include low-set and abnormally protruding pinnae, cupped auricles and narrowing of the external auditory canal ([340](#), [341](#)). In addition, hearing abnormalities are likely related to abnormal craniofacial morphology, including delayed development of the cranial skeleton, a downward slope of the external auditory canal and abnormal orientation of the Eustachian tubes.

A subnormal immune response, leading to an increased rate of OM and the effects of X chromosome-related factors (estrogen deficiency) may also be contributory. Females with TS have decreased T-follicular helper-cell frequencies in peripheral blood that, together with haploinsufficiency of the X-linked *UTX* gene in T-cells, may induce an immune deficit predisposing to chronic OM ([342](#)).

The rate of hearing problems is much higher with a single or absent short arm of the X chromosome ([340](#), [343](#)), as a lack of growth-regulating genes may induce auricular malformations, increase risk for OM and contribute to early-onset sensorineural hearing loss (SNHL) ([344](#)).

Estrogen receptors- $\alpha$  and - $\beta$  have been shown to exist in the human ear (345). Estrogens have neuroprotective and neurotrophic effects on the brain and likely have positive effects on hearing. Thus, lack of endogenous estrogens might be a contributory factor particularly in SNHL.

Normal hearing is present in about one-third of females with preserved short-arm mosaic karyotypes and in younger age groups (7–30 years) (341, 346). In contrast, in those 50 years and older, none had normal hearing (346). Overall, hearing loss was observed in about one-third of patients with TS and is consistent throughout published literature (341, 346, 347).

Conductive hearing loss (CHL), defined as an air-bone gap of >10 dB of hearing loss, is common due to middle-ear effusion, frequent OM and tympanic membrane pathology and is most commonly seen in younger age (359). Middle-ear disease has been reported in 9–66% of the patients studied (341, 346). Isolated and recurrent cholesteatoma has a high prevalence. Risk factors for cholesteatoma include 45,X and 46,XisoXq karyotypes, a history of chronic OM, retraction of the tympanic membrane, persistent otorrhea and older age (340, 348). Aggressive treatment of middle-ear disease, and OM is crucial and includes antibiotics and placement of myringotomy tubes as indicated to offset the future necessity of more extensive tympanic procedures (349).

SNHL is the prevailing hearing impairment in females with TS, occurring with and without previous significant middle-ear pathology (346). The exact pathology is not clearly understood. A mid-frequency sensorineural dip can occur as early as 6 years. It is progressive and becomes deeper and more basin-shaped over time. It was present in 11% of females between 11 and 20 years of age and is a strong predictor of a future high rate of hearing decline, especially if associated with impairment in the high-frequency region (347). Patients may develop an early presbycusis (<35 years of age) with high-frequency SNHL, which adds to the already existing dip and causes accelerated hearing loss. This requires hearing aids early in life. Some degree of SNHL has been reported to occur in one-third of females with TS (341, 346, 347). Mixed hearing loss was found in 3% of the patients and was typically present in individuals 30 years and older (346).

Variable effects of GH therapy on ear problems in TS patients (121, 350) could be due to the variations in possible effects of the X-chromosomal origin (351) and/or previous estrogen therapy. Oxandrolone has no long-term effects on hearing (352). Women who have low BMD and impaired hearing, particularly CHL, are at increased

risk for fractures. Hearing impairment and impaired body balance were also found in women with TS and especially in those with fractures (353, 354).

Careful follow-up during early childhood, at least annually, is necessary to detect middle-ear disease and prevent sequelae. In addition, periodic examinations throughout the lifespan are mandatory even after the resolution of the middle-ear disease to detect SNHL. Continuous long-term follow-up is indicated for those with history of cholesteatoma surgery because of a high recurrence rate.

### 6.1.2. Autoimmunity

**R 6.3.** We recommend screening for hypothyroidism at diagnosis and then annually with (free) T4 and TSH measurements beginning in early childhood and throughout the lifespan (⊕⊕○○).

Individuals with TS have an increased rate of development of several autoimmune disorders, including thyroid disease (thyroiditis, hyperthyroidism and hypothyroidism), celiac disease and, to a lesser degree, type 1 diabetes mellitus, alopecia areata, juvenile rheumatoid arthritis, uveitis and inflammatory bowel disease (IBD) (355, 356). While the genetic basis for the predisposition is not known, there is a decrease in the CD4–CD8 lymphocyte ratio, suggesting an immune alteration that may predispose to autoimmunity (357). The frequency of Addison disease and type I or II autoimmune polyglandular syndrome seems not increased (358). Hypothyroidism due to Hashimoto thyroiditis is the most prevalent autoimmune disorder found in patients with TS. It may begin in early childhood, and its prevalence increases with age (355). One study suggests that the annual incidence of hypothyroidism in adult women with TS is 3.2% (359). The incidence of Graves' disease in children and young adults is 1.7–3.0%. However, it tends to present at a later age, but with a similar clinical course to that in girls without TS (360, 361). The risk for development of one or more of these conditions increases with age and, therefore, it is important that the child and adult have regular follow-up and screening.

The mechanism(s) whereby X-chromosomal monosomy give(s) rise to autoimmunity remain(s) unknown. However, data that compare women with TS to those with primary ovarian failure suggest that, while the absence of a second X chromosome is a major contributor to the autoimmunity, there may be an association between ovarian failure *per se* and chronic lymphocytic thyroiditis (359).



Regular screening for anti-thyroid antibodies does not alter management, so a specific protocol cannot be recommended. However, their measurement is usually recommended at first detection of thyroid dysfunction and/or with thyroid enlargement. The thyroid gland is, on ultrasound, not different from the general population (362). Management of thyroid dysfunction during pregnancy should follow local clinical practice guidelines for any pregnant woman.

### 6.1.3. Obesity

**R 6.4.** We suggest counseling on healthy nutrition and physical activity starting in early childhood (⊕⊕○○).

Because TS is a high-risk condition for early cardiovascular disease, aggressive lifestyle and medical management should be in place to avoid risk factors, such as obesity. The prevalence of obesity in youth and adults with TS reflects the population means in some studies; yet, other research suggests an increased burden of obesity (363, 364). Individuals with TS have a higher BMI, higher percent body fat, larger waist circumference and lower percent lean body mass than age- and BMI-matched peers (363, 365, 366). The degree of central obesity in TS youth and adults is unclear with discrepancies in current literature (364, 366, 367). GH therapy may mitigate some of these abnormalities (117, 119). Youth with TS may have an increased risk of impaired glucose tolerance (IGT) and hypertension independent of obesity (282, 367).

### 6.1.4. Diabetes

**R 6.5.** We recommend lifelong annual measurement of HbA1c with or without fasting plasma glucose starting at the age of 10 years (⊕⊕○○).

The risk of both type 1 and type 2 diabetes mellitus is about 10-fold and 4-fold increased in patients with TS across all ages in epidemiological studies (166, 268, 356, 368). Various abnormalities in glucose homeostasis (without overt diabetes) have been described, including hyperinsulinemia, insulin resistance, decreased insulin secretion and IGT (131, 133, 191, 367, 369), which are likely due to both diminished first-phase insulin release and decreased  $\beta$ -cell responsiveness (131, 369). No additional increase in the incidence of insulin-requiring diabetes has been noted during GH therapy. In fact, at least one study suggests treatment with GH may lead to lower adiposity and less IGT (117). Confirmation of diabetes should prompt assessment of antibodies related

to type 1 diabetes, as well as evaluation by a diabetes specialist.

### 6.1.5. Lipid disorders

**R 6.6.** We recommend that a lipid profile be performed in individuals who have at least one risk factor for cardiovascular disease starting at age 18 years (⊕⊕○○).

TS may be associated with an atherogenic lipid profile in youth (149, 176, 367, 370, 371), contributing to an already elevated cardiovascular risk. Hypercholesterolemia has been reported to occur in 37–50% of women with TS, which is higher than that in the general population. However, the relationship to BMI and other cardiovascular risk factors was not analyzed (372, 373). While studies demonstrate higher total cholesterol, LDL cholesterol and triglycerides than controls, severe elevations are rarely reported (325, 372, 374). Another study showed no difference in lipids in non-obese TS adults compared to controls (315). A different study using death certificates to identify causes of mortality identified that the standardized mortality ratio for ischemic heart disease was raised, but few deaths occurred prior to age 45 years (268). The hypercholesterolemia is partly influenced by a multitude of factors intrinsic to TS (325, 363, 372, 375). There is evidence that estrogen modifies lipid concentrations (149, 176, 370, 375, 376), but there is none that the type or route of administration increases risk of mortality.

In the United States, the American Academy of Pediatrics and American Heart Association recommend that children have measurement of non-fasting non-HDL cholesterol (calculated by subtracting HDL cholesterol from total cholesterol) on two occasions: once between 9 and 11 and again between 17 and 21 years prior to transition to adult care. If non-HDL cholesterol is  $\geq 145$  mg/dL ( $\geq 3.7$  mmol/L), then a full fasting lipid profile should be obtained. Finding an elevated cholesterol concentration should first prompt an assessment for secondary causes, e.g., hypothyroidism, and treatment could follow the recommendations for the general population.

### 6.1.6. Lymphatics

**R 6.7.** We recommend that, while peripheral edema mostly resolves by 2 years of age without therapy, any serious compromise of fingernails, toenails or extremity skin at any age be assessed and treated by a professional edema therapist (⊕○○○).

Cystic hygroma and lymphedema occur in many conceptuses with TS as a consequence of lymphatic malformations and obstruction, primarily at the communication between the jugular lymphatic sac and the internal jugular vein (377). The genetic basis for the impaired development is unknown. Peripheral lymphatic hypoplasia or aplasia has also been demonstrated in adult women with TS using lymphangiography (378). Many of the severely affected fetuses fail to survive (379); those that do will usually demonstrate the residua of the fetal lymphedema as peripheral edema, primarily of the hands and feet and webbed neck (resulting in the *pterygium colli* deformity). There is also a strong association between a webbed neck and left-sided congenital heart defects (380). Further consequences include lowering of the posterior hairline, rotation of the pinnae, the appearance of hypoplastic nipples and distortion of the nails of the hands and feet. In a lymphedema-focused survey of 219 girls and women with TS, 65% of those with monosomy X reported lymphedema symptoms, especially toenail problems and dry skin (381). Other implications include problems with writing and buying shoes. The peripheral edema usually resolves or improves by 2 years of age without therapy, but, if the fingernails, toenails and/or skin are compromised, professional edema therapy may need to be started early. Even if the lymphedema resolves or was not present at birth, it may (re)occur at any later age, possibly in association with initiation of salt-/fluid-retaining therapies (estrogen). A relationship to GH therapy has not been reported. If affected, lifelong examination of the nails and skin of feet and toes should be done by the individual or a family member.

#### 6.1.7. Dental and orthodontics

**R 6.8.** We recommend dental/orthodontic evaluation at diagnosis if no previous dental/orthodontic care was established. Future management and follow-up should be based on the standard of dental/orthodontic care, individual clinical findings and patient needs (⊕○○○).

Females with TS may present with variations in dental eruption, changes in crown and root morphology, and an increased risk for root absorption with subsequent tooth loss especially during orthodontic treatment. They may also have a retrognathic lower face (including a recessed and small mandible), increased cranial base angle and abnormal palate (382). In addition, distal molar occlusion, large overjet and lateral cross-bite and anterior and lateral open bite are commonly found. They also have

smaller primary and permanent teeth with two-rooted mandibular first and second premolars (383). Permanent dentition often erupts 12 months earlier than that in controls (range 6 months–3.5 years). The teeth have thinner enamel and abnormal dentin (384). The palatal and gingival indices are abnormal and there is higher-than-normal tooth mobility (385). Decreased crown width is commonly found (386). Paradoxically, the prevalence of caries is significantly lower despite the findings of poorer oral hygiene when compared with controls (385).

Females with 45,X or with 45,X/46isoXq mosaicism have more severe oral and dental anomalies, while those with a 45,X/46,XX karyotype tend to have abnormalities in line with the general population (386).

Historically, it was believed that females with TS have a 'high-arched palate'. Recent research indicates that palatal height is not affected, as a narrower dental maxillary arch with the presence of lateral palatal ridges gives the false illusion of increased palatal height (387). A low tongue position may further contribute to oral and dental pathology (388).

Cleft palate is occasionally reported in females with TS; thus, early diagnosis and treatment are recommended to minimize adverse effects on speech development (389). A comprehensive assessment should involve a pediatrician or endocrinologist; cardiologist (for possible antibiotic prophylaxis) and, as indicated, a cleft palate team because of risk of hypernasal speech and velopharyngeal insufficiency if maxillary orthognathic surgery is needed, and periodontic and prosthodontic specialists. In addition, if orthodontic surgery is considered, an anesthesia consultation may be needed to assess abnormal cervical vertebral morphology and possible neck involvement (390).

There is significant disparity between delayed linear growth, an absent or delayed pubertal growth spurt and delayed skeletal age, with the paradoxically advanced dental age. Evaluation of these factors is crucial to develop the correct dental treatment plan for females with TS as they often present with dental and skeletal malocclusions that should be treated according to skeletal age and maturity (390). Skeletal malocclusion is caused by distortion of proper mandibular and/or maxillary growth during fetal development which, if untreated, may lead to dental deformities, bruxism, teeth-crowding, trismus, mastication difficulties, breathing obstruction and disturbed digestion. We recommend dental/orthodontic evaluation at diagnosis if no previous dental/orthodontic care was established. Future management and follow-up should be based

on the standard of dental/orthodontic care, individual clinical findings and patient needs.

### 6.1.8. Ophthalmology

**R 6.9.** We recommend a comprehensive ophthalmological examination between 12 and 18 months of age or at the time of diagnosis, if at an older age, with emphasis on early correction of refractive errors (⊕○○○).

Refractive errors are present in about 40% of girls and women with TS, with increased prevalence of both hyperopia and myopia (391). Importantly, strabismus and amblyopia each occur in roughly one-third of females with TS. Ptosis (16%), epicanthal folds, hypertelorism and downward-slanting palpebral fissures are also common. The prevalence of red-green color blindness is similar to that of males (8%). Multiple visual deficits are found in about 35% those with TS (392). Early detection and correction of refractive errors are vital to prevent vision loss.

### 6.1.9. Dermatology

Girls and women with TS have an increased number of melanocytic nevi compared to the general population,

with prevalence ranging from 15 to 64% (19, 23, 393, 394). Studies conflict with regard to the question whether TS is associated with and increased melanoma risk (167, 168, 395, 396). Other skin conditions that have a greater prevalence include pilomatricomas (2.6%) (397, 398), vitiligo (2.7–6%) (399, 400) and halo nevi (18%) (399). Psoriasis is frequently reported in patients with TS, but a study of 594 women with TS did not find an increased prevalence over the general population (166, 401). Clinical practice suggests that keloids commonly occur, but one report showed that only about 3% developed keloids or hypertrophic scars after surgical procedures (402). Prevalence data are not available for alopecia areata (23, 400, 403) and for cutis verticis gyrata (402, 404, 405, 406) though case reports exist. Whorling skin pigmentation patterns, such as hypomelanosis of Ito, may accompany mosaic karyotypes (407). The prevalence of other skin conditions does not differ by karyotype (399).

Therapy with GH may trigger melanocyte growth, but it has been shown neither to increase the number of nevi nor to trigger malignant transformation (393, 408, 409). No clear relationship has been found between GH therapy and other skin lesions (399).

**Table 7** Musculoskeletal abnormalities.

Abnormality	Prevalence (%)
Craniofacial features (547)	
Retrognathia or apparent high-arched palate	60
Short posterior cranial base	
Short and posteriorly rotated mandible and maxilla	
Sternum (548)	
Short – leading to shield chest, fusion of bones, or bowing	80
Pectus excavatum	20
Upper extremities	
Cubitus valgus (549)	79
Madelung deformity (550, 551, 552)	0–7
Distal radio-ulnar physical disparity (551)	86
Short 4th and/or 5th metacarpals (551, 552)	23–42, 35
Spine	
Short neck (553)	87
Scoliosis (414, 415, 554, 555)	12–59
Kyphosis (415, 555)	40–75
Lower extremities	
Increased upper-to-lower segment ratio (556)	97
Genu valgum (416, 557)	63–86
Prominent, abnormally located tibial tuberosities (552)	46
Hypertrophic medial femoral condyle (552)	54
Foot	
Hyperextension of the great toe (558)	78
Splayed foot (416)	31
Flat feet (416)	31
Short broad feet (416)	65

References are mentioned in parentheses.

### 6.1.10. Orthopedics

**R 6.10.** We recommend clinical evaluation for scoliosis every 6 months during GH therapy or otherwise annually until growth is completed (⊕○○○).

**R 6.11.** We suggest treatment with GH be coordinated with orthopedic care if spine abnormalities are present at the start of therapy or if they develop during therapy (⊕○○○).

#### 6.1.10.1. Hip pathology, kyphosis and scoliosis

Musculoskeletal abnormalities are extensive in TS. The phenotype is different from person to person and is not consistently associated with specific karyotypes. Reported prevalence of major abnormalities is noted in [Table 7](#).

GH therapy does not appear to cause acromegaloïd craniofacial features in girls with TS ([410](#), [411](#), [412](#)), but may increase the longitudinal axis and anterior rotation of the mandible, yet pre-existing retrognathia persists ([410](#), [412](#)). Therapy with GH, however, may augment foot and hand size ([112](#)). Slipped capital femoral epiphysis has been reported with and without GH therapy ([413](#)).

An increased risk of kyphosis, vertebral wedging and scoliosis occurs in patients with TS. The etiology of scoliosis is most likely multi-faceted and can be congenital or mimic the pattern of idiopathic scoliosis ([414](#)). Scoliosis is more common with increasing age and height ([415](#)). Scoliosis may progress or develop during GH therapy. No data are available regarding the relationship of the timing of estrogen replacement and the natural history of scoliosis or on management approaches and outcomes specifically for girls with TS.

Infants may have an increased risk of congenital hip dysplasia. Abnormalities of the lower extremity, including knee alignment (*genu valgum*) and arch irregularities, are common. Abnormalities can be different in one extremity compared to the other and foot abnormalities may be independent of knee misalignment ([416](#)).

#### 6.1.10.2. Osteopenia, fracture risk and vitamin D therapy

**R 6.12.** We recommend that all patients should be counseled on healthy lifestyle measures, and on the role of estrogen replacement in bone health (⊕⊕○○).

**R 6.13.** We recommend that dietary intake of calcium and vitamin D follow region-specific recommendations (⊕⊕○○).

**R 6.14.** We suggest screening for vitamin D deficiency with a serum 25-hydroxyvitamin D measurement between 9 and 11 years of age and every 2–3 years thereafter throughout the lifespan and treating with inactive vitamin D (ergocalciferol) as necessary (⊕○○○).

**R 6.15.** We suggest using DXA scans to monitor bone density after adult hormone replacement therapy has been instituted (⊕⊕○○).

**R 6.16.** We recommend using DXA scans to monitor bone density in all women when considering discontinuation of estrogen therapy (simulating menopause) (⊕⊕○○).

Girls and women with TS have an increased risk for fracture even with normal BMD ([417](#), [418](#), [419](#)). Increased fracture risk is associated with lower BMD, history of parental fracture, hearing impairment and older age ([166](#), [420](#), [421](#)). Conversely, endogenous and exogenous estrogen exposure is associated with higher BMD ([180](#), [418](#), [422](#), [423](#), [424](#), [425](#)). GH therapy is associated with increased bone size, but with neither BMD nor fracture risk ([426](#)). Karyotype itself is not associated with BMD or fracture risk ([23](#), [166](#)).

Many women with TS have osteopenia or osteoporosis resulting from inadequate estrogen exposure. Their BMD may appear falsely reduced when evaluated by DXA due to the small bone size accompanying short stature and the differences in bone geometry due to *SHOX* deficiency ([427](#)). Furthermore, quantitative CT (QCT) evaluation of BMD has shown normal trabecular bone density ([428](#)) with falsely reduced cortical bone mineral content due to the partial volume effect ([429](#)), while high-resolution peripheral QCT has shown compromised microarchitecture and lower bone strength in both the tibia and radius ([430](#)). Therefore, radiographic evaluation of BMD may be difficult to interpret.

Decreased calcium status may also contribute to the increased risk of fracture. Women with TS appear to have lower 25-hydroxyvitamin D concentrations and vitamin D metabolism may be abnormal as well ([431](#), [432](#)). Vitamin D3 supplementation (20 μg or 800 IU daily) in those with low 25-hydroxyvitamin D, along with estrogen replacement, may preserve BMD ([433](#)). However, there is no literature supporting the benefits of universal vitamin D therapy in girls, adolescents or women with TS.

#### 6.1.11. Gastrointestinal and liver disease

**R 6.17.** We recommend screening for celiac disease by measurement of transglutaminase antibodies beginning at 2–3 years of age at a frequency of every 2 years throughout childhood and with suggestive symptoms in adulthood (⊕○○○).



**R 6.18.** We recommend monitoring liver function tests (including AST, ALT, GGT and alkaline phosphatase) yearly throughout the lifespan starting at age 10 years (⊕⊕○○).

**R 6.19.** We recommend appropriate timing (see **R 2.8**) for the initiation of female hormone replacement therapy for improvement of liver function (⊕⊕○○).

Celiac disease is more frequently diagnosed in the TS population (prevalence of 4.5%) (434), with a relative risk based on biopsy data of 2 and 5 times the general population for those under 5 and over 10 years of age respectively. This suggests increasing prevalence in childhood with age (435). Endomysial and/or tissue transglutaminase (tTG) antibody positivity is detected in 2–16.6%. Endoscopy with intestinal biopsy should be considered in those with positive serological testing. Human leucocyte antigen (HLA) typing may be considered, in order to determine the necessity of long-term screening. It has been suggested that HLA typing be used as a first-line screen in high-risk groups such as TS. If testing reveals that HLA-DQ2 and HLA-DQ8 are both negative, a future diagnosis of celiac disease is highly unlikely. This testing may also be used in patients in whom the diagnosis is indeterminate (436).

Asymptomatic liver test (ALT, AST and GGT) abnormalities are a common finding, with increasing prevalence by age (20–80%) and an annual incidence of 2.1–3.4% (188, 437, 438, 439). Liver enzyme elevations tend to persist or progressively increase and rarely revert to normal (439). Importantly, few progress to life-threatening complications, although the risk of cirrhosis is sixfold more than that in the general population (166). Liver ultrasound with Doppler blood flow may be done in those with biochemical abnormalities to identify nodules, portal hypertension or steatosis. Persistent liver enzyme elevations should prompt assessment for liver stiffness and controlled attenuation parameter measurements as determined by transient elastography to evaluate for fibrosis and steatosis (440). Concerning findings may necessitate biopsy.

The mechanism for liver disease in TS is not well-understood, but thought to be multifactorial with obesity and metabolic syndrome as likely contributors (186, 366, 439). Other possible risk factors include vascular anomalies, as evidenced by nodular regenerative changes, biliary lesions (e.g., primary sclerosing cholangitis) and autoimmunity (e.g., primary biliary cirrhosis) (441).

Several studies have now documented improvement or resolution of liver enzyme elevation with estrogen replacement therapy, regardless of the route of administration (187, 190). In the case of isolated

cholestatic syndrome (often indicated by elevations in GGT and alkaline phosphatase), ursodeoxycholic acid should be considered. If liver architectural changes are present, upper gastrointestinal endoscopy is required to detect esophageal varices, which could require either  $\beta$ -blocker treatment or surgical ligation. Finally, weight loss has been shown to be effective for prevention or amelioration of steatosis (442).

The prevalence of IBD in patients with TS is increased (0.15–3%) (443, 444, 445). Crohn's disease seems to be more frequent than ulcerative colitis. Onset of disease tends to occur at a younger age and symptoms are more severe compared to the general population. Patients with an isoXq encompass more than half of those with IBD (445, 446). It is recommended that any patient who has abdominal pain, unexplained weight loss, diarrhea and/or intestinal bleeding be evaluated for IBD.

While gastrointestinal bleeding should prompt an evaluation for IBD, vascular malformations of the gut should also be considered (447, 448). Hemangiomas, telangiectasias and venous ectasias involving the mesentery, large bowel and small bowel have been described. Although the prevalence of a gut vascular malformation is reported to be 7%, it remains a relatively rare cause of gastrointestinal bleeding.

#### 6.1.12. Renal disease

**R 6.20.** We recommend a renal ultrasound at the time of diagnosis (⊕⊕⊕⊕).

The spectrum of renal anomalies in patients with TS is broad and affects 24–42% (449). Embryological failure in budding or migration or the compressive effects of lymphatic stasis, may be the underlying basis (450). Anomalies described include horseshoe (11%) and partially or totally duplicated (5–10%), absent (2–3%), multicystic (<1%) or ectopic (<1%) kidneys. Collecting duct and ureteral anomalies, both congenital and acquired, are also common, and include duplications, obstructions and hydronephrosis (5–15%). The majority with renal anomalies do not have secondary morbidity, e.g., chronic renal failure, although mortality related to renal disease is sevenfold higher than that in the general population (268). Urinary tract infections are thought to be more frequent as a result of obstruction or reflux. Therefore, a high index of suspicion for urinary tract infections is necessary. Proper intervention (including antibiotic treatment/prophylaxis or surgical correction of obstruction or reflux) is critical to prevent permanent renal scarring and resultant sequelae. Congenital renal



**Table 8** Guidelines for adult health surveillance.

	Action	Suggested frequency	Comments
Obesity	Weight	Annually	Many comorbidities are weight-related, e.g., diabetes, elevated cholesterol, and liver dysfunction. Weight management is the most important health intervention at annual visits. Obesity may be due to low physical fitness, sedentary lifestyle, and poor food choices
Cardiovascular	Echocardiogram	3–5 years – yearly if aortic root >3 cm	Management shared with GUCH (Grown-ups with congenital heart defects) clinic preferable. Congenital malformations include bicuspid aortic valve, coarctation of the aorta, and aortic dilatation
	MRI aorta	As appropriate	Some units use echocardiography for routine monitoring and reserve MRI for ambiguous findings or as part of pre-pregnancy assessment. The place of MRI scanning depends on expertise of the echocardiography service
	Blood pressure	Annually	Hypertension affects up to 50% of young adults and contributes to the risk of aortic dissection. Refer to age-specific reference data. Hypertension can be treated to normal guidelines including use of beta-blockers or angiotensin receptor blockers. For aortic root >3.0 cm and BAV, aim for systolic blood pressure <140 mmHg if tricuspid aortic valve or <120 mmHg if bicuspid valve
Bone metabolism	DEXA scan	Every 5 years	Estrogen replacement required until ~50 years (or older if there have been many years of estrogen deficiency) to prevent osteoporosis. Bone density of spine reads low in short stature with DEXA. Osteoporosis can be treated as in other situations
	Vitamin D and calcium profile	3–5 years	Monitor bone profile in those with low calcium and low vitamin D levels; exclude celiac disease (see below)
Liver	Liver function tests	Annually	Liver enzymes, especially gammaglutamyl transaminase (GGT), are commonly elevated. Slowly progressive, but improves with estrogen and weight loss. Consider viral screen for acute changes (rarely positive)
	Liver ultrasound	As appropriate	Liver US required for markedly raised (GGT), alkaline phosphatase or transaminases. Consider special scans measuring fibrosis and steatosis, and biopsy if structural defects identified on US
Diabetes	HbA1c ± fasting plasma glucose	Annually	Consider OGTT if HbA1c is elevated. High risk of developing impaired glucose tolerance (50%) due a combination of insulin deficiency and insulin resistance. Fasting plasmagluose underestimates defect of insulin secretion
Fertility	Adoption and oocyte donation education	As appropriate	Spontaneous pregnancy occurs in 2–5%. Ovarian failure occurs in 90%. Medical review on advisability of pregnancy with regard to risk of aortic dissection is required
	Uterine ultrasound	As appropriate	US of the uterus should take place on arrival in the adult clinic and again during the work-up for pregnancy
Psychological	Review psychological issues	As appropriate	Increased risk of social isolation, anxiety, and obsessive behavior. Higher levels of shyness and social anxiety, and reduced self-esteem. Review problems in work place or in relationships. Problems are responsive to clinical psychology support. See Section 7 and Tables 9 and 10
Audiology	Audiogram ENT History	3–5 years	Deafness is common and under reported. Self-reporting unreliable. Otitis media is common in childhood (60–80%) which can lead to conductive hearing loss. Sensorineural hearing loss common and progressive in adults
Dermatology	Skin inspection	Annually	Assess for keloid and changes and in pigmented nevi
Orthodontics	Teeth inspection	Annually	Referral recommended if required
Blood tests	Thyroid function	Annually	Increased risk of autoimmune thyroiditis. In hypothyroidism (24%) or hyperthyroidism (2.5%) include TPO antibodies if previously negative
	Celiac screen	With suggestive symptoms	Increased risk (4–6%) of celiac disease. Check transglutaminase IgA antibodies (and total IgA) and vitamin B12

anomalies have, in a single study, not been shown to increase the risk of hypertension (451). However, renal scarring due to prolonged reflux or recurrent infections can also result in elevated blood pressure.

## 6.2. The adult clinic

**R 6.21.** We recommend that girls and women with TS attend specialist inter- or multidisciplinary clinics for health surveillance (⊕⊕○○).

The burden of health care issues for adults is sufficiently great to warrant an annual assessment preferably in a multidisciplinary clinic familiar with the natural history of TS. Items for a medical review are listed in Table 8. Recommendations on the frequency of testing are based on the incidence of new complications arising in adults with TS. For instance, hypertension and hypothyroidism affect approximately 25–50% of adults with a prevalence increasing with age.

As women with TS frequently report suboptimal care when they attend multiple specialty clinics without central coordination, a multidisciplinary clinic should strive to provide one-stop-shopping patient-centered care. Because of the multisystem nature of health surveillance, a variety of practitioners should be accessible either on the day of the visit or through a direct referral system for another day. Relevant specialties include endocrinology, gynecology (including fertility), cardiology (preferably with expertise in adult congenital heart disease), genetics, psychology, otolaryngology, audiology, dermatology and gastroenterology (including hepatology). Allied health care providers, such as nutritionists and physical therapists make useful additions to the team.

Clinic participation should also cover lifestyle factors such as exercise, diet and weight control, psychosocial issues including relationships both personal and work related, sexual function and plans for future fertility. A clinic care coordinator can be helpful as the point of contact, be vigilant for psychosocial issues, ensure access to tests that may be required and follow-up on non-attendance.

In common with the general population, obesity is a central factor determining many long-term health outcomes including risk of hypertension, diabetes and steatohepatitis. Therefore, weight management should be a core activity of the adult TS clinic.

Contraception and fertility options should be reviewed regularly taking into account the evidence presented in Section 6. In addition to assisted reproduction

technologies, the team should be familiar with the pathways to adoption.

Given that multidisciplinary coordination at a specialty center may occur annually, engagement with a primary provider to care for urgent issues as well as routine preventative adult care is highly encouraged.

### 6.2.1. Sexual function in adults

Women with TS move away from home later, are older at sexual debut compared to average population reference data (206, 452, 453) and show impaired sexual function particularly relating to arousal (454). They should have access to a gynecologist experienced in ovarian insufficiency in young women. Improved sexual function may require additional topical estrogen *per vaginum* or systemic androgen supplements, but so far, there is little information on their use in women with TS (455, 456).

Women with spontaneous ovarian activity require routine advice on contraception. If combined oral contraceptive pills are required, those containing 20 µg of EE are preferred to higher-dose preparations because they are associated with a lower risk of thrombosis (457).

### 6.2.2. Cancer surveillance

Three large retrospective observational studies have undertaken a comparison of cytogenetic and cancer registries recording data from over 5400 women with TS (167, 168, 396) and report that the overall risk of cancer is possibly slightly raised (in one study only) with standardized incidence ratios (SIR) between 0.9 and 1.34. All report that the incidence of breast cancer is reduced to at least 30% of the population average, the risk of melanoma increased between twofold and threefold, and the risk of nervous system malignancy increased between 4.3- and 6.6-fold with the SIR ratio for meningioma increased between 12 and 14. Until prospective studies clarify the cost-effectiveness of routine screening, the consensus group does not recommend a specific cancer screening protocol.

The reduced incidence of breast cancer probably reflects lower-than-average exposure to estrogen in retrospective studies. The excess incidence of melanoma is less than one might expect from the heightened number of pigmented nevi in women with TS, considering the increased ascertainment rate that might exist. Nevertheless, surveillance of nevi should be included in routine follow-up.

The cause of the excess risk of meningioma is unclear. Although meningioma is in part hormone sensitive, no close links with the use of GH or estrogen replacement therapy have been identified (458).

Although the risk of gonadoblastoma in individuals with a Y chromosome is not exactly quantified, gonadectomy for individuals with a fragment of Y chromosome should continue to be mandatory (56).

Women with TS have no increased risk of endometrial cancer (459); however, those women who retain spontaneous menstruation are not completely free of risk of endometrial cancer presumably because anovulation is common with low ovarian reserve (460).

## 7. Neurocognition and behavior

**R 7.1.** We recommend that neuropsychology and allied behavioral health services is integrated into the care for girls and women with TS (⊕⊕⊕○).

**R 7.2.** We recommend annual developmental and behavioral screenings until adulthood with referrals as indicated (⊕⊕⊕○).

**R 7.3.** We suggest conducting neuropsychological assessments at key transitional stages in schooling (⊕⊕○○).

**R 7.4.** We recommend academic and occupational adjustments if indicated, to accommodate learning/performance issues (⊕⊕⊕○).

**R 7.5.** We recommend aiming for on-time puberty and aggressive management of predictors of hearing impairment to facilitate positive psychosocial and psychosexual adaptation (⊕⊕○○).

**R 7.6.** We suggest that evidence-based interventions for cognitive or psychosocial problems in other populations may be adapted to meet the needs of girls/women with TS (⊕○○○).

### 7.1. Background

Turner syndrome is associated with a neurocognitive profile, which may negatively impact educational attainment and HRQoL (Table 9). Behavioral health specialists, trained to diagnose or provide interventions for the educational and psychosocial difficulties sometimes associated with TS, include clinical neuropsychologists and clinical psychologists.

Although not yet the standard of care in many countries, regular screenings for developmental or emotional/behavioral problems are increasingly called

for by national and international health organizations (461, 462). In the United States, recommended preventive pediatric health care for all children (beginning in the first year) and adolescents includes annual developmental and behavioral screenings (462). Annual mental health screenings are also mandated in adult populations (463). These screenings are optimally part of routine visits to primary-care providers. In settings where such services are not delivered, then specialists caring for girls and women with TS should consider incorporating psychometrically robust screening tools (464) as a feature of the model of care (2). Ideal measures will share the characteristics of brief administration time, simple scoring and validation in multiple languages. An example of such a measure is the *Strengths and Difficulties Questionnaire* (SDQ) (465).

Following recommendations and guidelines in other chronic pediatric conditions involving threats to neurocognitive function (466, 467), behavioral screenings are optimally augmented by neuropsychological assessments sensitive to the well-documented neurocognitive profile in TS (Table 10). Changes in the social, emotional and educational environment associated with passage through childhood, adolescence and young adulthood, represent both reasonable and necessary indications to conduct a neuropsychological assessment. Accordingly, it is recommended that a neuropsychological evaluation be conducted in early life (preschool), at school entry, at transition to high school and higher education, or at any time that difficulties arise (468). If a neuropsychologist (or otherwise qualified psychologist) is not available to serve as a member of the multidisciplinary team, then effort should be directed at identifying such providers in the community to whom a referral can be made (e.g. school psychologists). It is also recommended that children be referred for occupational, physical and speech therapy in early life or at school entry, as warranted, given their emerging pattern of developmental strengths and weaknesses as well as substantial risk for motor and possible communication difficulties. While there is a growing literature that outcome is better for children who receive early intervention with a host of developmental disorders (469), the intensity or dosage of treatment required to substantially alter outcome is an area of active research (470, 471) and contingent on the deficit being targeted and therapy employed (472).

The following sections review the neurocognitive, psychoeducational and psychosocial domains most likely affected in TS and their potential impact on adaptive

**Table 9** Summary of neurocognitive, academic, social, and psychological phenotypes in Turner syndrome.

Domain	Summary of findings	Manifestation	Associated diagnoses	Intervention
Intellectual	90% with average or above-average IQ 10% with intellectual disability (IQ <75) FSIQ > PIQ (208, 494, 497, 513, 559, 560, 561, 562, 563, 564)	Poor adaptive skills, if intellectual disability is present	Intellectual disability (~10%)	If intellectual disability is present, provide appropriate support to optimize adaptive functioning and educational/vocational attainment
Academic achievement	50–75% with dyscalculia (mathematics learning disorder) and numerical processing deficit Inconsistent phonological processing and word-reading, but most often a strength with some hyperlexia (accelerated reading) Inconsistent reading comprehension (507, 512, 513, 565, 566)	Poor performance in mathematics; may be less efficient in reading	Specific learning disorder (dyscalculia)	Establish academic accommodations that enable developmentally appropriate mastery of concepts when there is evidence of learning difficulties, including tutoring and empirically supported interventions, extensions of time demands, and capitalization on verbal strengths Referral to occupational or physical therapy for perceptual-motor and visuospatial issues in academic and daily function Target core deficits known to underlie mathematics disorders such as numerical magnitude representation and linking exact numerosities with number symbols using neuroscience research-supported methods (e.g., The Number Race or Graphogame respectively)
Attention	Deficits in attentional control, preserved orienting attention, and inconsistent results for sustained attention (14, 473, 481, 494, 561)	Distractibility, poor organization, and inability to sit still	Increased risk of attention-deficit/hyperactivity disorder (25%)	Neuropsychological testing Behavioral therapy, including parent management training
Working memory	Deficits in verbal and visuospatial working memory (performance –1 to –2 SD below the mean) (14, 74, 567)	Difficulty with multi-tasking, mental calculations, and holding information ‘in a mind’s eye’		Classroom modifications to enhance in-class behavior Medications for ADHD when indicated
Executive/cognitive control	Domains most affected: planning, response inhibition, and mental flexibility; problems may be limited to those with ADHD symptoms (14, 74, 473, 494, 497)	Difficulty with planning, thinking flexibly, and inhibiting thoughts and behaviors		
Perceptual-motor and visuospatial	Poorer performance on visuospatial and perceptual-motor tests (performance –1 to –2 SD below the mean) Sensorimotor findings less consistent (14, 476, 494, 495, 497, 513, 567, 568, 569, 570)	Difficulties with visual tasks (e.g., getting lost, trouble driving, and rotating objects in space) Poor performance in mathematics Difficulties with switching tasks, sequencing, and working memory	Learning disorders: deficits or inefficiencies can contribute to both mathematics and reading disorders	Referral for academic support if visuospatial deficits are interfering with academic functioning Referral to occupational therapy to learn compensatory strategies

(Continued)

Table 9 Continued

Domain	Summary of findings	Manifestation	Associated diagnoses	Intervention
Memory	Inconsistent. Object and location memory may be worse than verbal memory Average to low-average facial memory (measured as statistical differences in performance vs deficits) (14, 491, 493, 494, 495, 496, 497)	Inefficiency (e.g., slow and more effortful) when learning through visual means (e.g., pictures and diagrams)		Use verbal strengths in educational curriculum Enhance visual learning by describing materials aloud, using verbal mnemonics
Language	Phonological processing may be enhanced Decreased fluency (1–1.5 SD below the mean) and naming Enhanced receptive and expressive vocabulary Semantic language preserved or enhanced Problems with syntactic processing Pragmatic language not studied (478, 490, 491, 492, 512, 513)	Strengths in various aspects of oral and written communication		Use verbal strengths to enhance academic and work performance (e.g., use oral testing or verbal presentations as a means to assess skill or knowledge acquired) Consider occupations that rely on verbal strengths (e.g., library science)
Motor	Poorer performance on perceptual-motor tests, but sensorimotor findings less consistent (476)	Clumsiness Delayed motor milestones (e.g., walking, feeding self, and dressing self) Difficulties with writing	Developmental coordination disorder	Referral to occupational or physical therapy for coaching and training of (specific) motor skills Early intervention for preschool-age children Establish academic accommodations as appropriate for school-age children
Social cognition	Inconsistent findings Children – average/low-average- to-impaired facial processing/affect recognition (impaired fear recognition) Average/low-average theory of mind Adults – experimental tasks – poor classification of fear, gaze estimation, and attribution of mental states (500, 501, 503, 571, 572)	Difficulty identifying facial emotions Poor recognition of nonverbal cues Difficulty initiating or maintaining peer relationships	Social communication disorder Autism spectrum disorder	Referral to psychologist/psychiatrist for further evaluation and treatment of poor social skills, as well as co-morbid issues with anxiety, depression, or low self-esteem Social skills group therapy through school or community provider
Psychological well-being	Social withdrawal Loss of interest or pleasure in activities Distress about teasing or bullying Excessive dissatisfaction with self-concept or self-image Limited and equivocal support for higher rates of autism spectrum disorder (49, 205, 475, 523, 524, 525, 526, 527, 528, 529, 530, 532, 573, 574)		Major depressive disorder Anxiety Adjustment disorder	Referral to psychologist or psychiatrist for full clinical evaluation Individual psychosocial therapies when indicated (e.g., Cognitive Behavioral Therapy and Insight-Oriented Therapy) Medications for treatment of mood and anxiety symptoms when indicated

References are mentioned in parentheses.



**Table 10** Suggested neuropsychological and psychological assessment tools.

Domain	Child assessment	Adult assessment
Intellect/development	Mullen Scales of Early Learning (birth to ~5 years) Wechsler Preschool and Primary Scale of Intelligence (~2–7 years) Wechsler Intelligence Scale for Children (~6–16 years)*	Wechsler Adult Intelligence Scale (~16–90 years)*
Academic achievement (arithmetic)	Wide Range Achievement Test* Woodcock-Johnson Test of Achievement* Wechsler Individual Achievement Test <sup>#</sup>	Wide Range Achievement Test* Woodcock Johnson Test of Achievement* Wechsler Individual Achievement Test <sup>#</sup>
Attention	Test of Variables of Attention (TOVA) <sup>#</sup> Conners Continuous Performance Test* NEPSY (Attention and Executive Function) (3–16 years) <sup>#</sup> Conners Rating Scales <sup>#</sup> NICHQ Vanderbilt Assessment Scales	Test of Variables of Attention (TOVA) <sup>#</sup> Conners Continuous Performance Test <sup>#</sup> Conners Rating Scales <sup>#</sup>
Working memory	Complex span tasks*	Complex span tasks*
Executive/cognitive control	Stroop Test/DKEFS Color Word* Wisconsin Card Sorting Test* Trails Making Test* Contingency Naming Test Tower Tests <sup>#</sup> NEPSY-Executive Function subscales <sup>#</sup> Behavioral Rating Inventory of Executive Function <sup>#</sup>	Stroop Test/DKEFS Color Word* Wisconsin Card Sorting Test* Trails Making Test* Contingency Naming Test Tower Tests <sup>#</sup> Behavioral Dyscontrol Scale Behavioral Rating Inventory of Executive Function <sup>#</sup>
Perceptual-motor and visuospatial	Developmental Test of Visual Motor Integration <sup>#</sup> Developmental Test of Visual Perception Motor-Free Visual Perception Test Wide Range Assessment of Visual Motor Abilities Rey Complex Figure (ROCF) (copy)*	Judgment of Line Orientation* Rey Complex Figure (ROCF) (copy)*
Memory	California Verbal Learning Test (child)* Children's Memory Scale* Rey Complex Figure Test (recall)*	California Verbal Learning Test (adult)* Wechsler Memory Scale* Rey Complex Figure Test (recall)*
Language	Clinical Evaluation of Language Fundamentals <sup>#</sup> Controlled Oral Word Association Test (semantic and phonemic fluency)* Peabody Picture Vocabulary Test <sup>#</sup> Test of Pragmatic Language	Token Test <sup>#</sup> Boston Naming* Controlled Oral Word Association Test (semantic and phonemic fluency)* Peabody Picture Vocabulary Test <sup>#</sup>
Motor	Assessments of gross and fine motor ability Movement Assessment Battery for Children Pegboard test* Finger-tapping test* Physical and Neurological Examination for Soft Signs (PANESS)	Assessments of gross and fine motor ability Finger-tapping test*
Social cognition	NEPSY Affect Recognition* NEPSY Theory of Mind* Assess quality and nature of social relationships Standardized clinical assessments when appropriate (e.g., ADOS)	Benton Facial Recognition <sup>#</sup> Warrington Faces Assess quality and nature of social relationships Standardized clinical assessments when appropriate (e.g., ADOS)
Adaptive functioning <sup>†</sup>	Vineland Adaptive Behavior Scales <sup>#</sup> Adaptive Behavior Assessment System <sup>#</sup>	Vineland Adaptive Behavior Scales <sup>#</sup> Adaptive Behavior Assessment System <sup>#</sup>
Psychological well-being	Clinical assessment Social Responsiveness Scale (SRS) Behavioral Assessment System for Children (BASC) <sup>#</sup> Multi-dimensional Anxiety Scale for Children Children's Depression Inventory <sup>#</sup> Strengths and Difficulties Questionnaire (SDQ)	Clinical assessment Social Responsiveness Scale (SRS) Beck Depression Inventory* Beck Anxiety Inventory*

The assessment methods listed in this table serve as examples of the tools used to assess the respective domains. There will be substitute measures in different languages with accompanying norms. Versions/editions of the measures not specified to simplify the table. Examiners should adopt the most currently available version/edition. \* and # specify those tools most frequently used in assessment practices of clinical neuropsychologists in the United States and Canada and ranked within top 15 (575, 576).

\*≥10% of respondents; #<10% of respondents for the domain. Preschool and developmental measures were not included in references; <sup>†</sup>in the U.S., demonstration of adaptive deficits is required for a diagnosis of 'intellectual disability.'

function (Table 9). Interventions specifically targeting biological mechanisms related to the core cognitive phenotype of TS have yet to be developed. However, the cognitive and psychosocial challenges associated with TS align with recognized diagnoses, including attention-deficit/hyperactivity disorder (ADHD) (72, 473), specific learning disorders (474), social communication disorder, autism spectrum disorders (475) and developmental coordination disorder (476), and evidence suggests that generic interventions developed for non-TS populations may be adapted with similar positive effects (477) (Table 10).

As in other genetic syndromes, it is critical to note the high degree of individual variability in the somatic, cognitive and psychosocial phenotypes of girls and women with TS; one should never assume the presence (or absence) of a deficit based on karyotype. Furthermore, neurodevelopmental function changes dynamically over the course of development and may significantly improve with appropriate intervention. Nevertheless, awareness of the challenges that TS can present around academic, interpersonal and vocational goals reflects a prudent course of action for clinicians, girls and women with TS and their families.

### 7.2. Intellectual functioning

The majority of individuals with TS are of average intelligence; nevertheless, approximately 10% experience intellectual disability (9). Verbal reasoning is consistently higher than is perceptual reasoning, likely reflecting specific impairments in executive functions and visuospatial abilities (478). A ring X chromosome is associated with the highest risk for intellectual disability (479, 480). When intellectual disability is present, appropriate support must be provided to optimize adaptive functioning and educational attainment (479, 480).

### 7.3. Attention, working memory and cognitive control

Deficits in executive functioning occur in a subset of girls and women with TS. These may include problems in switching attention between tasks, planning, inhibiting inappropriate responses and working memory (the transient holding, processing and manipulation of information) (478, 481). Reduced processing speed (the pace at which one takes in information, makes sense of it and begins to respond) is also a frequent finding (478). ADHD is observed in approximately 25% of school-aged girls with TS and is often accompanied by a high rate of

hyperactivity symptoms. It is unclear if these symptoms continue in adulthood. Executive impairments are less common in girls with TS without ADHD behaviors and appear to be independent of visuospatial deficits (473). Problems stemming from executive function issues – in children or adults – can be ameliorated via cognitive-behavior therapy (482, 483, 484). For children, this approach commonly includes parent management training and classroom modifications (485, 486). Workplace accommodations for adults may also be beneficial (482, 483).

### 7.4. Visuospatial, perceptual-motor and sensorimotor development

The most frequently observed cognitive challenges in girls and women with TS are in the visuospatial domain. Visuospatial issues may manifest as difficulties with everyday tasks that involve a visual component (e.g., aspects of driving, finding one's way around a new place and/or judging distances (445, 487)) and contribute to poor performance in mathematics courses. Studies on motor function are relatively limited, but suggest both general and specific motor impairments, including difficulties in visuo-motor coordination, learning and fine motor function (354, 476, 488). In some cases, a diagnosis of developmental coordination disorder may be appropriate. Children should be referred for academic support if spatial deficits are interfering with academic functioning. Occupational and physical therapies are additional strategies for achieving therapeutic gains (489).

### 7.5. Speech and language

Average to above-average performance on standardized batteries of receptive and expressive language functioning (490, 491) has been noted in girls with TS. However, weaknesses are reported in language tasks that incorporate executive demands (490) or which rely on spatial language (492). When speech and language issues arise that substantially impact communication or academic performance, referral to a speech and language pathologist is warranted. Verbal strengths can be used to enhance academic and work performance.

### 7.6. Declarative memory

Long-term memory for verbal information may be preserved or enhanced (493, 494, 495), though some studies report deficits (496, 497). In contrast, object and location memory

are reported as less efficient, which may be secondary to accelerated forgetting (498). Visual learning may be improved by describing materials aloud and incorporating verbal mnemonics (499). Strong verbal memory can be used to enhance academic and work performance.

### 7.7. Social cognition

Girls and women with TS may demonstrate poor facial and emotion recognition (500, 501, 502) and difficulty understanding the mental states of others (503). Some literature suggests that individuals with TS are at greater risk for autism spectrum disorder (ASD) (480, 504), although this remains controversial (505). When symptoms are present, referral to a psychologist, a specialist with training in applied behavior analysis or a psychiatrist is indicated for further evaluation and treatment. Social skills group therapy through a school or community provider may prove helpful. Social skills interventions developed for individuals with ASD, such as the Program for the Education and Enrichment of Relational Skills (PEERS) (506), may be adapted for individuals with TS.

### 7.8. Educational attainment and professional satisfaction

The academic phenotype of TS includes a mathematics learning disorder (dyscalculia) (507, 508, 509, 510), with an estimated prevalence of about 50% relative to a 6–10% estimate in the general population (511). School-aged children with TS display advanced reading and word recognition (490). Findings regarding phonological processing (512, 513) and reading comprehension are inconsistent (512, 514). When learning issues are present, academic accommodations should be made, including tutoring, empirically supported interventions, extension of time demands and utilizing learning/teaching strategies that capitalize on verbal strengths.

Despite these well-documented learning issues, women with TS show a similar or increased level of educational attainment compared to the general population (206, 515). The employment status of young women with TS is equal (452, 516, 517) or higher (206, 518) than comparison groups; however, retirement occurs earlier (517, 519). Adult women with TS, especially older cohorts, show a lower occupational status than would be expected from their level of education and report less positive/challenging working experiences (519, 520). Women with TS often choose careers in health care, social services and

teaching (206, 515, 518), but such a finding should not be viewed as a recommendation. Instead, career guidance ideally includes vocational/career counseling (521).

Some researchers and clinicians have used the label nonverbal learning disability to characterize the neurocognitive phenotype of TS. Yet, the nonverbal learning disability construct is still in the scientifically 'formative' stage (522), and neither the Diagnostic and Statistical Manual of Mental Disorders nor the International Classification of Disease and Related Disorders (ICD-10) offer a specific category for nonverbal learning disability. As such, we have opted to describe the pattern of strengths and weaknesses seen in TS rather than use this label until future research is able, to clearly distinguish essential from non-essential features in various risk groups.

### 7.9. Psychosocial issues

Studies on the incidence of anxiety or depression in girls (473, 475, 523) and women (516, 524, 525) with TS show conflicting data, possibly due to selection bias, disparate outcome measures and small sample sizes. In general, girls (526, 527) and women (205, 524, 528) with TS experience lower self-concept compared to girls/women without TS. During school age, but also continuing in adulthood, teasing appears to be a frequent problem in TS (49, 516, 529, 530). Studies have failed to detect a relationship between the presence of TS stigmata (e.g., cubitus valgus and webbed neck) and social adaptation (526, 531) or psychological well-being (532). Girls and women with TS experience higher degrees of social isolation (452, 516). They report fewer close friendships (523, 525), marry at lower rates (206, 515, 518, 533) and are less likely to cohabitate (515, 516, 517). These observations may arise, due to difficulties in social cognition. In addition, hearing impairment and limited sexual experience (associated with delayed puberty) predict lower self-esteem and poorer psychosocial adaptation (205, 534, 535, 536).

### 7.10. Impact of hormonal therapies on neurocognition and behavior

Available data indicate that, on average, adult women with TS demonstrate characteristic neurocognitive profiles (intact verbal abilities and impaired visuospatial skills) despite preserved ovarian function or adequate estrogen replacement (208). These cognitive differences are seen

in comparison to women with premature ovarian failure of different etiologies (496), suggesting that, at least by adulthood, endogenous or exogenous estrogen has limited impact on modifying cognitive differences that likely arise much earlier in development. However, a trial of low-dose estrogen administration in girls with TS, between the ages of 5 and 8 years, demonstrated modest improvements in verbal and nonverbal memory (145) and replacement in girls aged 10–12 years demonstrated improvement in processing speed and motor function (144), suggesting a possible treatment effect within specific developmental windows. A relationship between age-appropriate somatic sexual development and positive self-concept, social adaptation and perceptions of health has been reported (49, 534, 537). These data support age-appropriate induction of puberty. Evidence supporting androgen administration in youth with TS is conflicting, with one study indicating that low doses of oxandrolone may improve working memory in girls aged 10–14 years (538), while another study found no effect on neurocognition and higher reports of anxiety and depression with oxandrolone administration in adult women with TS (142).

Studies of GH in TS have failed to demonstrate an effect on neurocognition (539), and some research calls into question the long-standing assumption that short stature leads to psychosocial dysfunction (540, 541). However, research that target shorter-than-average children in the general population may not be representative of the experiences of children who present to pediatric endocrinologists with concerns regarding short stature. Furthermore, tools available for assessment of the impact of short stature on QoL in individuals with TS may lack sensitivity and specificity. A systematic review examining psychological and cognitive effects of GH treatment for short stature in a wide range of syndromes, including TS, indicated that 94% of reported outcomes suffered from a high risk of bias (542). In the sole, epidemiologically oriented study of GH effect on psychosocial (e.g., self-esteem, social adjustment and HRQoL) and psychosexual (e.g., sexual milestones and degree of sexual experiences) adaptation of young adult women with TS, neither AH nor estimated height gained through GH treatment had an effect (452, 534).

## 8. Optimizing care across the lifespan

### 8.1. Exploring alternatives to hospital clinics

It is estimated that only a minority of women with TS attend any type of health care provider. Increasingly, patients access health information through Internet

searches and social media. However good a clinic set up there is, it can only cater to those who attend, and so all teams should have a strategy to engage with a wider population of women with TS. There are several alternatives to face-to-face clinic encounters. Care for women with TS lends itself to telemedicine and the use of online medical records so that disparate specialists can access one set of records. Such a system can reduce the number of tests and ensure that vital data such as cardiac status are available when acutely unwell.

### 8.2. Role of patient support organizations

The value of peer support for adolescents with chronic conditions is well established. A systematic review of peer-support interventions in adolescents with chronic illness indicated improvement in adolescents' behavioral and emotional symptoms (543). We recommend that information regarding access to patient support organizations be made available to each individual with TS on a regular basis. Members of each medical care team should take part in combined meetings with patient groups in order to share experience and develop future care pathways. Many women with TS indicate that belonging to a peer-support group has had a positive impact on their lives (544). Parents of young girls, adolescents and women with TS should be advised to contact a local TS peer-support organization to diminish the risk of isolation and to get specific information and support from peers.

Patient support organizations are vital in providing expertise outside of clinic attendances and for the support of careers or partners of individuals with a new diagnosis of TS. Support organizations can also assist in developing a care network of providers on a national basis. In addition, it is important to link patients and families to local, regional and national patient/advocacy TS groups that offer activities geared to adolescents and toward increasing their developmental autonomy.

Patient and family TS advocacy groups have taken the lead in providing educational and networking forums for patients, families, adolescents, young adults and women with TS. Their advocacy efforts have and continue to lead to important advances in research and care for girls and women with TS.

### 8.3. National registries for Turner syndrome

Several countries have developed registries recording data for women with TS, and information from these sources



has greatly expanded our knowledge regarding the natural history of this condition. Elsewhere, registries are at an early phase of development, and it is likely that improved stratification of risk for rare events will be achieved with the development of these resources.

Examples of registries include one from Sweden that has recorded data on morbidity, including cancer and mortality (all causes shown) in all women with a TS karyotype since 1957 (545). In Denmark, the Central Cytogenetic Registry has been valuable in allowing comparison with clinical data with reduced ascertainment bias compared to clinical registries (37, 517). France and the United Kingdom have developed National Centers for Rare Diseases under the umbrella of which specialist expertise for the care of TS can develop.

We recommend that registries recording clinical and psychosocial data from individuals with TS are established at a national level and that data from them be combined in order to determine factors contributing to rare outcomes such as AoD. Ideally, data are contributed by providers and patients ('stakeholders').

## 9. Summary

This guideline arose from two simultaneous developments in Europe and the USA and through meetings on both sides of the Atlantic. This development led to the gathering of an interdisciplinary group of professionals with a stake in TS in Cincinnati in July 2016. It has been 10 years since the last set of recommendations for the care of females with TS had been published, and our goal was to update knowledge and focus on all areas of care. We have aimed at presenting evidence-based guidelines and we therefore also asked four questions that could be submitted to GRADE evaluation. However, as can be appreciated, most of these questions could not be answered, based on evidence, and consequently, most of the recommendations that we present are still only based on expert opinion. It is important to acknowledge this fact, and it should serve as an impetus for future well-designed and large studies. Much research in TS, and, indeed, in almost all rare conditions, lack sufficient numbers of participants. Large collaborative efforts will therefore be necessary in the future.

### Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-17-0430>.

### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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