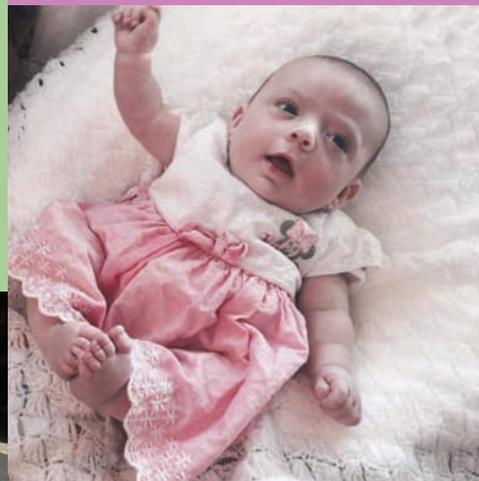


# Clinical Practice Guidelines for the Care of Girls and Women with Turner Syndrome

## Brief Synopsis for Turner Syndrome Girls and Women and for their Parents/Caregivers/Families



This document summarizes the 2017 "Clinical Practice Guidelines for the Care of Girls and Women with Turner Syndrome [TS]" (<http://www.eje-online.org/content/177/3/G1.full.pdf+html>). The summary is intended to improve care by encouraging communication between individuals with TS/parents/caregivers and their health-care provider(s) during visits.

## 1. Introduction

- The Clinical Practice Guidelines were developed for health-care providers of patients with TS, including primary care providers (pediatricians, family doctors, internists) and specialists (specialist pediatricians, geneticists, endocrinologists, cardiologists, fertility doctors, and internists).
- This document is based on an international effort that concluded with a Consensus Meeting in Cincinnati, Ohio, in 2016. TS experts were appointed by the European Society for Endocrinology (ESE), Pediatric Endocrine Society (PES), European Society of Human Reproduction and Embryology (ESHRE), Endocrine Society (ES), European Society for Cardiology (ESC), American Heart Association (AHA), and the European Society for Pediatric Endocrinology (ESPE).
- The chairs of the consensus working group, Dr. Claus H. Gravholt and Dr. Philippe F. Backeljauw, were appointed by the ESE Clinical Committee and PES, respectively.
- Patient advocates from organizations within the TS community represented patient and family concerns throughout the revision of the guidelines.

## 2. Diagnosis and Genetics of TS

### 2.1 Definition, genetic analysis, and indications for testing

- TS occurs in 1 out of 2,000–4,000 females, when only one complete X chromosome is present and the second X chromosome is missing entirely or partially, or has a different structure.
- The most frequent chromosomal changes in individuals with TS are: 45,X (monosomy X), affecting 40–50%; 45,X/46,XX (TS with mosaicism), affecting 15%; and 45,X/46,XY (mosaicism with Y chromosome materials), affecting 10–12%.
- These chromosome changes are usually accompanied by one or more medical symptoms or characteristics (**Table 1**).

**Table 1. Major Symptoms and Characteristics of TS**

<ul style="list-style-type: none"> <li>• Facial appearance, such as down-turning eyelids, low-set and prominent ears, small jaw, narrow roof of mouth</li> <li>• Neck webbing (thick, short)</li> <li>• Lymphedema (puffy hands/feet)</li> <li>• Short stature</li> <li>• Ovarian insufficiency (delayed puberty, infertility)</li> </ul>	<ul style="list-style-type: none"> <li>• Hearing loss</li> <li>• Distinctive heart,<sup>1</sup> skeletal,<sup>1</sup> and kidney defects</li> <li>• Particular neurodevelopmental profile<sup>2</sup></li> <li>• Other disorders, including underactive thyroid and gluten intolerance</li> </ul>
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<sup>1</sup> Some clinically significant heart defects and skeletal issues may not be evident at birth.

<sup>2</sup> The neurodevelopmental profile refers to brain development affecting intellectual functioning, reading ability, social communication skills, memory, and attention or focus skills.

- The specific *karyotype* (genetic makeup of the chromosomes) does not always predict the appearance of someone with TS. However, a person with 45,X may have more TS symptoms and characteristics than someone with 45,X/46,XX mosaicism. An individual with mosaicism may have fewer health concerns, including less frequent or less severe heart problems and fewer problems with hand/foot swelling (lymphatic abnormalities). A girl or woman who also has a fragment of the Y chromosome has an increased risk for developing gonadoblastoma (a growth in the ovaries).
- TS is most often diagnosed during fetal life, in infancy, during the late pre-teen period (8–12 years), or in late adolescence/early adulthood. Although TS can be diagnosed at any age, diagnosis after age 50 necessitates some additional tests beyond those discussed below.
- TS should be a foremost consideration in any female with certain physical characteristics (**Table 2**).

**Table 2. Indications for Genetic Testing to Diagnose TS**

If one of the following major features is present	If at least two of the following are present
<ul style="list-style-type: none"> <li>Hydrops (fetal accumulation of fluids)</li> <li>Short stature of unknown cause</li> <li>Left-sided heart defect<sup>1</sup></li> <li>Unexplained delayed puberty/menstruation</li> <li>Infertility problems</li> <li>Characteristic facial features<sup>2</sup></li> </ul>	<ul style="list-style-type: none"> <li>Kidney irregularity (horseshoe shape, absence, or unusually small)</li> <li>Malformed wrist and forearm bones</li> <li>Neuropsychologic profile that fits TS<sup>3</sup></li> <li>Multiple birthmarks</li> <li>Unusual shape of finger and/or toenails</li> <li>Multiple middle ear infections</li> </ul>

<sup>1</sup> Typically abnormal (bicuspid) aortic valve, coarctation (narrow aortic arch), aortic valve narrowing, other left heart valve anomalies, and underdeveloped left heart.

<sup>2</sup> See Table 1.

<sup>3</sup> Dyscalculia (a mathematics learning problem); attention deficit issues, poor working memory, poor executive/cognitive control, perceptual-motor, and visual-spatial deficits; diminished psychological well-being (anxiety state).

## 2.2 Prenatal diagnosis

- Ultrasound results can suggest an increased likelihood of TS.
- Abnormal “triple” or “quadruple” blood screening result for the pregnant mother (alpha-fetoprotein, human chorionic gonadotropin, inhibin A, and unconjugated estriol) may also suggest a TS diagnosis.
- Genetic karyotype testing for confirmation of TS after the baby has been delivered is essential, because ultrasound and maternal serum screening are not always 100% reliable to confirm that a baby has TS.

## 2.3 Postnatal diagnosis

- All females with suspected TS should have a genetic blood test, called a *karyotype*.
- If mosaicism (form of TS when the second X chromosome is only partially present or structured differently) is strongly suspected, but not confirmed with a standard karyotype, additional genetic tests should be done to confirm or rule out TS.
- A blood karyotype is usually adequate, but skin cells or cheek (via swab) cells may be examined if there is an ongoing suspicion of TS or low-level mosaicism.

## 2.4 Newborn screening

- Missed and delayed diagnoses of TS remain a major problem.
- Early diagnosis allows for timely screening and intervention for problems such as abnormal alignment of one or both eyes, hearing loss, heart and kidney abnormalities, underactive thyroid function, gluten intolerance, and learning disabilities, thus improving quality of life. It may also improve height outcomes and fertility options.
- There is currently no routine newborn screening for TS.

# 3. Growth and Puberty

## 3.1 Growth-promoting therapies

- Goals of growth-promoting therapies are for the patient to reach a height that lessens physical limitations and allows puberty to begin at an age similar to that of her peers.
- The essential component of growth-promoting therapy is growth hormone (GH), which increases growth velocity and results in a modest increase in adult height.

- Most girls will require female hormone replacement (estrogen and progestin) to initiate and/or complete the puberty process while receiving GH therapy. The way estrogen is taken, its dosage, and the speed at which the dose is increased will affect the growth and adult height.
- An adult height close to 152 cm/60 in or greater (within the lower average range for the general female population) is the likely outcome for those with TS at completion of growth-promoting therapy.

### 3.2 Efficacy and safety of GH treatment

- GH treatment was associated with height gains of 5 to 8 cm (2 to 3.5 in) over treatment periods ranging from 5.5 to 7.5 years in several medical studies. Height gain of about 1 cm per year is a reasonable expectation of GH therapy. Some studies showed height gains exceeding this, with adult height improvement sometimes reaching 4 to 5 inches over the predicted adult height at the beginning of GH treatment.
- If a girl attains the normal height range within the first 2 years of growth treatment, the rate of growth is maintained close to the average for girls her age, and there are satisfactory pubertal changes, adult height within the lower normal range (about 152 cm/60 in) is possible.
- A woman with TS may be taller than predicted after completing GH therapy if she is relatively tall at the start of treatment, has tall parents, is younger at the start of therapy, has a longer GH treatment period before puberty, takes GH therapy for a long time, or receives a higher GH dose.
- Beginning GH around 4–6 years of age, or earlier if growth failure is already noticeable, is likely to result in greater height gains during childhood and allow for age-appropriate induction of female development (like breast growth), to aim for the best adult height and timing of puberty.
- Therapy may be continued until a girl is satisfied with her height or until little growth potential remains (occurring when x-rays show that bone age is more than 13.5 to 14 years and height increase is less than 2 cm per year).
- GH therapy dosages for TS at treatment initiation:
  - North America, 0.350–0.375 milligram [mg]/kilogram [kg]/per week (equivalent to 50–54 micrograms [μg]/kg/per day)
  - Europe, 1.3–1.4 mg/square meters [m<sup>2</sup>]/day (4.0–4.3 international units [IU]/m<sup>2</sup>/day; 45–50 [μg]/kg/per day)
  - Australia, 4.5–9.5 mg/m<sup>2</sup>/week (0.6–1.4 mg/m<sup>2</sup>/day)
- Dosages are divided into 7 doses, one for each day of the week.
- GH is given in the fat tissue under the skin.
- In TS, safety of GH treatment in long-term medical studies has generally been reassuring with respect to blood pressure and risk factors for heart-related disease, blood sugar and fat metabolism, body composition (percentages of fat, bone, water, and muscle), bone mineralization (essential for bone hardness and strength), body proportions, and prevalence of ear infections and hearing loss.
- Girls with TS appear to have an increased risk of intracranial hypertension (pressure built-up in the head) and slipped capital femoral epiphysis (hip pain and limp) during GH treatment compared with children with simple GH deficiency or certain other conditions with short stature. However, these complications are still rare.
- Development or progression of scoliosis (abnormal curvature of the back) may be more common in girls with TS than in children with other growth disorders.
- Girls with TS may be at greater risk of pancreatitis than children with other growth disorders who are treated with GH. However, there is still a very low risk of pancreatitis.

### 3.3 GH treatment with the anabolic steroid oxandrolone

- Well-controlled studies have shown slight improvement in growth (of approximately 2–5 cm/1–2 in) by adding a prescription medication called oxandrolone during GH treatment.

- There is a chance of unwanted effects such as delayed breast development and dose-dependent virilization (eg, an increase in the size of the clitoris, voice-deepening, male-pattern hair growth, and acne), so there is a need for caution in using oxandrolone. When oxandrolone is correctly dosed, these complications can be avoided easily.
- Oxandrolone should not be prescribed until around 9–10 years of age and should be started at a dose of 0.03 mg/kg/day and maintained at no more than 0.05 mg/kg/day.

### 3.4 GH treatment with childhood ultra-low-dose estrogen

- Use of a very-low-dose estrogen replacement before puberty to promote growth is not currently recommended.

### 3.5 Sex-hormone replacement

- Most individuals with TS need hormone replacement therapy for puberty induction, maintaining female secondary sex characteristics, developing strong bones, and normalizing the size and overall health of the uterus.
- The main consideration supporting the use of transdermal (by a skin patch) rather than oral estrogen (a tablet) replacement therapy is that the transdermal medication does not pass through the liver.
- Giving vaginal hormone replacement is not recommended for young girls.
- The goal of estrogen replacement therapy is to mimic the progression of puberty in an average girl.

**Table 3. Recommended Estrogen Replacement Options for Feminization in TS**

Preparation	Pubertal initiation dose	Adult dosing
Transdermal E2	3-7 µg/day <sup>1</sup>	25-100 µg/day
Micronized 17β oral E2 (E2)	0.25 mg/day	1-4 mg/day
Ethinyl estradiol (EE) <sup>2</sup>	2 µg/day	10-20 µg/day
Depot E2 <sup>3</sup>	0.2 mg/month	2 mg/month

E2: 17 estradiol

<sup>1</sup> See text for information about applying patches.

<sup>2</sup> Ethinyl estradiol is not available in the United States as monotherapy.

<sup>3</sup> Depot E2 is not available in Europe.

- To mimic normal physical and social development, treatment should begin at 11–12 years, as long as lab testing indicates that there is no chance of spontaneous puberty.
- If the puberty laboratory values are normal for age, observation for spontaneous puberty is appropriate, with future hormone replacement therapy if ovarian failure occurs. The doctor can use several blood tests to determine whether or not the ovaries will function.
- Initiating replacement therapy with low estrogen doses is very important for preserving height, whether or not GH treatment has already been initiated.
- Incremental dose increases of estrogen can occur approximately every 6 months until adult dosing is reached over a 2-3 year period.
  - This approach means that there is a 25-100% dose increase every 6 months using 4 to 6 dose changes between the initiation and adult doses shown in Table 3.
  - Clinical assessment, patient satisfaction, patient age, and remaining growth potential are the primary determinants of a dose increase.
  - If attaining taller stature is still possible, girls may remain on lower estrogen doses longer. If girls are older at initiation, the interval until adult dosing may be shortened.

- Progesterin must be added once breakthrough bleeding (a period, or spotting) occurs, or after 2 years of treatment.
  - In women, micronized crystalline progesterone (eg, Prometrium® 100-200 mg) is preferred because there may be a (slight) decrease in breast cancer risk. Medroxyprogesterone acetate is an acceptable alternative to micronized crystalline progesterone.
  - The risk of breast cancer is low in TS anyway, and long-term treatment with hormone replacement therapy does not seem to induce breast cancer.
  - These progestins can be added for 10 days each month to cause a period. Women should continue treatment with estrogen in combination with a sequential progestin agent.
- Once adult replacement doses are reached, treatment should persist until the risk of continuation outweighs the benefits, around the average age of menopause in the general population. *Remember that this hormone therapy is replacing a pure deficiency – it is not the same as hormone treatment in a non-TS individual who takes birth control pills.*
- Screening for blood clot risk is necessary for those with a personal or family history of blood clots.
- An estrogen patch can be cut into smaller parts (one-quarter of a 25- $\mu$ g patch, or about 6.25  $\mu$ g, for example) to begin treatment with a small dose.
  - Although not recommended by product labels or pharmacists, two studies report on successfully achieving puberty estrogen concentrations and/or breast development with such partial patch use, and those papers include general recommendations for cutting and applying the patch. For optimal results, partial-patch therapy should be individualized, and patients should receive detailed directions from their health-care provider about cutting the patch, when and where to apply it, and for how long it should be worn.
  - It is suggested that conjugated equine estrogens (eg, Premarin®) not be used in children due to heart and stroke risks reported in postmenopausal women, especially in the presence of risk factors such as obesity.
- Low-dose oxandrolone (0.03-0.05 mg/kg/day, maximum 2.5 mg/day) may modestly slow puberty progression in response to estrogen replacement, delay the onset of periods, and increase clitoral size slightly, but these effects are minor and/or transient, and usually occur with the higher doses used in the past. A reasonable suggestion is that added oxandrolone treatment be considered in very short girls with TS only until estrogen therapy is started.

## 4. Fertility and Reproductive Assisted Technologies

- Due to early ovarian failure, most women with TS cannot conceive on their own.

### 4.1 Spontaneous pregnancies

- Spontaneous pregnancies occur occasionally in women with TS, but the frequency of miscarriages is high, and malformations occur frequently in live-born infants of these pregnancies.

### 4.2 Counseling and ethical considerations about fertility preservation or fertility treatment

- Counseling regarding fertility issues should begin at the time of diagnosis, and motherhood options such as adoption or using a gestational carrier should be mentioned.
- Whether conceiving with one's own or donated eggs, the patient needs to be counseled fully regarding increased risks of maternal complications and even death due to such complications, with an emphasis on cardiac risks.
- Intensive heart and blood pressure screening is recommended before pregnancy, but normal results do not rule out potential severe complications.

### 4.3 Assisted reproductive technologies with autologous oocytes (individual's own eggs)

- The clinical pregnancy rate was 8.6% and the live-birth rate was 5.7% with *in vitro* fertilization stimulation in women with mosaic TS.

- Individuals with TS have a rapidly decreasing ovarian reserve from a very young age. Fertility treatment options, including standard *in vitro* fertilization, should be discussed with young women, without unnecessary delay.

#### 4.4 Assistive reproductive technologies with oocyte donation (with eggs from another woman)

- For most patients with TS, oocyte donation is the only way to achieve a viable pregnancy.
- Women, both TS and non-TS, who conceive with oocyte donation are at higher risk for obstetrical complications, including blood pressure problems, cesarean section, and premature delivery, and for having a low-birth-weight infant. Risks are magnified in multiple pregnancies.
- It is imperative that any woman with TS undergoing *in vitro* fertilization or oocyte donation have only a single embryo transfer.

#### 4.5 Recommendations for follow-up during pregnancy

- Management of pregnancy should be undertaken by a multidisciplinary team including maternal-fetal medicine specialists and cardiologists with expertise in managing women with TS.

#### 4.6 Fertility preservation in TS

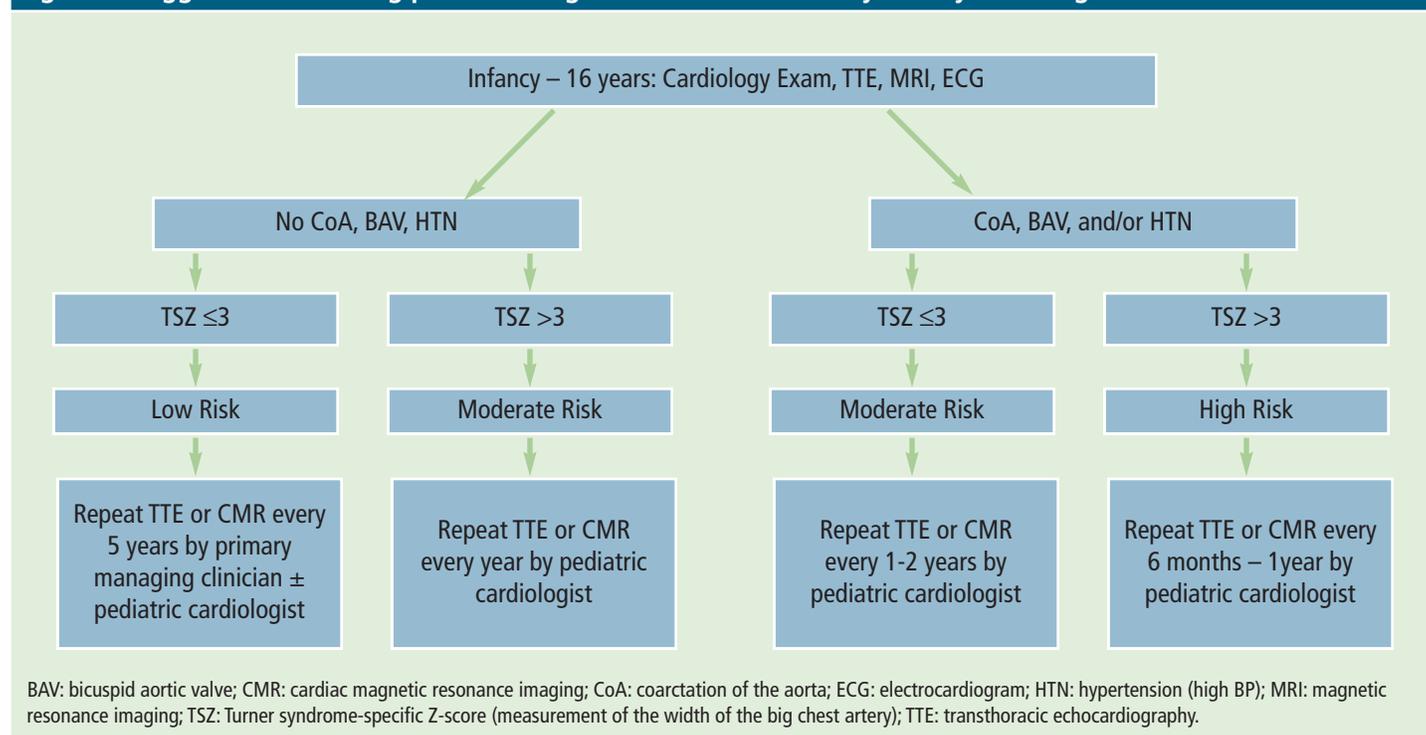
- Egg cell freezing after controlled ovarian hyperstimulation is a possible fertility preservation option in young women with mosaic TS and persistent ovarian function.
- There is not enough evidence to recommend routine fertility preservation for girls younger than 12 years old.

## 5. Cardiovascular Health Issues in TS

### 5.1 Background

- Patients encounter lifelong concerns of inborn and acquired cardiovascular disease.
- Congenital or inborn heart disease occurs in up to 50% of girls and women with TS and includes a high occurrence of abnormally shaped (bicuspid) aortic valve, coarctation (narrowing) of the aorta, and a widened aorta (dilatation) that may lead to rare but often fatal thoracic aorta dissection. Generalized altered artery quality also is seen.
- Cardiovascular conditions such as systemic high blood pressure, ischemic/coronary heart disease, and cerebrovascular disease (stroke) are additional major factors that could reduce the lifespan of an individual with TS.
- Suggested cardiovascular monitoring protocols are shown in **Figure 1** and **Figure 2**. Pediatric and adult cardiologists can undertake self-guided diagnosis and management of cardiovascular problems by following these guidelines and the timetable in Figure 1 and Figure 2. The follow-up plan will be determined by the presence or absence of widening of the aorta, and also the degree of such widening. The approach will be slightly different for children and growing teenagers versus women with TS. Deviations from the protocols in the figures are possible, based on the individual patient's progress. In any case, input from an experienced cardiologist with knowledge of TS cardiac risks is very important.

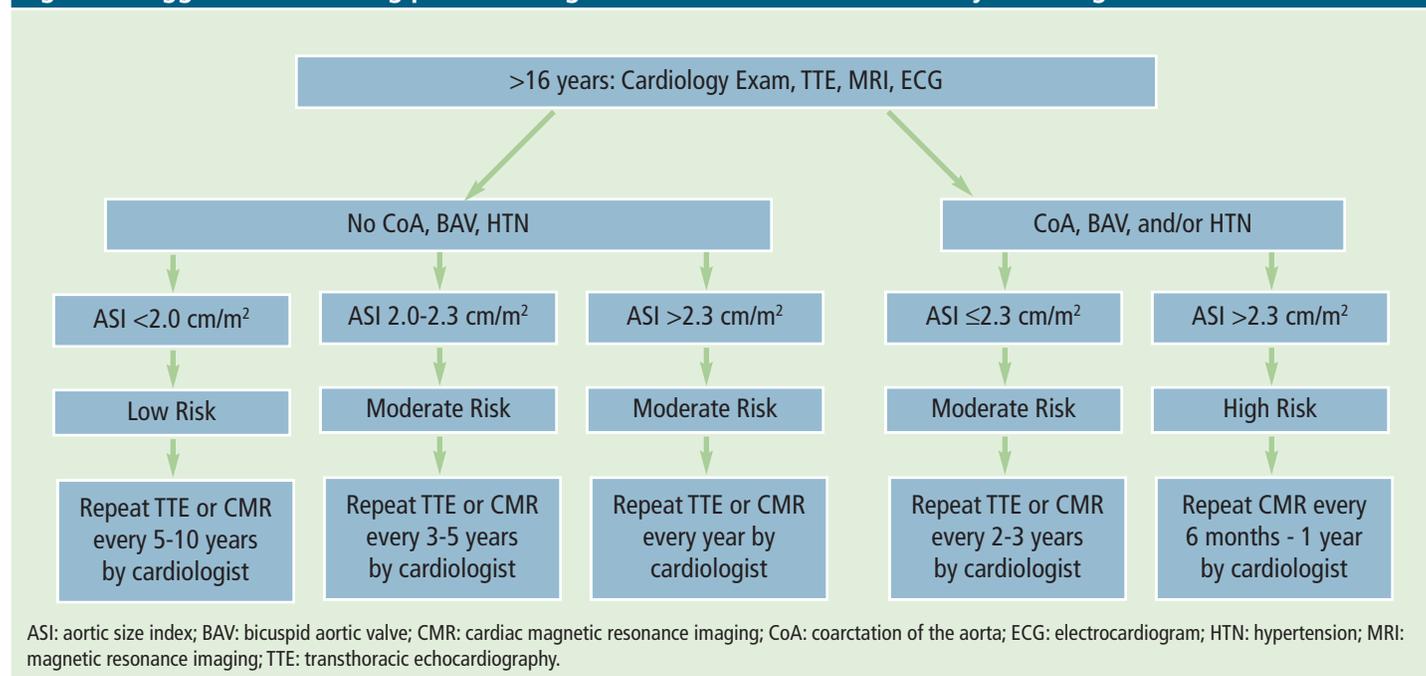
Figure 1. Suggested monitoring protocol for girls with TS from infancy to 16 years of age



## 5.2 Medical and operative management of aortic enlargement and aneurysm

- Dissection or tearing of the aorta occurs in approximately 40 per 100,000 person-years (statistic for expressing frequency rates) in women with TS compared with only 6 per 100,000 person-years in the general population.
- In women with tearing of the aorta, a cardiovascular abnormality such as bicuspid aortic valve, elongation of the transverse aorta, coarctation of the aorta, and/or high blood pressure is common.

Figure 2. Suggested monitoring protocol for girls and women with TS over 16 years of age



- A dependable predictor of the risk for developing a tear in the aorta is the calculation of the aortic size index (absolute aortic diameter in cm divided by body surface area [BSA]). The cardiologist should use this measurement to guide the recommendations for further monitoring – especially in patients 16 years or older. In assessing the risk status of a younger patient, it is helpful to compare the patient's aortic diameter with the diameter of girls with TS who have and have not had a tear in the aorta.
- An absolute ascending aorta diameter of 4 cm may predict tearing of the aorta more reliably than the calculated aortic size index in patients who are  $\geq 16$  years old, short-statured and obese, or who weigh very little relative to their height.
- Because maintenance of normal blood pressure may lessen the risk of aortic tearing, it is reasonable to begin preventive medical therapies earlier than what is recommended for the general population.

### 5.3 Cardiac imaging

- Non-invasive cardiac imaging, including transthoracic echocardiography (TTE) or ultrasound, cardiac magnetic resonance imaging (CMRI) or MRI scan, and computed tomography (CT) or CT scan, is crucial for diagnosis, management, and risk assessment.

### 5.4 Congenital heart disease

- Congenital heart disease occurs in up to 50% of individuals with TS, is the most frequent cause of early mortality, and is more common in those with a 45,X karyotype.
- Left-sided heart defects are most common, with frequencies of 15-30% for bicuspid (abnormally shaped with only two leaflets) aortic valve and 7-18% for coarctation (narrowing) of the aorta. Other abnormalities frequently seen with TS are partial anomalous pulmonary venous connection, left superior vena cava, elongated transverse arch, and dilatation (enlargement) of the brachiocephalic arteries.
- Less frequent anomalies are hypoplastic left heart syndrome, mitral valve anomalies, interrupted inferior vena cava with azygous continuation, cardiac dextroposition (displacement to the right), ventricular or atrioventricular septal defect, pulmonary valve abnormalities, coronary artery anomalies, and patent (open) ductus arteriosus.

### 5.5 Electrocardiogram (ECG)

- An ECG is a recording of the electrical activity of the heart, performed by placing electrodes on the chest. Differences between ECG results in those with TS and the general population include PR and QT intervals (measure of time between the start and end of electrical cycle of the heart) and morphological issues (bundle branch block, T-wave changes, and P-wave changes) and time intervals (PR and QT intervals). The estimated frequency of these occurrences is 50% in TS compared with 30% in those without.
- QT-prolonging medications need to be prescribed with caution in individuals with TS. Obtaining a baseline ECG at diagnosis and again after such drugs are started is recommended.

### 5.6 Sports participation

- Consideration of the risk of aortic tearing should be tempered by the importance of encouraging individualized levels of physical activity in those with TS. The new guidelines, found online at <http://www.eje-online.org/content/177/3/G1.full.pdf+html>, contain specific recommendations for what type of sports an individual can participate in based on the findings of her heart evaluation. The cardiologist will counsel the individual with TS about which sports activities should be avoided.

### 5.7 Hypertension (high blood pressure)

- Estimated systemic hypertension rates are 20-40% in children and up to 60% in adults with TS.
- Treatment for hypertension in TS is similar to that in other individuals and includes encouragement of healthy lifestyle choices and weight management.
- It is essential to diagnose and treat underlying causes of hypertension, such as kidney anomalies or narrowing of the aorta, which may also lead to higher blood pressure.

### 5.8 Cardiovascular risks during pregnancy

- Women with TS are at an increased risk for complications from pregnancy, whether with spontaneous pregnancy or after the use of assisted reproductive technology including *in vitro* fertilization and implantation. Women are at increased risk for tearing of the aorta and high blood pressure-associated disorders of pregnancy, including preeclampsia.
- Treatment includes anti-hypertensive treatment and drugs to prevent (further) aortic dilatation.
- A delivery plan should be made by a team consisting of a minimum of an obstetrician, cardiologist, and anesthesiologist, all with expertise in pregnancy associated with maternal heart disease and/or disease of the aorta.

### 5.9 The coagulation (clotting) system

- Compared to the general population, individuals with TS have a higher risk of fatal cerebrovascular disease (stroke).
- Some women with TS have excessive activation of their clotting system, but its impact on stroke risk is unknown. Certain estrogen preparations may further increase the risk for stroke, and this should be discussed with the doctor when evaluating the estrogen replacement options.

## 6. Health Surveillance for Associated Health Issues Throughout Life

### 6.1 Adult care

- The multitude of health-care issues for adults warrants an annual assessment, preferably in an interdisciplinary or multidisciplinary clinic familiar with the natural history of TS (**Table 4**).

**Table 4. Guidelines for Adult Health Surveillance: Items for Review and Suggested Frequency**

Item	Action	Suggested frequency
<b>Obesity</b>	Weight	Annually
<b>Cardiovascular</b>	Electrocardiogram	3-5 years; annually if aortic root >3 cm
	MRI aorta	As appropriate
	Blood pressure	Annually
<b>Bone metabolism, osteoporosis, scoliosis</b>	DEXA scan	3-5 years, and annually at start of specific treatment
<b>Liver</b>	Liver function tests	Annually
	Liver ultrasound	As appropriate
<b>Diabetes</b>	HbA1c test ± fasting glucose	Annually
<b>Fertility</b>	Adoption or oocyte donation education	As appropriate
	Uterine ultrasound	As appropriate
<b>Psychology</b>	Review psychological issues	As appropriate
<b>Audiology</b>	Audiogram, ENT history	3-5 years
<b>Dermatology</b>	Skin inspection	Annually
<b>Orthodontics</b>	Teeth inspection	Annually
<b>Blood tests</b>	Thyroid function	Annually
	Celiac screen	5 years

\*DEXA: dual-energy x-ray absorptiometry; ENT: ear, nose, and throat; MRI: magnetic resonance imaging.

## 6.2 Gynecological care in adults

- Women with TS should have access to a gynecologist experienced in ovarian insufficiency. If combined oral contraceptive pills are required for women with spontaneous ovarian activity, those containing 20 µg of ethinyl estradiol are preferred to higher-dose preparations because they are associated with lower clotting risk.

## 6.3 Cancer surveillance

- The overall cancer risk is possibly slightly raised, the risk of melanoma is increased between 2- and 3-fold, and the risk of nervous-system malignancy is increased between 4.3- and 6.6-fold.
- The incidence of breast cancer is reduced by at least 30% compared to that of the general population.

**Table 5. Recommendations for screening in TS at diagnosis and throughout life<sup>1,2</sup>**

Item	Children		Adults
	At diagnosis	After diagnosis, throughout childhood	After diagnosis
Weight/BMI	Yes	Every visit	Every visit
Blood pressure	Yes	Every visit	Every visit
Thyroid function (TSH and [free] T4)	Yes	Annually	Annually
Lipids (cholesterol)	—	Starting during the transition phase (~ 17-18 years of life)	Annually
Liver tests (Aminotransferases and alkaline phosphatase)	—	Annually after 10 years of age	Annually
HbA1c (blood sugar) with/without FPG	—	Annually after 10 years of age	Annually
Vitamin D	—	Every 2-3 years after 9-11 years of age	Every 2-3 years
Celiac disease screen	—	Starting at 2-3 years; thereafter every 2 years	Every 5 years
Renal (kidney) ultrasound	Yes	—	—
Audiometric evaluation	Yes <sup>3</sup>	Every 3 years	Every 5 years
Ophthalmological examination	Yes <sup>4</sup>	Annually	Annually
Dental evaluation	Yes, if no previous care has been established	Annually, unless issues related to malocclusion or other dental/skeletal disorders necessitate more frequent screening <sup>5</sup>	Annually, unless consequences of untreated or inadequately treated malocclusion necessitates more frequent screening
Assessment for congenital hip dysplasia	Yes, in newborns	—	—
Skin examination	At diagnosis	Annually	Annually
Skeletal assessment DEXA scan	—	5-6 years and 12-14 years	When discontinuing estrogen, if at risk of insufficient estrogen replacement, or at menopause age

BMI: body mass index; DEXA: dual-energy x-ray absorptiometry; FPG: fasting plasma glucose; T4: thyroxine; TSH: thyroid stimulating hormone.

1 The table does not include cardiovascular and neuropsychological screening recommendations, which are covered elsewhere.

2 Recommendations are for screening only. Clinical suspicion of active disease should always lead to relevant investigation.

3 When 9-12 months old

4 When 12-18 months old

5 Many individuals with TS require orthodontia. Modifications that might need to be made to standard orthodontic treatment plans include antibiotic prophylaxis, adjustments to account for altered dental morphology, and altered treatment timing due to delayed growth.

- Gonadectomy (removal of the ovaries) for TS individuals with a fragment of the Y chromosome as part of their genetic make-up should continue to be mandatory. Upon genetic diagnosis of TS, when such Y chromosome material is detected, a recommendation should be made to remove the ovaries as a preventive measure. This is done because there is an increased risk that those ovaries will develop growths over time, and those growths can become malignant.

#### 6.4 Comorbidity (presence of one or more additional diseases or conditions in a patient) in TS from childhood to adulthood: monitoring for associated health issues in TS

- **Table 5** shows recommendations for the management of TS comorbidities not covered elsewhere in the clinical practice guidelines.
- *Otolaryngology problems (hearing, ear health)*: Conductive hearing loss is common due to middle-ear effusion, frequent ear infections, and ear drum pathology. Sensorineural hearing loss is the prevailing hearing impairment in TS, is seen in one-third of patients, and occurs with and without significant middle-ear pathology.
- *Autoimmunity*: Individuals with TS are at increased risk for developing thyroid disease (thyroiditis, hyperthyroidism, and hypothyroidism), celiac disease (sensitivity to gluten in the diet), and, to a lesser degree, diabetes, juvenile rheumatoid arthritis, uveitis (eye inflammation), and inflammatory bowel disease.
- *Obesity*: Many individuals with TS have a higher body mass index (BMI), higher percent of body fat, larger waist circumference, and lower percent of lean body mass than age- and BMI-matched peers.
- *Diabetes*: The risk of type 1 and type 2 diabetes is increased in patients across all ages. Various glucose (blood sugar) homeostasis (maintenance of stable conditions) abnormalities (without apparent diabetes) have been described; these include hyperinsulinemia, insulin resistance, decreased insulin secretion, and impaired glucose tolerance.
- *Lipid disorders*: TS may be associated with an arterial plaque promoting lipid profile (elevations of the fat in the blood) in youth, contributing to an already elevated cardiovascular risk. Hypercholesterolemia (high cholesterol levels) occurs in 37-50% of women with TS, a higher rate than that observed in the general population.
- *Lymphatics*: Many fetuses with severe lymphedema (accumulation of fluid within tissues) fail to survive. Surviving fetuses usually are born with peripheral edema (primarily of the hands and feet) and some degree of webbing of the neck. This is strongly associated with left-sided congenital heart defects. Further consequences include a lower neck hairline, altered ear position, small nipples, and unusual shape of finger nails and/or toe nails.
  - Peripheral edema (hand and/or foot swelling) usually resolves or improves greatly by 2 years of age without therapy, but professional edema therapy may be started early if the fingernails, toenails, and/or skin are compromised.
  - Even if lymphedema resolves or was not present from birth, it may (re)occur at any age, possibly in association with initiation of estrogen therapy, but more frequently in association with excessive weight gain.
- *Dental and orthodontics*: Individuals with TS may have a wide range of dental and orthodontic issues including advanced dental age, an increased risk for root shortening that could lead to tooth loss especially during orthodontic treatment, and other issues that may affect feeding/eating or speech. Teeth may have a thinner enamel and abnormal dentin, yet the cavities (caries) are less common than the general population. To prevent tooth deformities, teeth-crowding, trismus (jaw-muscle spasm), chewing difficulties, breathing obstruction, and disturbed digestion, treatment of tooth misalignment is essential. Guidelines for the orthodontic treatment of patients with TS reflect modifications to routine care that may be necessitated by TS-related differences in the rate and timing of growth, the development of craniofacial structures, and dental morphology.
- *Ophthalmology*: Early detection and correction of refractive errors such as nearsightedness are vital to prevent vision loss. Strabismus (abnormal alignment of the eyes) and amblyopia (weak eye) each occur in about one-third of females with TS. Ptosis (eyelid drooping) and unusual eyelid folds are also common.
- *Dermatology*: Individuals with TS have an increased number of pigmented nevi (moles), and may have a higher incidence of melanoma than the general population. Growth hormone treatment may trigger growth of these skin marks, but it neither increases the number of moles nor triggers cancerous transformation.

- *Orthopedics:* Musculoskeletal abnormalities are extensive in TS. The type differs from person to person, and is not consistently associated with specific karyotypes. Scoliosis may progress or develop during growth hormone therapy. An increased risk of kyphosis (upper spine bending forward), vertebral wedging (irregular shaped bones), and scoliosis occurs in patients with TS. Infants may have an increased risk of congenital hip dysplasia. Abnormalities including knee alignment and arch irregularities, are common.
- *Osteoporosis, fracture risk, and vitamin D deficiency:* Women and girls have an increased risk for fracture even with normal bone mineral density (BMD). Increased fracture risk is associated with BMD, history of parental fracture, hearing impairment, and older age. Many women with TS have osteoporosis resulting from inadequate estrogen exposure. Vitamin D metabolism may be abnormal, and Vitamin D3 supplementation (20 µg or 800 IU daily) in those with low 25-hydroxyvitamin D, along with estrogen replacement, preserves bone mass. Because of small bone size accompanying short stature, radiographic evaluation of BMD may be difficult to interpret.
- *Gastrointestinal disease:* The prevalence of inflammatory bowel disease, especially Crohn's disease, is increased, and inflammatory bowel disease (IBD) tends to have an earlier onset and more severe symptoms in individuals with TS compared to the general population. Celiac disease, an intolerance of gluten in the diet, also has an increased frequency, with a prevalence of 4.5%. It is recommended that any patient who has abdominal pain, unexplained weight loss, diarrhea, and/or intestinal bleeding be evaluated for IBD. Liver test abnormalities are common, despite individuals having no symptoms of liver problems, and the risk of cirrhosis is 6-fold more than in the general population. Liver enzyme elevations tend to persist or progressively increase, and rarely revert to normal, but may decrease or resolve with estrogen hormone replacement. Persistent liver enzyme elevations should prompt assessment by a liver ultrasound with Doppler blood flow.
- *Kidney disease:* Kidney anomalies affect 24-42% of patients. Anomalies include horseshoe shape (11%) and partially or totally duplicated (5-10%), absent (2-3%), multicystic (<1%), or ectopic (<1%) kidneys. Mortality related to kidney disease is 7-fold higher than in the general population. Urinary tract infections are thought to be more frequent because of obstruction or reflux. Kidney scarring due to prolonged reflux or recurrent infections can result in elevated blood pressure, therefore proper intervention (including antibiotic treatment or surgical correction) is critical.

## 7. Transition from Pediatric to Adult Care

- Many young women with TS do not receive adequate care, or recommended age-appropriate screening, leading to reports of under-recognition and treatment of related conditions and poor health outcomes.
- Early adolescence is an ideal time to promote the development of independent self-care behaviors, create awareness of her personal health history, and promote healthy lifestyles.

### 7.1 Transferring care to adult providers and meeting the transition challenge

- Generic and TS-specific tools have been developed to help patients with health-care transition preparation, planning, and implementation.
- The "TS Pediatric to Adult Care Transition Toolkit" ([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)) addresses core transition elements (readiness, transfer of records/information, self-care knowledge and skills), as well as TS-specific material.

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

- TS-specific topics to be addressed are: estrogen therapy and reproductive issues; TS Healthcare Checklist for Adults; TS-associated needs and lifestyle requirements to ensure optimal health outcomes; cardiovascular health-care throughout the lifespan; and psychosocial, educational, and vocational issues to ensure full potential and high quality of life.

## 8. Neurocognition (the brain's ability to understand) and Behavior

### 8.1 Background

- TS is associated with a neurocognitive profile that may negatively impact educational success.
- It is recommended that neuropsychology and allied behavioral health services be integrated into the care of girls and women with TS.
- It is recommended that a neuropsychological evaluation be conducted at preschool age, at school entry, at transition to high school and higher education, or at any time that difficulties arise. The evaluator should have knowledge of TS-specific cognitive deficits.
- It is recommended that children be referred for occupational, physical, and speech therapy in early life or at school entry.
- Cognitive and psychosocial challenges associated with TS include attention deficit/hyperactivity disorder (ADHD), specific learning disorders, social communication disorder, autism spectrum disorders, and developmental coordination disorder.
- Evidence suggests that generic interventions developed for non-TS populations may be adapted with similar positive effects.
- When learning issues are present, academic accommodations should be made, including tutoring, extension of time demands, and utilizing learning/teaching strategies that capitalize on verbal strengths.

### 8.2 Intellectual functioning

- Most individuals with TS have average intelligence, but approximately 10% experience intellectual disability (most commonly associated with a ring X chromosome). Verbal reasoning is consistently better than perceptual reasoning (using the senses), likely reflecting specific impairments in executive functions (control of behaviors) and visuospatial abilities (spatial relationship of objects). Language skills are often strong, but mathematics can be challenging, leading to academic difficulties.

### 8.3 Attention, working memory, and cognitive control

- Deficits in executive functioning and reduced processing speed are frequently reported, and attention deficit/hyperactivity disorder is observed in approximately 25% of school-aged children.
- Reduced processing speed (the pace at which one takes in information, makes sense of it, and begins to respond) is a frequent finding.
- Parent management training and classroom modifications are helpful for children. Workplace accommodations may benefit adults.

### 8.4 Visuospatial, perceptual-motor, and sensorimotor development

- The most frequently observed cognitive challenges in individuals with TS are in the visuospatial domain and may show up as difficulties with tasks like judging distances, driving, and mathematical calculations.
- Children should be referred for academic support if spatial deficits interfere with academic functioning. Occupational and/or physical therapy are often helpful.

### 8.5 Speech and language

- Average to above-average performance on standard batteries of receptive and expressive language functioning have been noted, but occasional weaknesses are reported in language tasks that incorporate executive demands (eg, giving multi-step instructions) or rely on spatial language (e.g., giving verbal directions using words such as "over," "behind," or "up there," to locate an item).

### 8.6 Declarative memory (memory of facts and events)

- Long-term memory for verbal information may be preserved or enhanced, but object and location memory are less efficient. Learning and initial retention of information appear normal, but information is often forgotten very quickly.

- Visual learning may be improved by describing materials aloud and incorporating verbal mnemonics (the pattern of letters, ideas, or associations).

### 8.7 Social cognition

- Girls and women with TS may not recognize facial expressions well and often have difficulty understanding the emotional feelings of others. Social skills group therapy may be helpful.

### 8.8 Education attainment and professional satisfaction

- A 50% prevalence of a mathematics learning disorder (dyscalculia) is common in those with TS compared to the general population.
- School-aged children with TS often display advanced reading and word recognition skills.
- Despite the challenges posed by the neurocognitive profile often seen in TS, women with TS frequently attain a level of education that is similar to or greater than that of the general population.
- The employment status of young women with TS is equal to or higher than that of comparison groups, although retirement occurs much earlier. Adults, especially older women, have a lower occupational status than would be expected from their educational level and report less positive/challenging work experiences. Employment and life-skills coaching can be helpful.

### 8.9 Psychosocial issues

- In general, girls and women with TS experience a lower self-concept than those without TS. They report higher degrees of social isolation and anxiety, form fewer close friendships, marry at lower rates, and are less likely to live with others. Providing support to individuals with TS who are attempting to integrate into social communities can be a key strategy in helping them form strong social networks.

### 8.10 Impact of hormonal therapies

- Women with TS usually have similar neurocognitive profiles despite preserved ovarian function or adequate estrogen replacement. Similarly, GH treatment does not appear to affect neurocognition.

## 9. Optimizing Care Across the Lifespan

### 9.1 Exploring alternatives to hospital clinics

- Care for those with TS lends itself to telemedicine and the use of online medical records. Families and women who do not live in an area with accessible care could explore using these options to connect with TS specialists.

### 9.2 Role of patient support organizations

- Adolescents and women with TS and parents of young girls with TS should contact a local or national TS organization for resources and peer-to-peer support.

### 9.3 National registries for TS

- The guidelines recommend that national registries recording clinical and psychosocial data from individuals with TS be established and that data from them be combined to determine factors contributing to research.

## TS Organizations that Provide Information and Support

- Turner Syndrome Society of the United States – <http://www.turnersyndrome.org>
- Turner Syndrome Global Alliance (US) – <http://tsgalliance.org>
- Turner Syndrome Foundation (US) – <https://www.turnersyndromefoundation.org>
- Turner Syndrome Society of Canada – <http://www.turnersyndrome.ca>
- Asociación Síndrome de Turner México – <http://turnermexico.org.mx>
- Turner Syndrome Support Society (UK) – <http://tss.org.uk>
- Turner Syndrome Association of Australia – <https://www.turnersyndrome.org.au>
- Turner Syndrome International Group – <https://tsint.org> (Links for worldwide TS organizations are available at this site.)

**Reference:** Gravholt CH, Andersen NH, Conway GS, et al. Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. *Eur J Endocrinol.* 2017;177:G1–G70.

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