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ADVANCES IN PEDIATRICS

Advances in the Interdisciplinary Care of Children with Klinefelter Syndrome

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Keywords

• Klinefelter syndrome • 47,XXY • Sex chromosome aneuploidy

Key points

- Klinefelter syndrome is a common but underdiagnosed genetic condition with significant phenotypic variability in childhood.
- The pediatrician needs to be aware of the increased risk for neurodevelopmental, psychological, and medical conditions that are associated with an additional X-chromosome.
- Over the next decade, we anticipate a sharp increase in diagnosis rates with advances in genetics, particularly prenatal and neonatal diagnoses.

Klinefelter syndrome (KS) is a common genetic disorder characterized by an additional X-chromosome in male individuals leading to a karyotype of 47,XXY. The clinical syndrome was first described nearly 75 years ago in several male individuals with small testes, tall stature, gynecomastia, and azoospermia [1]. Our construct of what KS entails has greatly changed

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since then with identification of the genetic etiology in 1959, epidemiologic studies of birth cohorts in the 1980s, the development of rodent models, and many observational and interventional clinical studies in boys and men with KS [2–4]. Characterization of the neuropsychological profile, along with earlier diagnosis, facilitates earlier developmental evaluation and intervention services [5]. Optimizing testosterone treatment may prevent some of the physical manifestations of the "classic KS phenotype" [6]. Advanced reproductive technology (ART) has made it possible for nearly half of men with KS previously deemed infertile to have an opportunity to have a biological child [7,8]. Despite these scientific advances, the underlying molecular mechanisms underlying primary testicular failure and the phenotypic heterogeneity of physical and neurocognitive features observed in KS remains elusive. In this review, we will provide the pediatrician with an update on what is known about the clinical manifestations and current treatment recommendations for boys and men with KS. Table 1 provides a summary of current treatment recommendations.

EPIDEMIOLOGY AND DIAGNOSIS

KS is the most common sex chromosomal aneuploidy, with estimated prevalence rates ranging between 1 in 448 to 1 in 917 male births [9–14]. A comparative analysis of newborn karyotyping studies published in the 1960s to 1970s and studies published in the 1970s to 1980s reported an increase in the prevalence of KS [14]. An increasing prevalence of KS could theoretically be explained by increasing maternal age, environmentally derived increase of errors in paternal meiosis I, and decreasing rate of elective termination for prenatally diagnosed KS, although this increasing prevalence needs to be confirmed and further evaluated [12,14,15]. Epidemiologic studies of sex chromosome aneuploidies have been limited to industrialized nationals, and to our knowledge, there have been no reports of ethnic differences in KS prevalence.

Currently, there is a significant discrepancy between the known prevalence of KS based on newborn screening studies and the rate of clinical diagnosis. It is estimated that only 25% to 35% of male individuals with KS are diagnosed in their lifetime, with the remaining 65% to 75% left undiagnosed. A study in the United Kingdom estimated that of all expected cases, approximately 10% of diagnoses are made in the prenatal period, 6% in childhood or adolescence, and 19% in adulthood [16]. The small number of children who are diagnosed before puberty are typically identified due to underdeveloped genitalia, hypotonia, developmental delays, or learning and behavior problems. Diagnoses made in adolescence are secondary to small testicular size, gynecomastia, or rarely, incomplete puberty. Adults are most commonly diagnosed for infertility; however, may present for symptoms of hypogonadism [13]. The low rate of diagnosis in the pediatric population is due to a combination of factors, including subtle or underrecognized features that overlap with typical children and genetic testing practices of most pediatricians that do not cover the most common neurodevelopmental features in KS, such as reading disabilities or

Table 1
Pediatric evaluation and treatment recommendations for XXY/KS

Neurodevelopmental/ psychological risk	Recommendation for follow-up and further evaluation
Developmental delay (age 0–3 y)	• Developmental and ASD screening by PCP per AAP recommendations, and • Referral for comprehensive developmental assessments for all children, with evaluation of cognitive, speech-language, motor, social, and adaptive functioning domains using standardized measures. ◦ If prenatal diagnosis: evaluations at 9–15 mo, 18–24 mo, and 30–36 mo; sooner or more frequent if any developmental concerns. ◦ If postnatal diagnosis: evaluation at diagnosis, and then at ages recommended above. • If indicated, initiation of early interventions including developmental, speech, occupational, physical, or behavioral therapies.
Learning disabilities	• Monitoring of learning and academic performance from preschool throughout education. • Psychological evaluations to assess cognitive functioning, learning disabilities (reading and/or math) at key times during education and transitions: early elementary, late elementary, middle school, high school, transition to postsecondary programming/education. • Special education supports (504 plans or Individual Education Plans) as needed. • Evidence-based interventions for learning disabilities if identified. • Consideration of additional academic supports, tutoring, options for schools/educational settings.
ADHD/EF problems	• Education of parents/caretakers about EF and manifestations of symptoms of EF deficits. • Screening by school system and PCP with input from family and school, as presentation may vary in different environments. Recognition that ADHD-inattentive symptoms are more common in XXY. • Formal evaluation of EF and attention by psychologist or neuropsychologist beginning at 7–8 y of age, and at key times during education: late elementary, middle school, high school, transition to postsecondary programming. • Implementation of educational strategies and supports for EF and ADHD symptoms at school and home if present. • Consideration of medication treatment for attention disorders/ADHD if present.
Speech-language disorders	• Assessment with an experienced pediatric speech and language pathologist with evaluation of expressive-receptive language abilities, higher-order language skills, pragmatic/social use of language, and disorders of speech production (developmental dyspraxia/apraxia) or hypernasality due to possible VPI. ◦ Recommended yearly from birth to 4 y, then every 2–3 y depending on presence or severity of impairment. ◦ Referral to ear, nose, and throat physician if concerns of hypernasality, VPI • Speech-language therapy through early intervention, school system, and/or privately if indicated. • Consideration of role of speech difficulties in behavior/frustration.

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Neurodevelopmental/ psychological risk	Recommendation for follow-up and further evaluation
Motor skills	• Beyond age 3, monitoring of fine and gross motor skills, balance, coordination, motor planning. OT and/or PT interventions if motor deficits causing difficulties with handwriting, play or recreational activities, dressing, eating, or other self-care skills.
Social skills difficulties	• Social development and ASD screening by PCP per AAP recommendations, and • Evaluation by developmental pediatrician, child psychiatrist and/or psychologist for evaluation if concerns of social functioning or ASD. • Consideration of whether social immaturity and/or language deficits contribute to social difficulties. • Therapy/counseling, school supports and/or medication treatment if indicated. • Consideration of social skills therapy/groups in academic setting or privately. • Involvement in clubs/activities of interest where peers share interests. • If ASD, evidence-based and individualized Applied Behavior Analysis therapies, such as ESDM.
Emotional/behavioral difficulties, anxiety	• Evaluation by developmental pediatrician, child psychiatrist, and/or psychologist for evaluation and treatment if concerns. • Involvement of school psychology/counseling team, incorporation of behavioral supports in school environment, consideration of contributions of bullying. • Consideration of behavioral responses relative to developmental level instead of chronological age. • Adaptations should be made in therapy approach if language deficits are present, parental involvement in therapy. • Consideration of medication treatment as indicated for anxiety, emotional lability, depression, mood dysregulation, irritability. • Consideration of OT/sensory-based approaches to address self-regulation, especially in younger ages or if difficulties with self-expression during therapy. • Consideration of complementary therapies, including equine therapy, art/music therapy, yoga.
Adaptive functioning problems	• Evaluation of adaptive functioning using standardized measures, including domains of self-care, communication, social, community use, safety and self-direction should be included as part of the psychological or educational evaluations recommended above. • Consideration of OT or other therapies for support throughout childhood and adolescence.

Medical features/risks	Recommendation for follow-up and further evaluation
Cardiovascular	
Congenital anomalies	• Cardiology consultation and/or echocardiogram/electrocardiogram for all new diagnoses or after birth in a prenatal diagnosis.
Dyslipidemia	• Cholesterol screening with lipid panel at age 9–11 and then again after puberty per AAP. ○ Sooner and/or more frequent if family history and/or noted abnormalities.
Abdominal obesity, fatty liver disease, insulin resistance, metabolic syndrome	• Anticipatory guidance for establishing a healthy diet and active lifestyle in childhood. • If obesity is present, screening should include alanine aminotransferase and HbA1C.Referral to weight management programs if indicated.
Dental	
Enamel defects/caries Taurodontism	• Dental evaluation beginning at age 1, followed by dental visits twice per year or per dentist recommendation.
Endocrinologic	
Hypogonadism/ testosterone deficiency	• Consider consultation with Pediatric Endocrinology at approximately 2 mo of age. • Pubertal examination with every annual physical examination. • Referral to Pediatric Endocrinology at first sign of puberty or by age 10 y. • Monitoring of serum gonadotropins and testosterone every 6 mo when pubertal. • Consideration of testosterone supplementation based on provider assessment and family preference. The goal of treatment is to replace deficient endogenous testosterone production and support development of secondary sex characteristics, bone health, metabolic function, psychosocial health, and prevent consequences of hypogonadism, including gynecomastia and tall stature. Overtreatment should be avoided.
Gynecomastia	• Palpation for breast tissue with every annual physical examination. • Early referral to Endocrinology for any gynecomastia. Consideration of treatment with testosterone, aromatase inhibitors, and antiestrogens, and/or surgical resection if medical management fails.
Subfertility	• Consider semen analysis in adolescence if developmentally appropriate. • Consider referral to reproductive urologist with experience in testicular sperm extraction in KS if desired.
Osteopenia/ osteoporosis	• Ensure adequate dietary intake of calcium and vitamin D. • Consider measurement of vitamin D stores and replacement if deficient. • No current role for routine bone density measurement in pediatrics.

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Medical features/risks	Recommendation for follow-up and further evaluation
Genetics	• If a prenatal diagnosis, postnatal confirmatory genetic testing is recommended, including florescence in situ hybridization testing for mosaicism. • Consultation with genetic counselor and/or clinical genetics on diagnosis. • Consultation in early adulthood; consider preimplantation genetic testing if paternity is pursued.
Genitourinary	
Undescended testes, inguinal hernia, hypospadias	• Referral to Urology if present. • Consider testicular tissue biopsy and preservation if surgery is indicated.
Microphallus	• Referral to Pediatric endocrinology or Urology if present in infancy. Short course of testosterone can be discussed.
Gastrointestinal/feeding	
Newborn feeding difficulties	• Lactation specialist, feeding therapy through occupational or speech therapist if indicated. • Weight/growth monitoring by PCP.
Reflux/constipation/ abdominal complaints	• Evaluation and treatment with primary care provider if present.Referral to gastrointestinal consult if indicated. Consideration of eosinophilic esophagitis.
Hematology/oncology	
Hypercoagulability	• Awareness of increased hypercoagulable risk and symptoms (deep vein thrombosis, pulmonary embolism). • Prophylaxis in high-risk clinical situations (eg, orthopedic surgery, central lines). • Hypercoagulability evaluation and/or referral to Hematology if blood clot diagnosed.
Malignancy risk	• Palpation for breast tissue with every annual physical examination. Evaluation of any discrete masses. • CXR to rule out mediastinal mass if symptoms of cough, dyspnea, or chest pain.Immediate evaluation/endocrine referral for precocious puberty. Evaluation to include serum β-HCG and alpha-fetoprotein.
Immunology	
Autoimmune diseases	• Discussion and monitoring of symptoms of autoimmune disease with PCP. • Thyroid function screening every 1–2 y starting at age 10, sooner or more frequent if symptoms of hypothyroidism or hyperthyroidism are present.

Musculoskeletal	
Pes planus (flat feet)/ ankle pronation	• Referral to PT or orthopedics for consideration of orthotics if causing pain, limiting activities, or affecting motor coordination or motor skills.
Tall stature	• Considerations of adaptations if needed at home and school (ie, larger chairs/desks).Recognition that tall stature can lead to expectations of more mature behavioral functioning, when social maturity in KS may be average or slightly delayed relative to peers.
Neurologic	
Seizures	• Neurologic history, including questions about staring spells or atypical movements. Neurology consultation and/or EEG and brain MRI may be indicated. Anticonvulsant medication(s) if indicated.
Tremor	• Monitoring for intention and/or postural tremor, most commonly in upper extremities. Referral to Neurology and consideration of medication as needed or for daily use if interfering with school (handwriting), work tasks, daily living skills (dressing, eating).
Pulmonary	
Allergies/reactive airways/respiratory infections	• Management through PCP, referral if needed.
Sleep apnea	• Sleep study if symptoms of sleep apnea present (ie, daytime fatigue, short sleep latency, difficulty with morning awakening, snoring, apnea).

Abbreviations: AAP, American Academy of Pediatrics; ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; CXR, chest radiograph; EEG, electroencephalogram; EF, executive function; ESDM, early start denver model; KS, Klinefelter syndrome; OT, occupational therapy; PCP, primary care practitioner; PT, physical therapy; VPI, velopharyngeal insufficiency.

speech-language disorders. Additionally, although most boys with KS will have mild to moderate neurodevelopmental and/or learning difficulties, there is phenotypic heterogeneity and approximately a quarter of boys with KS do not exhibit these challenges [5]. Finally, there appears to be a delay in diagnosis relative to when parents first expressed concern about their child to their physician, particularly for concerns of development [17]. When initial parental concerns were due to developmental delays, there was on average 4.8 years before genetic testing confirmed KS. The delay in diagnosis was only 2 years when parental concern was pubertal development, microorchidism, or gynecomastia; however, the average age of diagnosis in that cohort was still older than 20 years [17]. Therefore, recognition of features of KS by the pediatrician can result in increased diagnosis rate and more appropriate care.

The diagnosis of KS is made with prenatal or postnatal karyotype or DNA microarray. Historically, prenatal screening by ultrasound and/or maternal serum biochemical markers dramatically increased identification of pregnancies at risk for autosomal aneuploidies, yet KS pregnancies have failed to correlate with these screening markers. However, new prenatal genetic screening technology, referred to as noninvasive prenatal testing (NIPT), analyzes cell-free fetal DNA circulating in maternal blood. This low-risk screening modality is typically performed in the first trimester and can detect sex chromosome aneuploidies (SCA). Although sensitivity and specificity of NIPT is high for the detection of autosomal trisomies, there is a lower accuracy for SCA. In a recent study by Meck and colleagues [18], NIPT specific to XXY was shown to have a positive predictive value of only 67% (confidence interval 22.3%–95.7%). Moreover, a 2014 study by Wang and colleagues [19] identified that 8% of NIPTs positive for SCA were due to an abnormal maternal karyotype. Thus, in cases of NIPT positive for SCA, both follow-up diagnostic testing (by prenatal chorionic-villous sampling, amniocentesis, and/or postnatal blood testing) and maternal karyotyping are recommended. Although a relatively high rate of false positives remain, NIPT creates a landmark opportunity to dramatically increase prenatal ascertainment of KS, with estimates citing the diagnosis rate for infants would increase tenfold if NIPT were to be standard screening for all pregnancies. There has also been discussion about including Fragile X on standard newborn screen, which would also identify some cases of KS [20]. With the possible increasing prevalence and significantly increasing childhood ascertainment rate, the pediatrician will likely care for more infants and children with a known diagnosis of KS.

GENETICS

KS was confirmed to be attributed to the presence of a supernumerary X-chromosome resulting in a karyotype of 47,XXY by Drs Jacobs and Strong in 1959 [21]. The supernumerary X-chromosome is acquired randomly predominantly through meiotic nondisjunction events during maternal or paternal gametogenesis or secondarily through postzygotic nondisjunction during early embryonic mitotic divisions [22]. The supernumerary X-chromosome is inherited from the

mother in approximately 50% of cases, and from the father in the other 50% [23]. Up to half of cases with maternally derived supernumerary X cases are due to errors in meiosis I and become more common with increasing maternal age, whereas maternal meiosis II nondisjunction errors and paternal errors are not associated with parental age. The 2008 study by Morris and colleagues [14] describing an increase in the prevalence of KS proposes that environmental factors have led to increased paternal meiosis I errors; however, this finding remains controversial.

Mosaicism

Although approximately 90% of KS cases are nonmosaic 47,XXY, mosaicism is identified in approximately 7% of cases, and the other 3% are made up of rare variants [13]. Mosaic forms of KS are identified when the XXY cell line is found in the presence of another cell line, such as 46,XY or other karyotypes (ie, 47,XYY or 47,XXX). The phenotypic variability of mosaic KS is dependent on the karyotype and percentage of the additional cell lines. In cases of XXY/XY mosaicism, phenotypic symptoms may present more mildly and many cases fail to be identified. In cases of XXY mosaicism with abnormal karyotypes, such as XXY/XXYY or XXY/XXXY, phenotypic presentation may be more severe. Routine karyotype studies analyze approximately 20 cells; however, in the case of possible mosaicism, additional testing should be pursued by florescence in situ hybridization of the X and Y chromosomes to analyze a larger number of interphase nuclei. A significant limitation to testing for mosaicism is that peripheral blood may not accurately reflect levels of mosaicism across different tissue types, so phenotypic interpretation continues to be heavily dependent on clinical evaluation.

Since the original 1959 report of KS being caused by a single extra X-chromosome, several other rare sex chromosome variations in male individuals have been identified and characterized by the presence of 2 or more extra X and Y chromosomes, including 48,XXYY, 48,XXXY, and 49,XXXXY syndromes, occurring in 1:18,000 to 1:100,000 male births. Although these syndromes have been labeled as ''variants'' of KS because of shared features, including hypergonadotropic hypogonadism and tall stature, these syndromes are characterized by a more severe phenotype, including additional physical findings, congenital malformations, medical problems, and psychological features [24,25].

The mechanisms of how the presence of supernumerary X-chromosome(s) impact phenotypic features and variability observed in KS continue to be poorly understood. Studies continue to investigate the most implicated mechanisms, including gene dosage, skewed X-inactivation, genetic polymorphisms, and parental origin of the supernumerary X-chromosome. Many of these potential mechanisms suggest an important role of epigenetic processes in KS.

Gene dosage and expression

Gene dosage compensation is the mechanism of equalizing gene expression between male (XY) and female (XX) individuals due to the different number of

genes contained on the sex chromosomes. This genetic equalization is achieved through a process of X-inactivation, in which one of the X-chromosomes in every female cell is randomly silenced, leaving only 1 X-chromosome transcriptionally active. In cases of X-chromosome aneuploidy, each X-chromosome in excess of 1 is inactivated by this same mechanism. However, 2 homologous regions of the sex chromosomes, known as pseudoautosomal regions (PAR1 and PAR2), as well as an additional 5% to 15% of X-chromosome genes, escape inactivation and are expressed from both X-chromosomes [26,27]. An extra copy of these ''escapee'' genes are therefore transcriptionally active in male individuals with KS, and overexpression then leads to excess mRNA and gene product, subsequently affecting the cellular and developmental pathways affected by these genes. The observation that clinical phenotype progressively deviates as the number of supernumerary sex chromosomes increases further supports this theory. This overexpression of escapee genes continues to be heavily studied as a likely mechanism leading to the phenotype and impacting phenotypic variability in KS.

An example of such an X-linked escapee gene is the short stature homeobox gene (SHOX), which has demonstrated a gene dosage impact in SCAs. SHOX is located within the pseudoautosomal region (PAR1) of the X-chromosome and encodes a transcription factor expressed in the developing skeleton impacting height. Short stature seen in Turner syndrome (45,X) has been established to result from haploinsufficiency of SHOX. Although tall stature in KS partially results from slower closure of epiphyseal plates secondary to hypogonadism, SHOX overexpression has also been implicated in the accelerated growth velocity and increased height observed in sex chromosome trisomies [28].

Further studies have analyzed differential genetic expression patterns in men with KS compared with male and female controls with the hope of elucidating differences in gene expression and regulation. In 2007, Vawter and colleagues [29] compared 11 men with KS with 6 XY male individuals by whole genome expression array and identified differential expression of 129 genes, 14 of which were X-linked genes and many of which showed correlation with verbal cognition. Additional studies evaluating genetic expression differences in brain, testes, and blood further suggest that autosomal genes are also differentially expressed in KS [30–32]. More recently, Zitzmann and colleagues [33] compared gene expression patterns of 132 male individuals with KS with male and female controls. This study identified differential gene expression in 36 total genes (21 X-linked and 15 autosomal) compared with male controls and 86 total genes compared with female controls (46 Y-linked, 10 X-linked, and 30 autosomal). Several of these identified X-linked genes are known to escape X-inactivation and are involved in pathways associated with phenotypic physical findings commonly seen in KS and therefore considered likely candidates to the pathophysiology of KS. Understanding the role of differential gene expression differences in KS is made more complex by the recent finding of increased copy number variations of X-chromosome genes in KS compared with typical male and female individuals, most of which were duplications and falling

within areas that escape X-inactivation [34]. Further work is needed to investigate regulatory mechanisms influencing differential gene expression, not only in escapee genes, but also across the entire genome as it relates to KS.

Skewed X-inactivation

Another genetic mechanism possibly leading to phenotypic variation in KS is skewed X-inactivation. Typically, X-inactivation is a random process resulting in a ratio of active to inactive X-chromosome alleles (outside of the PARs) of approximately 50%. Skewed X-inactivation, defined as greater than 80% methylation of 1 allele, results from preferential inactivation of a specific X-chromosome. Studies analyzing skewed X-inactivation in patients with KS have ranged in finding fewer than 10% to more than 40% of subjects with skewing, and conflicting results regarding association of phenotypic features with skewing [35–37].

In 2014, the evaluation of Skakkebaek and colleagues [38] of 73 male individuals with KS found no association between skewed X-inactivation and cognition or psychological phenotypic variation. They did however find a significant correlation between skewed X-inactivation and smaller gray matter volume in the left insula of the brain. The insular cortex area of the brain plays an important role in social, emotional, and mental processing, all of which are variably affected in KS [39]. Caution should be taken for interpretation of results from any study of X-inactivation, however, as X-inactivation is typically measured in peripheral blood but can vary between tissues. Further, effects of skewed X-inactivation itself remain dependent on the polymorphisms and activity of the genes expressed from the more active chromosome, which varies between individuals.

Parental origin

Several studies have analyzed phenotypic variability in KS based on parental origin of the supernumerary X-chromosome and possible differential expression of maternal versus paternal alleles. To date, these results have been inconsistent. Although most studies are unable to establish a significant correlation between parental origin and phenotypic variability [36,38,40,41], some studies have demonstrated a higher incidence of findings when the supernumerary X-chromosome was paternally derived, including developmental problems, altered steroidogenesis, increased hematocrit, later puberty, insulin resistance, and cardiac findings of a shorter QTc time [33,42,43].

Gene polymorphisms

Another gene of interest in KS is the androgen receptor gene (AR), which is located on the X-chromosome and contains a highly polymorphic CAG trinucleotide repeat, with a normal range of 9 to 37 CAG repeats [36,44,45]. Studies have correlated the CAG repeat length with physiologic androgen effects, in which receptor activity is inversely related to the length of CAG repeat [36]. Several studies have demonstrated the CAG repeat length to be correlated with variable characteristics of the KS phenotype. Studies have

reported a correlation of long CAG repeat length (low receptor activity) with height, arm span, likelihood for gynecomastia, small testes, HDL cholesterol, hematocrit, and later reactivation of pituitary-testicular axis, all of which are more characteristic of a more "severe" KS phenotype [36,41,46]. Additional studies have also demonstrated correlations of short CAG repeat length (high receptor activity) to longer penile length, higher bone density, and higher likelihood of having a stable partnership or professional employment [36,43,47]. Not all studies have supported phenotypic correlations with CAG repeat number, however, including a study of 73 men with KS in which there was no correlation with psychological phenotypic variation [38], and a study of 50 boys with KS in which there was no relationship with cognitive or motor development [48].

Genetic counseling

Genetic counseling in KS is important in multiple settings, including in the setting of a prenatal diagnosis, pediatric/adolescent cases with a new diagnosis, and in adulthood. For parents with an intrauterine diagnosis of KS, it is important for them to know there is no increased risk for miscarriage [49]. Prenatal or pediatric counseling should provide a comprehensive depiction of the phenotypic variability in KS, as well as include recommendations for developmental assessments/interventions, neuropsychological assessments/academic supports, social and emotional assessments/supports, indicated medical evaluations, including endocrinology evaluation for testosterone replacement, current reproductive options, timing and approach to disclosure, and information regarding both local and national support groups [50].

Counseling regarding fertility and options for fathering children in KS has changed significantly in the past decade with advancing reproductive technology. Historically the presence of infertility in KS was considered universal, and azoospermia continues to be present in the vast majority of men with KS. However, research has supported that up to 8% of men with KS have a small number of sperm in ejaculate [51,52], and there are rare case reports of spontaneous pregnancies. Much more promising is the current success rate of 50% to 60% in fathering biological children using advance reproductive techniques including microsurgical dissection of sperm from the testicle followed by in vitro fertilization, described in more detail in the endocrinology section later in this article. Although reported outcomes of children fathered from men with KS have been reassuring overall and most children have normal karyotypes, there have been slightly increased rates of children with KS and autosomal abnormalities reported. Preimplantation genetic diagnosis is available [53]. Due to a relatively young field, these risks require additional research. Regardless, it is important that counseling in all cases of KS emphasizes updated information about successes in the field of fertility, as this is a significant area of concern for parents, adolescents, and adults with KS [54–56]. It is also important to provide counseling related to other options for fatherhood chosen by many men with KS, including sperm donation and adoption.

Disclosure

With the advances in prenatal screening and increasing attention about KS in the medical literature, rates and ages of ascertainment are bound to improve. As such, pediatricians are often consulted by parents regarding decisions on when and how to disclose the diagnosis to the child. Research into other types of parent-to-child disclosures have identified barriers to communication causing possible avoidance of disclosure, including parents having difficulty understanding and/or being emotionally upset by the information, as well as being uncertain when and how to explain the information to the child and the child's ability to understand [57–59]. A recent study by Dennis and colleagues [60] evaluated the disclosure process of an SCA diagnosis from both parents and individuals, including 68 parents of male individuals with XXY and 58 individuals with XXY. Study results identified important common themes and experiences, which led to formulation of recommendations supporting that the disclosure process include discussing the diagnosis gradually, honestly, and simply with age-appropriate terms and a positive attitude. Results further supported telling the child early, such as during childhood or before puberty, possibly prompted by when the child starts asking questions or if interventions are being pursued. Parents and individuals participating in this study encouraged the disclosure process to incorporate elements of support, including pointing out the child's strengths, encouraging the child to ask questions, recognizing the common prevalence of the condition, and acknowledging research advancements and future possibilities [61]. Resources for parents about disclosure are available at www.genetic.org.

DEVELOPMENT, BEHAVIOR AND PSYCHOLOGY

Early development

There is significant variability in the developmental profiles of boys with KS; however, there is an elevated risk for mild to moderate developmental delays for which monitoring is important so interventions can be implemented if needed. Prospective studies of infants with KS diagnosed by newborn screening identified speech-language delays in 75% and motor skills delays in 50% [62–65]. Average age of milestones, including first words and first steps, are each approximately 2 to 3 months later compared with typical XY peers. Although these delays are milder in comparison with other genetic disorders, such as Fragile X or Down syndrome, speech and motor deficits do not generally resolve without therapies, and thus early intervention is recommended on identification of a delay in 1 or more developmental domains. In 25% to 50% of cases, early development progresses typically without significant developmental concerns or apparent need for intervention.

In young boys with speech delays, language testing most often shows a pattern, with receptive language skills higher than expressive skills [62,66,67]. An increased frequency of difficulties with oromotor planning and coordination called apraxia or dyspraxia of speech has also been described and can contribute to the expressive language delays in XXY [68]. Language

difficulties can take a toll early in the development of self-expression and can impact tolerance for frustration, regulation of interpersonal challenges, and are often cited as likely contributory factors to behavioral concerns [69]. Speech-language evaluation of the young child with KS should occur yearly for the first 3 years of life or on diagnosis, and should include assessment of all language domains as well as evaluation for features of apraxia so that appropriate therapy techniques can be implemented.

Motor delays are present in approximately 50% of boys with KS, and hypotonia is commonly associated [48,70]. Other common features such as mild hypermobility, pes planus with ankle pronation, and/or genu valgum can further affect motor development. Motor domains, including dexterity, coordination, and graphomotor skills, are commonly areas of weakness, which can then lead to difficulties with handwriting and self-care skills, such as dressing, tying shoes, and eating (Martin S, Cordeiro L, Richarson P, et al. The association of motor skills and adaptive functioning in XXY/Klinefelter and XXYY syndromes. Manuscript Pending Review.) [48,70]. Physical and/or occupational therapy can be helpful for addressing motor and self-care difficulties. Orthotics are often prescribed for pes planus to support motor development and prevent lower extremity pain.

Cognitive, language, and learning profiles

Early studies of KS that reported increased rates of intellectual disability were flawed by ascertainment bias as they sampled populations from mental health settings and long-term care facilities rather than a broader representative sample [71–74]. Since that time, our understanding of the cognitive profile in KS has evolved, and studies have established that the average full-scale IQ ranges from 90 to 100, with expected variability around the mean from low to above average following a standard distribution [3,5,75]. In this respect, many individuals with KS will not be significantly impacted by cognitive concerns and will achieve success in academic, personal, and career endeavors. On the other hand, statistically significant discrepancies have been shown relative to the general population and biological sibling controls. The overall mean for individuals with KS falls in the 90s and 5 to 10 points lower than the population and sibling controls [66,76–78]. In most studies, Verbal IQ scores are found to be lower than Performance/Nonverbal IQ scores, and it is these deficits in the verbal conceptual domain that account for the downward skewing of Full-Scale IQ [75]. In this respect, nonverbal, visual perceptual, and spatial reasoning abilities are often an area of strength relative to verbal reasoning weaknesses.

Weaknesses in verbal skills align with speech-language profiles that commonly show difficulties in many language-related domains, and language disorders can be identified in 50% to 75% of boys with KS through adolescence [66,67,79]. Generally, basic receptive and expressive vocabulary skills are intact. As language skills advance and become more complex, higher-level language deficits are common, including poor grasp of verbal concepts, verbal

processing difficulties, slow verbal processing speed, decreased verbal fluency, word retrieval problems, social communication difficulties, and difficulty with open-ended narrative construction [62,66,77,79–82]. Understanding the behavior of male individuals with KS in the context of their language abilities is important, both in terms of processing language and formulating verbal responses. For example, slower verbal processing can make highly verbal situations, such as classroom lectures or interpersonal interactions, more challenging or anxiety-provoking, and difficulty with word retrieval and/or language formulation can then affect speed and content of verbal responses in both educational and social settings. Speech-language therapy can continue to play an important role beyond early language development, and speech-language evaluation is recommended for all children and teens with KS displaying behavioral, social, or educational difficulties to determine if therapies addressing higher-level language skills and social/pragmatic language may be helpful.

In the school-aged years, boys with KS are at higher risk than the general population for language-based learning disabilities, including dyslexia [83,84]. Occurrence ranges between 50% and 80% [62,66,78], and family history of learning disability increases this risk [85]. More broadly, approximately 80% of boys with KS require some form of specialized support in school for language-based learning or reading concerns [62]. This is typically provided in the form of an Individualized Education Plan (IEP) or 504 plan, and it is strongly recommended that providers take an assertive stance with regard to advocating for intervention and educational supports. Lapses in support and intervention tend to create significant delays that are difficult to remediate. Evidence-based treatment approaches for reading disorders such as Linda-Mood-Bell or Orton-Gillingham are recommended, either through special education and/or private reading therapy. The high prevalence of learning disabilities in KS justifies periodic neuropsychological evaluation for all children with KS, starting in early grade school when early literacy is developing and deficits are simpler to address. Reassessment of cognitive and academic skills approximately every 3 years is then recommended, as deficits may not arise in some individuals until material becomes more complex and abstract with age. If lack of a formal learning disability diagnosis disqualifies a student from an IEP or educational supports, then advocating for services under the medical/health condition of KS with associated learning and executive functioning deficits is often successful to provide additional support.

Neuropsychological studies in KS have also consistently identified an increased risk for deficits in executive function (EF), including attention, working memory, cognitive flexibility, task initiation, fluency, and inhibition [86–90]. Executive dysfunction can have broad effects across home, school, and occupational settings, where additional supports in initiating, organizing, and executing tasks and assignments are often needed. Recent research in KS has also linked decreased EF and inhibition to increased behavioral difficulties, including aggression, rule-breaking behavior, and thought problems [91]. Neuropsychological and educational assessment in KS should include direct

evaluation of EF, and parents and teachers should be educated about behavioral manifestations of EF difficulties, as well as effective interventions and supports, which should be included as part of a comprehensive educational plan.

There is an increased risk for attentional problems, and attention-deficit/hyperactivity disorder (ADHD) diagnosis rates range from 36% to 63% [48,92,93]. Distractibility and inattentive symptoms are more common than hyperactivity and impulsivity. It is important for children with KS who have attentional difficulties to have a neuropsychological evaluation that includes assessment of attention and EF, as well as other comorbidities that might present as inattention, such as learning disability, language disorder, or anxiety [77,94,95]. There is a positive response to treatment of ADHD symptoms with stimulant or nonstimulant ADHD medication in approximately 75% of patients, and thus a trial of medication(s) should be recommended as per standard ADHD treatment guidelines. However, as with other neurodevelopmental disorders, medications should be started at a lower dose and advanced conservatively while monitoring for side effects, and the contribution of comorbidities, such as anxiety or learning disabilities, should be considered if there is poor medication response or side effects. In complex or difficult cases, referral to developmental pediatrics or child psychiatry for medication management is recommended.

Behavior/social-emotional development

Studies report a range of behavioral features and psychological risks that can be associated with KS, including behavioral difficulties, social-emotional immaturity, low frustration tolerance, decreased self-esteem, and emotional sensitivity, along with higher rates of anxiety and depressive concerns [5,56,69,91,96–99]. As with other associated features, there is broad variability in the presence and severity of these symptoms between individuals with KS. Behavioral and emotional concerns should be screened for routinely, with referrals made for further psychological evaluation and therapy/counseling as needed. Counselors and therapists often have to modify therapeutic approaches due to the presence of language disorders and difficulties with self-expression, and thus identifying a therapist with experience working with children with delays or disabilities is helpful. Occupational therapy approaches to teach sensory-based self-regulation strategies are often less verbal and can be very successful for patients with KS throughout childhood. Psychopharmacologic medication treatment should be considered in childhood through adulthood to address behavioral or emotional regulation, anxiety, or depression if these symptoms are affecting home, school, and/or social functioning.

Social difficulties and elevated rates of autism symptoms have also been described in KS [82]. Most studies have focused on describing autism symptoms, which have identified features such as decreased social attention, decreased empathic skills, difficulty interpreting facial expressions, and social communication difficulties [67,100–102]. Studies that have included direct diagnostic assessment for autism spectrum disorders (ASDs) are more limited, and

report a rate of 27% in a Dutch cohort (n = 51) using a standardized diagnostic autism interview called the ADI-R [92], and a rate of 10% in an American cohort (n = 20) using a battery including the ADI-R and direct assessment via the Autism Diagnostic Observation Scales (ADOS) [5]. Two other studies that evaluated rates of previous clinical ASD diagnosis in their cohort with KS also reported approximately 10% with ASD [67,100]. Recent important studies comparing autism symptoms and neuroanatomy in XXY to a group with idiopathic autism demonstrated that although behavioral questionnaires indicated similar autism symptoms between the groups, there were significant neuroanatomical differences in XXY compared with idiopathic ASD, suggesting that autism symptoms in the respective groups may have, at least partially, different etiologies [102]. Taken together, these studies support that ASD is an important clinical consideration in KS.

Screening for ASD should begin in early childhood as per the American Academy of Pediatrics recommendations, with referral for ASD assessment if indicated by screening results or if there are other concerns for ASD or social development raised by parents, teachers, or other providers. During assessment of social or ASD concerns, it is important and sometimes nuanced to differentiate the atypical social development and decreased reciprocity of ASD from social-emotional immaturity and/or expressive language deficits common in KS that can both also impact social relationships with peers. Further, it is common for concerns about ASD to become more apparent in boys with KS, as social interactions become more complex beyond the first few years of life, and thus ASD evaluation should be included within a psychological evaluation for social or behavioral concerns. ASD diagnosis can be important so as to guide services and supports, as well as to help families, educators, and others better understand and support social development for the boy with KS.

Studies that drew subject participation from clinical settings have reported elevated rates of a number of more complex psychiatric conditions, including bipolar disorder and psychotic spectrum disorders, with symptoms of paranoia, delusional thinking, and hallucinations [92,101,103]. Hospitalization for disorders associated with psychosis is reported as small in KS, but increased over the general population [104]. Thus, providers should be aware of this increased risk and make referrals for psychiatric care if patients or parents bring up any concerns.

Although we have emphasized many different cognitive, behavioral, and social features that can be associated with KS, it is again important to emphasize the variability of the phenotype and the importance of also identifying areas of strengths and talent in each individual. Although therapies and supports for areas of difficulty may be needed, it is equally important to encourage constructive opportunities for development in areas of strength and interest for positive self-esteem and quality of life. Parents should be encouraged to balance therapies and interventions with playtime, recreational or community activities, clubs/organizations that interest the child, and other positive activities.

TESTICULAR DEVELOPMENT AND FUNCTION

One of the most commonly recognized features of KS is primary testicular insufficiency, which is present in the large majority of male individuals with KS by early adulthood. The molecular mechanisms underlying this nearly universal manifestation remain elusive; however, testicular development seems to be abnormal from very early in life [105]. The normal testis is made up of germ cells, Leydig cells, and Sertoli cells. From the limited studies reporting testicular biopsies in KS, germ cells are reduced in number from infancy and the deficit appears to be progressive, particularly after puberty, with only rare pockets of active spermatogonia seen in adulthood [106]. Evaluation of Leydig and Sertoli cell function largely relies on measurement of serum hormone concentrations. The Leydig cells produce testosterone, which has important local and systemic effects, and Sertoli cells produce inhibin B and anti-Müllerian hormone (AMH), both of which have important local effects but unknown systemic effects. Assessment of serum hormone concentrations, particularly testosterone, is limited by assay variability, insensitivity of the assays in the hormone ranges typical of prepubertal children, and the observation that serum measurements do not necessarily accurately reflect intratesticular hormone concentrations. Regulation of gonadal function is primarily via the hypothalamic-pituitary-gonadal axis in which luteinizing hormone (LH) and follicle-stimulating hormone (FSH) stimulate Leydig and Sertoli cells respectively. The hypothalamic-pituitary-gonadal axis is activated in boys during the first 2 to 3 months of life (often called the mini-puberty period of infancy), then again during puberty and remains active throughout the adult life span. There is overlap in testosterone levels in boys with and without KS; however, male individuals with KS on average seem to have lower serum testosterone (Fig. 1).

Infancy

Hypogonadism in KS may start as early as fetal life or early infancy [107]. Evidence to support this includes a higher prevalence of underdeveloped genitalia and cryptorchidism in infants, reduced germ cell number in testicular biopsies, smaller testicular size, and several studies suggesting a blunted testosterone

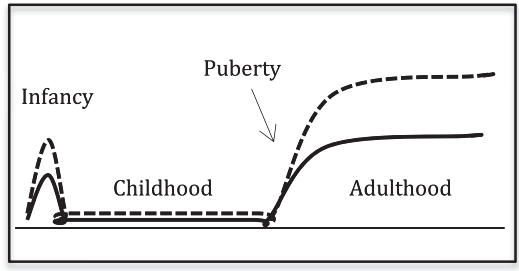

Fig. 1. T levels are abnormal throughout the lifespan in KS (*solid*) compared to normal male (*dashed*).

surge during the mini-puberty period of infancy [108–111]. Some endocrinologists measure testosterone, LH, and FSH at approximately 6 to 12 weeks of life during the mini-puberty period of infancy. However, the mini-puberty period in the healthy infant is vaguely defined, so it is not clear if this information has prognostic or management implications. Similarly, some providers will give testosterone during the first few months of life in infants with KS; however, there is currently insufficient evidence to support this practice [112]. Recent report of cognitive and behavioral benefits in male individuals with KS who had previously received testosterone has stimulated a great deal of interest from families [113,114]; however, these findings have to be replicated with prospective, randomized study designs. A randomized trial of intramuscular testosterone during the mini-puberty period of infancy is currently enrolling (NCT02408445).

Endocrine evaluation during infancy should include measurement of stretched penile length and documentation of bilateral descended testes. If micropenis is present (<1.9 cm from 0–6 months of life) or the family desires further discussion regarding endocrinologic manifestations in infancy, referral to a pediatric endocrinologist should be sought [115]. If cryptorchidism (persistent >6 months), inguinal hernia, or any other urogenital malformations are present, the infant should be referred for urology consultation.

Childhood

Before puberty in boys with KS, testicular volume is often less than 2 mL and penile growth throughout childhood has been noted to be slow [40,116]. The hypothalamic-pituitary-gonadal axis is quiescent in childhood; therefore, evaluation of LH, FSH, and testosterone concentrations are generally not clinically useful. However, 10% to 20% of boys with KS may have prepubertal elevation of FSH, low inhibin B, and/or elevated AMH reflecting abnormal Sertoli cell function [117]. Whether prepubertal Sertoli cell function is related to overall gonadal function in puberty and adulthood is yet to be determined. Results from a recently completed randomized controlled trial of oxandrolone (a non-aromatizable androgen) are expected soon. At this time, there are no recommendations for prepubertal hormonal evaluation or treatment.

Puberty

Most studies report a normal age of onset and tempo of early puberty in boys with KS [3,118].

Testes begin to enlarge but typically reach a peak volume of no more than 10 mL and then decrease down to smaller than 4 mL [119]. Serum testosterone may rise appropriately in boys with KS in early puberty, but often eventually plateaus or even declines when serially monitored [120]. FSH rises above the normal range on average a year after pubertal onset and LH approximately 2 years after pubertal onset. Endogenous testosterone usually supports virilization with penile enlargement and pubic hair development, although some young men with KS will not develop as much body or facial hair as would be expected for family. Fusion of the epiphyses may be delayed, contributing

to tall stature. Gynecomastia probably occurs about as often as in pubertal boys without KS (~50%); however, may be more likely to persist in KS [121,122]. Physical examination should always include palpation for breast tissue, and if present warrants consideration of testosterone supplementation. The pathophysiology of gynecomastia is an abnormal testosterone-to-estrogen ratio; therefore, aromatase inhibitors have been used, however a randomized controlled trial in pubertal boys with physiologic gynecomastia (not KS) did not find benefit of anastrozole compared with placebo [123]. Estrogen receptor inhibitors (tamoxifen) have been reported in uncontrolled trials to reduce breast tissue size; however, it is unclear if this is superior to the outcome without medication and no studies have been done in boys with KS [124]. Surgery can be considered if gynecomastia fails to resolve with time and hormone manipulation; however, surgery does have perioperative risks and gynecomastia can recur postoperatively [125].

We recommend referral to an endocrinologist at approximately 10 years of age or at the first sign of puberty, whichever is earliest. This initial visit is largely educational and establishes rapport. Boys with KS who have clinical signs of puberty should be monitored with pubertal examination and laboratory evaluation with serum LH, FSH, and testosterone approximately every 6 months. Currently there are no universally accepted guidelines for when (or if) to start androgen replacement. One option is waiting until clear biochemical and/or clinical evidence of hypogonadism with elevated LH, low or falling testosterone, and presence of gynecomastia, poor muscle mass, fatigue, or incomplete virilization. Another approach is to initiating low-dose testosterone when LH has risen outside the normal range for pubertal development. A more aggressive option would be initiating testosterone in early puberty before any overt evidence of gonadal insufficiency. A randomized controlled trial that is currently enrolling hypothesizes psychosocial and motor benefits to low-dose testosterone treatment in early puberty (NCT01585831). Until more evidence is available from research studies, the preference of the patient and parents should be greatly considered in determining the timing of androgen replacement.

Although there are many testosterone formulations available, options for adolescents are generally limited to depot injections of testosterone or topical testosterone gel, as other formulations do not allow for small enough dosing increments or are not well tolerated by adolescent boys [7]. Injections have been used for decades, and most endocrinologists are familiar with their use. Injections can be given at home or in the primary care physician's office, and dosing is typically titrated based on symptomatology and psychic examination. Disadvantages of injections include the presence of peaks and troughs in serum testosterone and the inconvenience and/or pain of shots. Topical testosterone gels are newer and may not be covered by all insurance carriers. If starting with gel, the smallest increment of the lowest potency available is recommended as the starting dose, with the goal of achieving serum testosterone concentrations in the normal range for pubertal stage. Disadvantages

of gels include the need for daily application, skin irritation, or sensory issues. Occasionally even the lowest available gel doses are too high for some pubertal boys, which may lead to elevated testosterone concentrations and subsequent rapid pubertal progression and/or premature fusion of the growth plates. Long-acting injections or testosterone pellets are being increasingly used in the United States; however, these are not recommended until late adolescence or adulthood when steady dose needs have been established.

Adulthood

The focus of this review precludes a comprehensive discussion on testicular function in adult men with KS. In brief, testicular size is universally small and usually firm, as the germ cells that should make up the bulk of the testis volume in adults are profoundly reduced in KS [122]. It is important to note, however, that the male genitalia otherwise has normal structure, size, and function. Nearly all untreated men with nonmosaic KS will have elevated LH and FSH, with low or low-normal testosterone and low or undetectable inhibin B and AMH [7]. Testosterone replacement should be offered to all men with evidence of hypergonadotropic hypogonadism, even if they are asymptomatic, as many manifestations of gonadal insufficiency may be subtle. The Endocrine Society has published guidelines for testosterone replacement in men with hypogonadism [126].

Azoospermia is nearly universal; however, the concept of "universal infertility" in KS has drastically changed with the ART technique of testicular sperm extraction (TESE) followed by intracytoplasmic sperm injection (ICSI) [8]. Using these techniques, small pockets of testicular tissue producing a few sperm can be identified during microsurgery, which are then extracted and injected through ICSI into a retrieved ovum, followed by in vitro fertilization. Currently, success rates of 50% to 75% are reported in adult men with KS seeking biological paternity using TESE and ICSI [127,128]. Studies have not found consistent predictors for which individuals will be more likely to have success with TESE, although mosaicism with a 46,XY cell line may have a more favorable outcome and older age (particularly more than 30 years), has been reported to have a less favorable outcome [129,130]. Many centers internationally have explored TESE for sperm cryopreservation from adolescents with KS, and current success rates do not consistently exceed those achieved in adulthood [127,131]. Based on this evidence and the relative newness of the field, we recommend that families are informed of the active and promising research in this field, and that consultation with a reproductive urologist is offered for all interested families, adolescents, or adults with KS seeking more information and options related to fertility. Invasive procedures for fertility preservation in childhood or adolescents are not currently routine practice outside of research protocols, although this may change as technology advances. Also important, several studies report similar fertility potential for male individuals with KS with previous exogenous testosterone exposure [127,128,130]; therefore, testosterone treatment should not be withheld from hypogonadal male individuals for future fertility concerns.

OTHER MEDICAL ISSUES

Insulin resistance and cardiovascular disorders

Adults with KS are known to have a high prevalence of disorders related to insulin resistance, including type 2 diabetes mellitus, dyslipidemia, and fatty liver disease [132]. Metabolic syndrome, a constellation of signs, including large waist circumference, dyslipidemia, elevated fasting blood glucose, and high blood pressure, is present in approximately 50% of men with KS [133–135]. The presence of these conditions correlates with abnormal body composition (particularly abdominal adiposity) and hypogonadism [135]. Together, type 2 diabetes and cardiovascular diseases yield a standardized mortality ratio of 5.8 in adults with KS [136].

Much less work has been done in children with KS; however, recent studies have found a high prevalence of metabolic syndrome features, as well as a high body fat percentage, in this population [137,138]. Importantly, features of metabolic syndrome in boys with KS appear to be independent of age or body mass index (BMI). Counseling regarding a healthy diet and regular exercise is imperative from an early age. We recommend cholesterol screening with a fasting lipid panel at age 9 to 11 years and after puberty is completed (consistent with American Academy of Pediatrics recommendations for all children), and sooner if additional risk factors are present [139]. Lipid panel should be repeated in puberty if the previous panel was abnormal or additional risk factors are present, such as obesity, untreated hypogonadism, or atypical antipsychotic use.

The risk of peripheral vascular disease and thromboembolic disease is increased in male individuals with KS, resulting in significantly increased mortality [136]. Venous stasis and recurrent leg ulcers are also quite common [140,141]. Although these conditions are more common with age, we have had several adolescents with KS who developed venous thrombus in at-risk situations, such as with a central venous catheter or surgery with immobilization. Consideration of prophylaxis measures should be considered if an adolescent or young adult is in a clinical situation that may predispose to clotting.

Bone health

Studies in adult men with KS report lower bone mineral density and a higher morbidity and mortality from hip and spine fractures [136,142]. It is speculated hypogonadism contributes to these findings; however, a mouse model suggests the additional X-chromosome itself results in abnormal bone structure [143]. A single study in 18 children and adolescents with KS reports normal bone mineral density [137]. In our anecdotal experience, we have not seen a high prevalence of pathologic fractures in children and adolescents with KS, and we do not recommend routine evaluation of bone mineral density. We do recommend attention to standard pediatric guidelines and ensuring adequate calcium and vitamin D intake, regular physical exercise, maintaining a normal BMI, and tobacco avoidance [144]. For postpubertal boys with KS, maintenance of sex steroid levels in the normal range likely helps bone density [145]. Chronic

or unexplained back pain in an adolescent or adult with KS should raise concern for a vertebral compression fracture and appropriate evaluation undertaken.

Autoimmunity

Many case series and later epidemiologic studies have reported an increased prevalence of several autoimmune diseases in KS compared with 46,XY male individuals. A recent medical record linkage study of hospitalized men in England found significantly higher rates of several autoimmune diseases in men with KS, including rheumatoid arthritis (Relative Risk [RR] 3.3), lupus, multiple sclerosis (RR 18.1), Addison disease (RR 11.7), Sjögren syndrome (RR 19.3), autoimmune hypothyroidism (RR 2.7), and type 1 diabetes mellitus (RR 6.1) [146]. Although these are all significantly higher in adult men with KS compared with men in the general population, most of these autoimmune conditions are known to have a female predominance, and the risk of these autoimmune diseases is similar to women in the general population [147]. No studies have evaluated autoimmune diseases in children with KS. Although screening for primary hypothyroidism is often recommended in KS [148], evidence is lacking to recommend this in pediatrics. It is important to be aware of the increased prevalence of autoimmunity in KS and evaluate if suggestive symptoms are present.

Malignancy

An excellent review of the literature of malignancies in KS was published in 2013 [149]. Despite abundant case reports, there are few epidemiologic studies available. Because only a minority of male individuals with KS are diagnosed before adulthood, the natural history of malignancies in children with KS is really not known. The 3 cancers that are consistently found to be more prevalent in KS compared with male individuals in the general population are breast cancer, extragonadal germ cell tumors, and non-Hodgkin lymphoma. No routine screenings are recommended for any of these malignancies in childhood, but suspicious symptoms should be evaluated.

Breast cancer is approximately 20 times more common in men with KS compared with men without KS; however, it is still less common than in women [150]. Overall, breast cancer affects approximately 3% to 7% of men with KS [151,152], but is rare in adolescents. Self-examinations as well as regular physician examinations should be routine, and any palpable mass should be evaluated.

Extragonadal germ cell tumors are diagnosed in approximately 0.1% of male individuals with KS, representing a large increased risk compared with the general population. Unlike breast cancer, which does not typically present until adulthood, approximately half the reported cases of extragonadal germ cell tumors occur in pediatrics, with a peak age in adolescence [153]. Precocious puberty is the most common presenting symptom in boys younger than 10 years, whereas cough, dyspnea, or chest pain was most common in adolescents and adults given the most common tumor location is the mediastinum [154]. If

these symptoms are present, extragonadal germ cell tumor should be suspected, and evaluation pursued with a chest radiograph to evaluate for a mediastinal mass as well as measurement of serum β-HCG and alpha-fetoprotein [149].

Finally, an association with non-Hodgkin lymphoma was reported in a large British cohort, particularly in boys with more than 3 sex chromosomes (48,XXYY); however, this was not found in other studies and requires further investigation [150]. There are many case reports of other hematological malignancies in male individuals with KS; however, epidemiologic studies do not show an increased incidence or mortality from leukemias or other lymphomas in KS [155]. It is important to keep in mind, however, that leukemia is the most common cancer in childhood, and therefore it would still be more likely for a boy with KS to develop leukemia than any of the other malignancies described previously.

Other medical conditions

Congenital anomalies are more prevalent in infants with KS than in the general population and lead to a higher mortality [136]. Congenital anomalies are much more common in boys with more than 3 sex chromosomes [156]. The most frequently reported anomalies include inguinal hernia, congenital heart disease, cleft palate and velopharyngeal insufficiency, and kidney malformations. Dental conditions, particularly taurodontism and frequent caries possibly from enamel defects, are common [24,157], and children with KS should have regular dental care.

Multiple case series have reported seizures in boys with KS, and a large epidemiologic study from Britain found a standardized mortality ratio from epilepsy of 7.2 in male individuals with KS compared with the general population [136]. Seizures are present in 15% of male individuals with 48,XXYY syndrome [24]. Seizures can present at any age. Tremor is also noted, particularly in male individuals with more than 3 sex chromosomes starting in adolescence [24,158].

Little is reported in the literature on atopy in KS; however, we appreciate a high prevalence of asthma and allergies in children with KS. In a study of 95 male individuals with 48XXYY syndrome, 55% and 60% had allergies and asthma, respectively [24]. Death from chronic lower respiratory disease, which would include asthma, was twice as likely in men with KS compared with the general population in Britain [136]. Further investigation is needed to explore whether this is a true association.

In summary, KS is a common but underdiagnosed genetic condition with significant phenotypic variability in childhood. The pediatrician needs to be aware of the increased risk for neurodevelopmental, psychological, and medical conditions that are associated with an additional X-chromosome. Over the next decade, we anticipate a sharp increase in diagnoses rates with advances in genetics, particularly prenatal and neonatal diagnoses. In the United States, more multidisciplinary clinics are being established to provide comprehensive

care for children and adults with KS and other sex chromosome variations [95]. More research is needed to further define the natural history of KS in infancy and childhood with these unbiased populations, as well as understand genetic and environmental contributors to phenotypic variability and determine best practice screening and management guidelines for boys with KS.

References

[1] Klinefelter HF, Reifenstein EC, Albright F. Syndrome characterized by gynecomastia, aspermatogenesis without aleydigism, and increased excretion of follicle-stimulating hormone. J Clin Endocrinol 1942;2:615–27.

[2] Lue Y, Rao PN, Sinha Hikim AP, et al. XXY male mice: an experimental model for Klinefelter syndrome. Endocrinology 2001;142(4):1461–70.

[3] Robinson A, Bender BG, Linden MG, et al. Sex chromosome aneuploidy: the Denver Prospective Study. Birth Defects Orig Artic Ser 1990;26(4):59–115.

[4] Klinefelter HF. Klinefelter's syndrome: historical background and development. South Med J 1986;79(9):1089–93.

[5] Tartaglia N, Cordeiro L, Howell S, et al. The spectrum of the behavioral phenotype in boys and adolescents 47,XXY (Klinefelter syndrome). Pediatr Endocrinol Rev 2010;8(Suppl 1):151–9.

[6] Rogol AD, Tartaglia N. Considerations for androgen therapy in children and adolescents with Klinefelter syndrome (47, XXY). Pediatr Endocrinol Rev 2010;8(Suppl 1):145–50.

[7] Davis SM, Rogol AD, Ross JL. Testis development and fertility potential in boys with Klinefelter syndrome. Endocrinol Metab Clin North Am 2015;44(4):843–65.

[8] Plotton I, Brosse A, Cuzin B, et al. Klinefelter syndrome and TESE-ICSI. Ann Endocrinol (Paris) 2014;75(2):118–25.

[9] Hook E. Chromosome abnormalities: prevalence, risks and recurrence. Prenatal diagnosis and screening. Edinburgh (Scotland): Churchill Livingstone; 1992. p. 351–92.

[10] Nielsen J. Sex chromosome abnormalities found among 34,910 newborn children: results from a 13-year incidence study in Arhus, Denmark. Birth Defects Orig Artic Ser 1990;26(4):209–23.

[11] Coffee B, Keith K, Albizua I, et al. Incidence of fragile X syndrome by newborn screening for methylated FMR1 DNA. Am J Hum Genet 2009;85(4):503–14.

[12] Herlihy AS, Halliday JL, Cock ML, et al. The prevalence and diagnosis rates of Klinefelter syndrome: an Australian comparison. Med J Aust 2011;194(1):24–8.

[13] Bojesen A, Juul S, Gravholt CH. Prenatal and postnatal prevalence of Klinefelter syndrome: a national registry study. J Clin Endocrinol Metab 2003;88(2):622–6.

[14] Morris JK, Alberman E, Scott C, et al. Is the prevalence of Klinefelter syndrome increasing? Eur J Hum Genet 2008;16(2):163–70.

[15] Boyd PA, Loane M, Garne E, et al. Sex chromosome trisomies in Europe: prevalence, prenatal detection and outcome of pregnancy. Eur J Hum Genet 2011;19(2):231–4.

[16] Abramsky L, Chapple J. 47,XXY (Klinefelter syndrome) and 47,XYY: estimated rates of and indication for postnatal diagnosis with implications for prenatal counselling. Prenat Diagn 1997;17(4):363–8.

[17] Visootsak J, Ayari N, Howell S, et al. Timing of diagnosis of 47,XXY and 48,XXYY: a survey of parent experiences. Am J Med Genet A 2013;161A(2):268–72.

[18] Meck JM, Kramer Dugan E, Matyakhina L, et al. Noninvasive prenatal screening for aneuploidy: positive predictive values based on cytogenetic findings. Am J Obstet Gynecol 2015;213(2):214.e1–5.

[19] Wang Y, Chen Y, Tian F, et al. Maternal mosaicism is a significant contributor to discordant sex chromosomal aneuploidies associated with noninvasive prenatal testing. Clin Chem 2014;60(1):251–9.

[20] Tassone F. Newborn screening for fragile X syndrome. JAMA Neurol 2014;71(3):355–9.

[21] Jacobs PA, Strong JA. A case of human intersexuality having a possible XXY sex-determining mechanism. Nature 1959;183(4657):302–3.
[22] MacDonald M, Hassold T, Harvey J, et al. The origin of 47,XXY and 47,XXX aneuploidy: heterogeneous mechanisms and role of aberrant recombination. Hum Mol Genet 1994;3(8):1365–71.
[23] Thomas NS, Hassold TJ. Aberrant recombination and the origin of Klinefelter syndrome. Hum Reprod Update 2003;9(4):309–17.
[24] Tartaglia N, Davis S, Hench A, et al. A new look at XXYY syndrome: medical and psychological features. Am J Med Genet A 2008;146A(12):1509–22.
[25] Peet J, Weaver DD, Vance GH. 49,XXXXY: a distinct phenotype. Three new cases and review. J Med Genet 1998;35(5):420–4.
[26] Berletch JB, Yang F, Disteche CM. Escape from X inactivation in mice and humans. Genome Biol 2010;11(6):213.
[27] Berletch JB, Yang F, Xu J, et al. Genes that escape from X inactivation. Hum Genet 2011;130(2):237–45.
[28] Ottesen AM, Aksglaede L, Garn I, et al. Increased number of sex chromosomes affects height in a nonlinear fashion: a study of 305 patients with sex chromosome aneuploidy. Am J Med Genet A 2010;152A(5):1206–12.
[29] Vawter MP, Harvey PD, DeLisi LE. Dysregulation of X-linked gene expression in Klinefelter's syndrome and association with verbal cognition. Am J Med Genet B Neuropsychiatr Genet 2007;144B(6):728–34.
[30] Huang J, Zhang L, Deng H, et al. Global transcriptome analysis of peripheral blood identifies the most significantly down-regulated genes associated with metabolism regulation in Klinefelter syndrome. Mol Reprod Dev 2015;82(1):17–25.
[31] Viana J, Pidsley R, Troakes C, et al. Epigenomic and transcriptomic signatures of a Klinefelter syndrome (47,XXY) karyotype in the brain. Epigenetics 2014;9(4):587–99.
[32] D'Aurora M, Ferlin A, Di Nicola M, et al. Deregulation of Sertoli and Leydig cells function in patients with Klinefelter syndrome as evidenced by testis transcriptome analysis. BMC Genomics 2015;16:1356.
[33] Zitzmann M, Bongers R, Werler S, et al. Gene expression patterns in relation to the clinical phenotype in Klinefelter syndrome. J Clin Endocrinol Metab 2015;100(3):E518–23.
[34] Rocca MS, Pecile V, Cleva L, et al. The Klinefelter syndrome is associated with high recurrence of copy number variations on the X chromosome with a potential role in the clinical phenotype. Andrology 2016;4(2):328–34.
[35] Tuttelmann F, Gromoll J. Novel genetic aspects of Klinefelter's syndrome. Mol Hum Reprod 2010;16(6):386–95.
[36] Zinn AR, Ramos P, Elder FF, et al. Androgen receptor CAGn repeat length influences phenotype of 47,XXY (Klinefelter) syndrome. J Clin Endocrinol Metab 2005;90(9):5041–6.
[37] Iitsuka Y, Bock A, Nguyen DD, et al. Evidence of skewed X-chromosome inactivation in 47,XXY and 48,XXYY Klinefelter patients. Am J Med Genet 2001;98(1):25–31.
[38] Skakkebaek A, Bojesen A, Kristensen MK, et al. Neuropsychology and brain morphology in Klinefelter syndrome—the impact of genetics. Andrology 2014;2(4):632–40.
[39] Nagai M, Kishi K, Kato S. Insular cortex and neuropsychiatric disorders: a review of recent literature. Eur Psychiatry 2007;22(6):387–94.
[40] Zeger MP, Zinn AR, Lahlou N, et al. Effect of ascertainment and genetic features on the phenotype of Klinefelter syndrome. J Pediatr 2008;152(5):716–22.
[41] Chang S, Skakkebaek A, Trolle C, et al. Anthropometry in Klinefelter syndrome—multifactorial influences due to CAG length, testosterone treatment and possibly intrauterine hypogonadism. J Clin Endocrinol Metab 2015;100(3):E508–17.
[42] Stemkens D, Roza T, Verrij L, et al. Is there an influence of X-chromosomal imprinting on the phenotype in Klinefelter syndrome? A clinical and molecular genetic study of 61 cases. Clin Genet 2006;70(1):43–8.

[43] Wikstrom A, Painter J, Raivio T, et al. Genetic features of the X chromosome affect pubertal development and testicular degeneration in adolescent boys with Klinefelter syndrome. Clin Endocrinol (Oxf) 2006;65(1):92–7.
[44] Choong CS, Wilson EM. Trinucleotide repeats in the human androgen receptor: a molecular basis for disease. J Mol Endocrinol 1998;21(3):235–57.
[45] Zitzmann M, Nieschlag E. The CAG repeat polymorphism within the androgen receptor gene and maleness. Int J Androl 2003;26(2):76–83.
[46] Bojesen A, Hertz JM, Gravholt CH. Genotype and phenotype in Klinefelter syndrome—impact of androgen receptor polymorphism and skewed X inactivation. Int J Androl 2011;34(6 Pt 2):e642–8.
[47] Zitzmann M, Depenbusch M, Gromoll J, et al. X-chromosome inactivation patterns and androgen receptor functionality influence phenotype and social characteristics as well as pharmacogenetics of testosterone therapy in Klinefelter patients. J Clin Endocrinol Metab 2004;89(12):6208–17.
[48] Ross JL, Roeltgen DP, Stefanatos G, et al. Cognitive and motor development during childhood in boys with Klinefelter syndrome. Am J Med Genet A 2008;146A(6):708–19.
[49] Hook EB, Topol BB, Cross PK. The natural history of cytogenetically abnormal fetuses detected at midtrimester amniocentesis which are not terminated electively: new data and estimates of the excess and relative risk of late fetal death associated with 47,+21 and some other abnormal karyotypes. Am J Hum Genet 1989;45(6):855–61.
[50] Dondorp W, de Wert G, Bombard Y, et al. Non-invasive prenatal testing for aneuploidy and beyond: challenges of responsible innovation in prenatal screening. Eur J Hum Genet 2015;23(11):1438–50.
[51] Lanfranco F, Kamischke A, Zitzmann M, et al. Klinefelter's syndrome. Lancet 2004;364(9430):273–83.
[52] Selice R, Di Mambro A, Garolla A, et al. Spermatogenesis in Klinefelter syndrome. J Endocrinol Invest 2010;33(11):789–93.
[53] Staessen C, Tournaye H, Van Assche E, et al. PGD in 47,XXY Klinefelter's syndrome patients. Hum Reprod Update 2003;9(4):319–30.
[54] Puck MH, Bender BG, Borelli JB, et al. Parents' adaptation to early diagnosis of sex chromosome anomalies. Am J Med Genet 1983;16(1):71–9.
[55] Gies I, Tournaye H, De Schepper J. Attitudes of parents of Klinefelter boys and pediatricians towards neonatal screening and fertility preservation techniques in Klinefelter syndrome. Eur J Pediatr 2015;175(3):399–404.
[56] Turriff A, Levy HP, Biesecker B. Prevalence and psychosocial correlates of depressive symptoms among adolescents and adults with Klinefelter syndrome. Genet Med 2011;13(11):966–72.
[57] Metcalfe A, Coad J, Plumridge GM, et al. Family communication between children and their parents about inherited genetic conditions: a meta-synthesis of the research. Eur J Hum Genet 2008;16(10):1193–200.
[58] Sutton EJ, Young J, McInerney-Leo A, et al. Truth-telling and Turner syndrome: the importance of diagnostic disclosure. J Pediatr 2006;148(1):102–7.
[59] Mac Dougall K, Becker G, Scheib JE, et al. Strategies for disclosure: how parents approach telling their children that they were conceived with donor gametes. Fertil Steril 2007;87(3):524–33.
[60] Dennis A, Howell S, Cordeiro L, et al. ''How should I tell my child?'' Disclosing the diagnosis of sex chromosome aneuploidies. J Genet Couns 2015;24(1):88–103.
[61] Tremblay I, Van Vliet G, Gonthier M, et al. Partnering with parents to disclose Klinefelter syndrome to their child. Acta Paediatr 2016;105(5):456–61.
[62] Bender B, Fry E, Pennington B, et al. Speech and language development in 41 children with sex chromosome anomalies. Pediatrics 1983;71(2):262–7.
[63] Linden MG, Bender BG. Fifty-one prenatally diagnosed children and adolescents with sex chromosome abnormalities. Am J Med Genet 2002;110(1):11–8.

[64] Robinson A, Bender BG, Linden MG. Summary of clinical findings in children and young adults with sex chromosome anomalies. Birth Defects Orig Artic Ser 1990;26(4):225–8.
[65] Ratcliffe SG. Speech and learning disorders in children with sex chromosome abnormalities. Dev Med Child Neurol 1982;24(1):80–4.
[66] Graham JM Jr, Bashir AS, Stark RE, et al. Oral and written language abilities of XXY boys: implications for anticipatory guidance. Pediatrics 1988;81(6):795–806.
[67] Bishop DV, Jacobs PA, Lachlan K, et al. Autism, language and communication in children with sex chromosome trisomies. Arch Dis Child 2011;96(10):954–9.
[68] Samango-Sprouse C, Rogol A. XXY the hidden disability and a prototype for an infantile presentation of developmental dyspraxia (IDD). Infants Young Child 2002;15(1):11–8.
[69] Bancroft J, Axworthy D, Ratcliffe S. The personality and psycho-sexual development of boys with 47 XXY chromosome constitution. J Child Psychol Psychiatry 1982;23(2): 169–80.
[70] Salbenblatt JA, Meyers DC, Bender BG, et al. Gross and fine motor development in 47,XXY and 47,XYY males. Pediatrics 1987;80(2):240–4.
[71] Eriksson B. Sex chromatin deviations among school children in special classes. A study of prevalence and an investigation of birth histories. J Ment Defic Res 1972;16(2):97–102.
[72] Singh DN, Osborne RA, Paul JR, et al. Cytogenetic survey of 504 mentally retarded individuals. J Ment Defic Res 1974;18(4):293–305.
[73] Bourgeois M, Benezech M. Cytogenic survey of 600 mentally retarded hospitalized patients [in French]. Encephale 1977;3(3):189–202.
[74] Johnston AW, Speed RM, Evans HJ. A chromosome survey of a population of mentally retarded persons. Birth Defects Orig Artic Ser 1974;10(10):30–5.
[75] Leggett V, Jacobs P, Nation K, et al. Neurocognitive outcomes of individuals with a sex chromosome trisomy: XXX, XYY, or XXY: a systematic review. Dev Med Child Neurol 2010;52(2):119–29.
[76] Ratcliffe SG, Masera N, Pan H, et al. Head circumference and IQ of children with sex chromosome abnormalities. Dev Med Child Neurol 1994;36(6):533–44.
[77] Rovet J, Netley C, Keenan M, et al. The psychoeducational profile of boys with Klinefelter syndrome. J Learn Disabil 1996;29(2):180–96.
[78] Bender B, Puck M, Salbenblatt J, et al. Cognitive development of children with sex chromosome abnormalities. San Diego (CA): College Hill Press; 1986.
[79] Netley C, Rovet J. Verbal deficits in children with 47,XXY and 47,XXX karyotypes: a descriptive and experimental study. Brain Lang 1982;17(1):58–72.
[80] Rovet J, Netley C, Bailey J, et al. Intelligence and achievement in children with extra X aneuploidy: a longitudinal perspective. Am J Med Genet 1995;60(5):356–63.
[81] Geschwind DH, Gregg J, Boone K, et al. Klinefelter's syndrome as a model of anomalous cerebral laterality: testing gene dosage in the X chromosome pseudoautosomal region using a DNA microarray. Dev Genet 1998;23(3):215–29.
[82] Bender BG, Linden MG, Robinson A. Verbal and spatial processing efficiency in 32 children with sex chromosome abnormalities. Pediatr Res 1989;25(6):577–9.
[83] Pennington BF, Bender B, Puck M, et al. Learning disabilities in children with sex chromosome anomalies. Child Dev 1982;53(5):1182–92.
[84] Bender BG, Linden MG, Robinson A. Neuropsychological impairment in 42 adolescents with sex chromosome abnormalities. Am J Med Genet 1993;48(3):169–73.
[85] Samango-Sprouse CA, Stapleton EJ, Mitchell FL, et al. Expanding the phenotypic profile of boys with 47, XXY: the impact of familial learning disabilities. Am J Med Genet A 2014;164A(6):1464–9.
[86] Boada R, Janusz J, Hutaff-Lee C, et al. The cognitive phenotype in Klinefelter syndrome: a review of the literature including genetic and hormonal factors. Dev Disabil Res Rev 2009;15(4):284–94.
[87] Boone KB, Swerdloff RS, Miller BL, et al. Neuropsychological profiles of adults with Klinefelter syndrome. J Int Neuropsychol Soc 2001;7(4):446–56.

[88] Lee NR, Wallace GL, Clasen LS, et al. Executive function in young males with Klinefelter (XXY) syndrome with and without comorbid attention-deficit/hyperactivity disorder. J Int Neuropsychol Soc 2011;17(3):522–30.
[89] van Rijn S, Swaab H, Magnee M, et al. Psychophysiological markers of vulnerability to psychopathology in men with an extra X chromosome (XXY). PLoS One 2011;6(5):e20292.
[90] Temple CM, Sanfilippo PM. Executive skills in Klinefelter's syndrome. Neuropsychologia 2003;41(11):1547–59.
[91] van Rijn S, Swaab H. Executive dysfunction and the relation with behavioral problems in children with 47,XXY and 47,XXX. Genes Brain Behav 2015;14(2):200–8.
[92] Bruining H, Swaab H, Kas M, et al. Psychiatric characteristics in a self-selected sample of boys with Klinefelter syndrome. Pediatrics 2009;123(5):e865–70.
[93] Tartaglia N, Davis S, Hansen R, et al. Abstract: Attention deficit hyperactivity disorder and autism spectrum disorders in males with XXY, XYY, and XXYY syndromes. J Intellect Disabil Res 2006;50(11):787.
[94] Tartaglia NR, Ayari N, Hutaff-Lee C, et al. Attention-deficit hyperactivity disorder symptoms in children and adolescents with sex chromosome aneuploidy: XXY, XXX, XYY, and XXYY. J Dev Behav Pediatr 2012;33(4):309–18.
[95] Tartaglia N, Howell S, Wilson R, et al. The eXtraordinarY Kids Clinic: an interdisciplinary model of care for children and adolescents with sex chromosome aneuploidy. J Multidiscip Healthc 2015;8:323–34.
[96] Bender B, Harmon RJ, Linden MG, et al. Psychosocial adaptation in 39 adolescents with sex chromosome abnormalities. Pediatrics 1995;96:302–8.
[97] Visootsak J, Graham JM Jr. Social function in multiple X and Y chromosome disorders: XXY, XYY, XXYY, XXXY. Dev Disabil Res Rev 2009;15(4):328–32.
[98] Close S, Fennoy I, Smaldone A, et al. Phenotype and adverse quality of life in boys with Klinefelter syndrome. J Pediatr 2015;167(3):650–7.
[99] van Rijn S, Stockmann L, Borghgraef M, et al. The social behavioral phenotype in boys and girls with an extra X chromosome (Klinefelter syndrome and Trisomy X): a comparison with autism spectrum disorder. J Autism Dev Disord 2014;44(2):310–20.
[100] Cordeiro L, Tartaglia N, Roeltgen D, et al. Social deficits in male children and adolescents with sex chromosome aneuploidy: a comparison of XXY, XYY, and XXYY syndromes. Res Dev Disabil 2012;33(4):1254–63.
[101] van Rijn S, Swaab H, Aleman A, et al. X chromosomal effects on social cognitive processing and emotion regulation: a study with Klinefelter men (47,XXY). Schizophr Res 2006;84(2–3):194–203.
[102] Goddard MN, Swaab H, Rombouts SA, et al. Neural systems for social cognition: gray matter volume abnormalities in boys at high genetic risk of autism symptoms, and a comparison with idiopathic autism spectrum disorder. Eur Arch Psychiatry Clin Neurosci 2015. [Epub ahead of print].
[103] DeLisi LE, Maurizio AM, Svetina C, et al. Klinefelter's syndrome (XXY) as a genetic model for psychotic disorders. Am J Med Genet B Neuropsychiatr Genet 2005;135B(1):15–23.
[104] Bojesen A, Juul S, Birkebaek NH, et al. Morbidity in Klinefelter syndrome: a Danish register study based on hospital discharge diagnoses. J Clin Endocrinol Metab 2006;91(4):1254–60.
[105] Mikamo K, Aguercif M, Hazeghi P. Martin-Du Pan R. Chromatin-positive Klinefelter's syndrome. A quantitative analysis of spermatogonial deficiency at 3, 4, and 12 months of age. Fertil Steril 1968;19(5):731–9.
[106] Wikstrom AM, Raivio T, Hadziselimovic F, et al. Klinefelter syndrome in adolescence: onset of puberty is associated with accelerated germ cell depletion. J Clin Endocrinol Metab 2004;89(5):2263–70.
[107] Fennoy I. Testosterone and the child (0-12 years) with Klinefelter syndrome (47XXY): a review. Acta Paediatr 2011;100(6):846–50.

[108] Lahlou N, Fennoy I, Ross JL, et al. Clinical and hormonal status of infants with nonmosaic XXY karyotype. Acta Paediatr 2011;100(6):824–9.
[109] Cabrol S, Ross JL, Fennoy I, et al. Assessment of Leydig and Sertoli cell functions in infants with nonmosaic Klinefelter syndrome: insulin-like peptide 3 levels are normal and positively correlated with LH levels. J Clin Endocrinol Metab 2011;96(4):E746–53.
[110] Lahlou N, Fennoy I, Carel JC, et al. Inhibin B and anti-Mullerian hormone, but not testosterone levels, are normal in infants with nonmosaic Klinefelter syndrome. J Clin Endocrinol Metab 2004;89(4):1864–8.
[111] Ross JL, Samango-Sprouse C, Lahlou N, et al. Early androgen deficiency in infants and young boys with 47,XXY Klinefelter syndrome. Horm Res 2005;64(1):39–45.
[112] Wosnitzer MS, Paduch DA. Endocrinological issues and hormonal manipulation in children and men with Klinefelter syndrome. Am J Med Genet C Semin Med Genet 2013;163C(1):16–26.
[113] Samango-Sprouse CA, Sadeghin T, Mitchell FL, et al. Positive effects of short course androgen therapy on the neurodevelopmental outcome in boys with 47,XXY syndrome at 36 and 72 months of age. Am J Med Genet A 2013;161A(3):501–8.
[114] Samango-Sprouse C, Stapleton EJ, Lawson P, et al. Positive effects of early androgen therapy on the behavioral phenotype of boys with 47,XXY. Am J Med Genet C Semin Med Genet 2015;169(2):150–7.
[115] Hatipoglu N, Kurtoglu S. Micropenis: etiology, diagnosis and treatment approaches. J Clin Res Pediatr Endocrinol 2013;5(4):217–23.
[116] Ratcliffe SG, Murray L, Teague P. Edinburgh study of growth and development of children with sex chromosome abnormalities. III. Birth Defects Orig Artic Ser 1986;22(3):73–118.
[117] Davis S, Lahlou N, Bardsley MZ, et al. Longitudinal study of boys with Klinefelter syndrome gives evidence of prepubertal testis defect. San Diego (CA): The Endocrine Society; 2015.
[118] Laron Z, Topper E. Klinefelter's syndrome in adolescence. Arch Dis Child 1982;57(11):887–8.
[119] Salbenblatt JA, Bender BG, Puck MH, et al. Pituitary-gonadal function in Klinefelter syndrome before and during puberty. Pediatr Res 1985;19(1):82–6.
[120] Bastida MG, Rey RA, Bergada I, et al. Establishment of testicular endocrine function impairment during childhood and puberty in boys with Klinefelter syndrome. Clin Endocrinol 2007;67(6):863–70.
[121] Mieritz MG, Raket LL, Hagen CP, et al. A longitudinal study of growth, sex steroids, and IGF-1 in boys with physiological gynecomastia. J Clin Endocrinol Metab 2015;100(10):3752–9.
[122] Pacenza N, Pasqualini T, Gottlieb S, et al. Clinical presentation of Klinefelter's syndrome: differences according to age. Int J Endocrinol 2012;2012:324835.
[123] Plourde PV, Reiter EO, Jou HC, et al. Safety and efficacy of anastrozole for the treatment of pubertal gynecomastia: a randomized, double-blind, placebo-controlled trial. J Clin Endocrinol Metab 2004;89(9):4428–33.
[124] Lapid O, van Wingerden JJ, Perlemuter L. Tamoxifen therapy for the management of pubertal gynecomastia: a systematic review. J Pediatr Endocrinol Metab 2013;26(9–10):803–7.
[125] Fischer S, Hirsch T, Hirche C, et al. Surgical treatment of primary gynecomastia in children and adolescents. Pediatr Surg Int 2014;30(6):641–7.
[126] Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2010;95(6):2536–59.
[127] Plotton I, d'Estaing SG, Cuzin B, et al. Preliminary Results of a prospective study of testicular sperm extraction in young versus adult patients with nonmosaic 47,XXY Klinefelter syndrome. J Clin Endocrinol Metab 2015;100(3):961–7.

[128] Mehta A, Bolyakov A, Roosma J, et al. Successful testicular sperm retrieval in adolescents with Klinefelter syndrome treated with at least 1 year of topical testosterone and aromatase inhibitor. Fertil Steril 2013;100(4):970–4.
[129] Gies I, De Schepper J, Van Saen D, et al. Failure of a combined clinical- and hormonal-based strategy to detect early spermatogenesis and retrieve spermatogonial stem cells in 47,XXY boys by single testicular biopsy. Hum Reprod 2012;27(4):998–1004.
[130] Rohayem J, Fricke R, Czeloth K, et al. Age and markers of Leydig cell function, but not of Sertoli cell function predict the success of sperm retrieval in adolescents and adults with Klinefelter's syndrome. Andrology 2015;3(5):868–75.
[131] Nahata L, Yu RN, Paltiel HJ, et al. Sperm retrieval in adolescents and young adults with Klinefelter syndrome: a prospective, pilot study. J Pediatr 2015;170:260–5.e2.
[132] Jiang-Feng M, Hong-Li X, Xue-Yan W, et al. Prevalence and risk factors of diabetes in patients with Klinefelter syndrome: a longitudinal observational study. Fertil Steril 2012;98(5):1331–5.
[133] Gravholt CH, Jensen AS, Host C, et al. Body composition, metabolic syndrome and type 2 diabetes in Klinefelter syndrome. Acta Paediatr 2011;100(6):871–7.
[134] Bojesen A, Host C, Gravholt CH. Klinefelter's syndrome, type 2 diabetes and the metabolic syndrome: the impact of body composition. Mol Hum Reprod 2010;16(6):396–401.
[135] Bojesen A, Kristensen K, Birkebaek NH, et al. The metabolic syndrome is frequent in Klinefelter's syndrome and is associated with abdominal obesity and hypogonadism. Diabetes Care 2006;29(7):1591–8.
[136] Swerdlow AJ, Higgins CD, Schoemaker MJ, et al, United Kingdom Clinical Cytogenetics Group. Mortality in patients with Klinefelter syndrome in Britain: a cohort study. J Clin Endocrinol Metab 2005;90(12):6516–22.
[137] Aksglaede L, Molgaard C, Skakkebaek NE, et al. Normal bone mineral content but unfavourable muscle/fat ratio in Klinefelter syndrome. Arch Dis Child 2008;93(1):30–4.
[138] Bardsley MZ, Falkner B, Kowal K, et al. Insulin resistance and metabolic syndrome in prepubertal boys with Klinefelter syndrome. Acta Paediatr 2011;100(6):866–70.
[139] Daniels SR, Greer FR, Committee on Nutrition. Lipid screening and cardiovascular health in childhood. Pediatrics 2008;122(1):198–208.
[140] Seth A, Rajpal S, Penn RL. Klinefelter's syndrome and venous thrombosis. Am J Med Sci 2013;346(2):164–5.
[141] Salzano A, Arcopinto M, Marra AM, et al. Management of endocrine disease: Klinefelter syndrome, cardiovascular system and thromboembolic disease. Review of literature and clinical perspectives. Eur J Endocrinol 2016;175(1):R27–40.
[142] Bojesen A, Gravholt CH. Morbidity and mortality in Klinefelter syndrome (47,XXY). Acta Paediatr 2011;100(6):807–13.
[143] Liu PY, Kalak R, Lue Y, et al. Genetic and hormonal control of bone volume, architecture, and remodeling in XXY mice. J Bone Miner Res 2010;25(10):2148–54.
[144] Bachrach LK. Diagnosis and treatment of pediatric osteoporosis. Curr Opin Endocrinol Diabetes Obes 2014;21(6):454–60.
[145] Jo DG, Lee HS, Joo YM, et al. Effect of testosterone replacement therapy on bone mineral density in patients with Klinefelter syndrome. Yonsei Med J 2013;54(6):1331–5.
[146] Seminog OO, Seminog AB, Yeates D, et al. Associations between Klinefelter's syndrome and autoimmune diseases: English national record linkage studies. Autoimmunity 2015;48(2):125–8.
[147] Sawalha AH, Harley JB, Scofield RH. Autoimmunity and Klinefelter's syndrome: when men have two X chromosomes. J Autoimmun 2009;33(1):31–4.
[148] Radicioni AF, Ferlin A, Balercia G, et al. Consensus statement on diagnosis and clinical management of Klinefelter syndrome. J Endocrinol Invest 2010;33(11):839–50.
[149] De Sanctis V, Fiscina B, Soliman A, et al. Klinefelter syndrome and cancer: from childhood to adulthood. Pediatr Endocrinol Rev 2013;11(1):44–50.

[150] Swerdlow AJ, Schoemaker MJ, Higgins CD, et al. Cancer incidence and mortality in men with Klinefelter syndrome: a cohort study. J Natl Cancer Inst 2005;97(16):1204–10.
[151] Sasco AJ, Lowenfels AB, Pasker-de Jong P. Review article: epidemiology of male breast cancer. A meta-analysis of published case-control studies and discussion of selected aetiological factors. Int J Cancer 1993;53(4):538–49.
[152] Brinton LA. Breast cancer risk among patients with Klinefelter syndrome. Acta Paediatr 2011;100(6):814–8.
[153] Hasle H, Mellemgaard A, Nielsen J, et al. Cancer incidence in men with Klinefelter syndrome. Br J Cancer 1995;71(2):416–20.
[154] Volkl TM, Langer T, Aigner T, et al. Klinefelter syndrome and mediastinal germ cell tumors. Am J Med Genet A 2006;140(5):471–81.
[155] Keung YK, Buss D, Chauvenet A, et al. Hematologic malignancies and Klinefelter syndrome. A chance association? Cancer Genet Cytogenet 2002;139(1):9–13.
[156] Tartaglia N, Ayari N, Howell S, et al. 48,XXYY, 48,XXXY and 49,XXXXY syndromes: not just variants of Klinefelter syndrome. Acta Paediatr 2011;100(6):851–60.
[157] Schulman GS, Redford-Badwal D, Poole A, et al. Taurodontism and learning disabilities in patients with Klinefelter syndrome. Pediatr Dent 2005;27(5):389–94.
[158] Lote H, Fuller GN, Bain PG. 48, XXYY syndrome associated tremor. Pract Neurol 2013;13(4):249–53.