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47,XXY Klinefelter Syndrome: Clinical Characteristics and Age-Specific Recommendations for Medical Management

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47,XXY (Klinefelter syndrome) is the most frequent sex chromosomal disorder and affects approximately one in 660 newborn boys. The syndrome is characterized by varying degrees of cognitive, social, behavioral, and learning difficulties and in adulthood additionally primary testicular failure with small testes, hypergonadotropic hypogonadism, tall stature, and eunuchoid body proportions. The phenotype is variable ranging from ''near-normal'' to a significantly affected individual. In addition, newborns with Klinefelter syndrome generally present with a normal male phenotype and the only consistent clinical finding in KS is small testes, that are most often not identified until after puberty. Decreased awareness of this syndrome among health professionals and a general perception that all patients with 47,XXY exhibit the classic textbook phenotype results in a highly under-diagnosed condition with up to 75% of the patients left undetected. Typically, diagnosis is delayed with the majority of patients identified during fertility workup in adulthood, and only 10% of patients diagnosed prior to puberty. Early detection of this syndrome is recommended in order to offer treatment and intervention at the appropriate ages and stages of development for the purpose of preventing osteopenia/osteoporosis, metabolic syndrome, and other medical conditions related to hypogonadism and to the XXY as well as minimizing potential learning and psychosocial problems. The aim of this review is to present the clinical aspects of XXY and the age-specific recommendations for medical management. © 2013 Wiley Periodicals, Inc.

KEY WORDS: androgen substitution; fertility; Klinefelter syndrome; hypergonadotropic hypogonadism; tall stature

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INTRODUCTION

47,XXY or Klinefelter syndrome (KS), characterized by the presence of one or more extra X chromosomes, is the most frequent cause of primary testicular failure. The majority carry an extra X chromosome, 47,XXY, whereas higher grade aneuploidies (e.g., 48,XXXY) or mosaicisms (e.g., 47,XXY/46,XY) make up approximately 20% of cases. 47,XXY is identified in 11% of azoospermic men and in 3% of infertile men and thus represents the most common genetic cause of infertility [Van Assche et al., 1996]. The prevalence of 47,XXY (KS) is estimated to approximately one in 660 newborn boys [Nielsen and Wohlert, 1990; Bojesen et al., 2003]. The syndrome is highly under diagnosed, and based on a large epidemiological study from Denmark, it has been estimated that less than 25% of the patients are ever diagnosed [Bojesen et al., 2003], with the majority of patients detected late in life.

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The phenotype is variable, but generally characterized by primary testicular failure with reduced testicular volume, hypergonadotropic hypogonadism, eunuchoidism, and tall stature. In addition, developmental, psychosocial, behavioral, and learning impairments including decreased verbal abilities are frequently reported in subjects with 47,XXY, and they are more likely than other boys to require educational help or speech therapy [Cohen and Durham, 1985a,b; Nielsen and Pelsen, 1987; Nielsen, 1990; Sorensen, 1992; Rovet et al., 1995, 1996; Ratcliffe, 1999; Van et al., 2006b, 2008a; Ross et al., 2008; Girardin et al., 2009]. The natural history of these characteristics is not completely elucidated. Some may be a consequence of hypogonadism, whereas others may be directly related to the chromosome abnormality. It has been hypothesized that multiple genes on the extra X chromosome escape X-inactivation and thereby exert a dosage effect. It is recognized that the phenotype of males with 47,XXY progressively deviates from normal with increasing numbers of extra X chromosomes present, whereas males with mosaicism most often are less severely affected [Lanfranco et al., 2004].

The aim of the present review was to describe the clinical characteristics of 47,XXY and the age-specific recommendations for medical management from infancy to adulthood.

TESTICULAR FUNCTION AND ENDOCRINOLOGICAL ASPECTS OF KS

The original description of KS published in 1942 by Harry F Klinefelter and colleagues included small testes with biopsy verified atrophy and hyalinization of the seminiferous tubules [Klinefelter et al., 1942]. The degeneration of the germ cells has since then been shown to start already in fetal life. It progresses during childhood, and accelerates during puberty and adolescence, resulting in extensive fibrosis and hyalinization of the seminiferous tubules, and hyperplasia of interstitium in the adult patient [for review see Aksglaede et al., 2006]. Consequently, testicular volume is significantly reduced in infants and prepubertal boys with 47,XXY [Ross et al., 2005; Zeger et al., 2008]. After an initial increase in testicular volume at the time of puberty, a reduction in testicular volume has been observed concomitantly with the described testicular deterioration [Wikstrom et al., 2004; Aksglaede et al., 2011b]. As a result testes volume is severely reduced in adulthood with a mean testes volume of 3.0 ml (range 1.0–7.0) as compared with 22 ml in healthy adult males [Aksglaede et al., 2011b].

The mini-puberty at three months of age represents a window, suitable for studying the function of the hypothalamic-pituitary-gonadal (HPG) axis by measuring the spontaneous, basal hormone levels [Main et al., 2002]. Some of the earliest studies on the mini-puberty in infants with 47,XXY indicated that these boys may already present with biochemical signs of hypergonadotropic hypogonadism at this early stage [Lahlou et al., 2004; Ross et al., 2005], whereas others reported high normal concentrations of testosterone (T) [Aksglaede et al., 2007b]. The most recent and largest study using the sensitive tandem mass spectrometry for measuring T in 68 prenatally diagnosed infants with 47,XXY, however, demonstrated normal concentrations of T and luteinizing hormone (LH) during the mini-puberty, thus questioning the previous indications of an impaired HPG-axis in infancy [Cabrol et al., 2011]. Importantly, however, the concentration of T was below the median of the controls in that study [Cabrol et al., 2011].

During childhood, boys with XXY are characterized by normal concentrations of T, follicle stimulating hormone (FSH), LH, antimüllerian hormone (AMH), inhibin B and insulin-like factor 3 (INSL3) [Topper et al., 1982; Salbenblatt et al., 1985; Christiansen et al., 2003; Wikstrom et al., 2004; Bastida et al., 2007; Aksglaede et al., 2008b, 2011; Wikstrom et al., 2006a,b,c].

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Concomitantly, inhibin B concentrations decline dramatically and remain undetectable at the end of puberty in the vast majority of patients with KS [Christiansen et al., 2003; Wikstrom et al., 2004; Aksglaede et al., 2008b]. The physiological pubertal decline in serum AMH occurs later in boys with KS than observed in healthy boys [Wikstrom et al., 2006c; Bastida et al., 2007; Aksglaede et al., 2010]. At midpuberty a relative hypogonadism is usually evident by increasing LH and FSH concentrations to hypergonadotropic levels [Topper et al., 1982; Salbenblatt et al., 1985; Wikstrom et al., 2006b; Aksglaede et al., 2011b] (Fig. 1).

Adults with KS are characterized by hypergonadotropic hypogonadism with highly elevated serum concentrations of FSH and LH. The serum concentration of T is most often in the lower half of the reference range of healthy males, and rarely below the reference range. Inhibin B is below the detection limit in the vast majority of adults with KS reflecting the impaired spermatogenesis [Aksglaede et al., 2008b], whereas the circulating concentrations of AMH and INSL3 are significantly reduced compared to healthy males [Foresta et al., 2004; Bay et al., 2005; Aksglaede et al., 2011a].

Data on serum estradiol (E2) concentrations are limited and contradicting. During childhood, E2 concentrations are normal [Aksglaede et al., 2008b], whereas studies on adult patients have shown increased concentrations

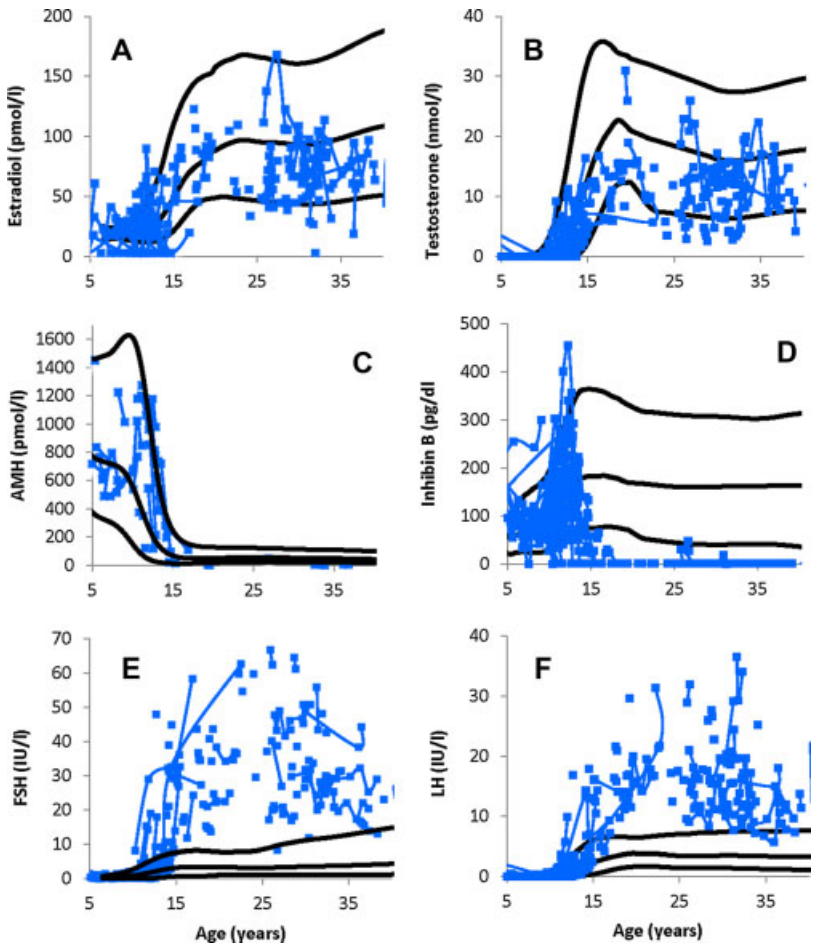

Figure 1. Serum concentrations of estradiol (**A**), testosterone (**B**), AMH (**C**), inhibin B (**D**), FSH (**E**), and LH (E) in relation to chronological age. Lines represent mean ± 2 SD in healthy control boys [Andersson et al., 1997] (Modified from [Aksglaede et al., 2011b]).

[Salbenblatt et al., 1985; Lanfranco et al., 2004; Ferlin et al., 2011b], whereas others found reduced E2 concentrations [Aksglaede et al., 2007a].

GROWTH

One of the classical clinical hallmarks in adults with KS is tall stature and eunuchoid body proportions. It is, however, important to emphasize that a normal stature or even a short stature does not exclude 47,XXY (KS).

During early infancy growth of the boy with XXY is usually within the normal range for healthy boys. However, growth velocity is significantly accelerated by the age of 3 years [Ratcliffe et al., 1990] resulting in significantly taller stature than expected from the age of 5–6 years and onwards [Tanner et al., 1959; Schibler et al., 1974; Stewart et al., 1982; Ratcliffe et al., 1990; Ratcliffe, 1999; Aksglaede et al., 2008b]. Boys with XXY are generally taller than their genetic target [Ratcliffe et al., 1990; Ottesen et al., 2010]. In addition, significantly increased leg length already before puberty has been reported by several authors [Tanner et al., 1959; Zuppinger et al., 1967; Schibler et al., 1974; Stewart et al., 1982, 1959; Aksglaede et al., 2008b].

Several hypotheses have been proposed for explaining the abnormal growth pattern observed in 47,XXY. It is well established that the interaction between sex steroids and the growth hormone-insulin-like growth factor (GH-IGF)-axis is of major importance in regulating linear bone growth. Male hypogonadism is associated with increased leg length [Smals et al., 1974; Tanner et al., 1976]. However, since this phenomenon is already present before puberty and before any biochemical signs of hypogonadism have been identified, impaired androgen secretion as the primary cause seems excluded. One study showed normal serum concentrations of IGF-I and insulin-like growth factor binding protein (IGFBP)-3 from infancy to adulthood [Aksglaede et al., 2008b], and it therefore seems that the abnormal growth pattern is also not explained by an abnormal concentration of these growth parameters.

Multiple genes especially located on the sex chromosomes are involved in regulating growth. During recent years a growing body of evidence indicates that the short stature homeobox-containing gene (*SHOX*) is involved in regulating growth [Rappold et al., 2012]. The *SHOX* gene is located on the pseudoautosomal region 1 (PAR1) of the sex chromosomes, a region known to escape X inactivation [Rao et al., 1997a]. *SHOX* thereby exerts a dosage effect i X and Y chromosomal disorders [Rao et al., 1997b], and has been shown to positively affect growth in patients with additional sex chromosomes, whereas haploinsufficiency of *SHOX* as seen in 45,X Turner syndrome may lead to short stature [Rao et al., 1997a; Ottesen et al., 2010]. One study on 255 patients with sex chromosome aneuploidy (including 129 males with KS) showed a nonlinear effect of the number of sex chromosomes and thereby the copy number of *SHOX* on growth [Ottesen et al., 2010]. In males, height increased with increasing number of sex chromosomes except in cases with 5 sex chromosomes. The presence of one X and two Y chromosomes (47,XYY) had the highest impact on growth indicating that yet unidentified genes on the Y chromosome also play a role in regulating growth [Ottesen et al., 2010].

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BODY COMPOSITION AND METABOLIC SYNDROME

It has previously been shown that adults with KS have a fivefold increased risk for developing the metabolic syndrome as compared with age-matched controls [Bojesen et al., 2006b], and in a recent study by Bardsley et al. [2011] insulin resistance and metabolic syndrome was present in 24% and 7%, respectively, of 89 children with 47,XXY as young as 4–12 years of age. In both studies truncal obesity, which is related to the metabolic syndrome [Timar et al., 2000], was characteristic in the patients with XXY. Increased deposits of body fat from early childhood as evaluated by whole body DEXA scan [Aksglaede et al., 2008a] and by measuring subscapular and triceps skinfolds has previously been reported in XXY [Ratcliffe, 1982; Ratcliffe et al., 1990]. Importantly, one study showed highly elevated body fat mass (BFM) despite normal body mass index (BMI) and normal lean body mass (LBM) for age suggesting an unfavorable body composition already in childhood and adolescence [Aksglaede et al., 2008a].

BONE MINERALIZATION

Androgen deficiency in otherwise healthy adult males is associated with an increased risk for developing osteopenia/osteoporosis [Seeman et al., 1983; Finkelstein et al., 1987]. Accordingly, adults with XXY often present with decreased bone mineral density (BMD) [Horowitz et al., 1992; Bojesen et al., 2010; Aksglaede et al., 2011b; Ferlin et al., 2011b]. In the study by Bojesen

et al. [2010] a lower BMD at the spine, hip and forearm in 70 adult patients with XXY as compared with 71 age-matched controls was not associated with serum T but with muscle strength, androgen substitution therapy, age at diagnosis and bone markers. Ferlin et al. [2011b] found no association between bone mass and serum T in a study of 112 patients with XXY not treated with androgens. It has been shown that young men with mutations in *RXFP2* (the gene encoding for the INSL3 receptor) have reduced bone mass [Ferlin et al., 2011a] and Ferlin et al. [2011c] therefore hypothesized that reduced bone mass in XXY may be related to low circulating concentrations of INSL3.

In contrast to the studies on adults with XXY, normal lumbar BMD, and whole body bone mineral content (BMC) as evaluated by whole body DEXA scan in 24 boys and adolescents with XXY (4.3–18.6 years of age) has been shown, indicating that the risk of osteopenia/osteoporosis may not be present until after puberty [Aksglaede et al., 2008a].

BREAST CANCER

Patients with XXY have an increased risk of developing breast cancer and several studies have addressed this issue. The mechanism for the higher risk for breast cancer among men with KS is not well understood. Long-standing gynecomastia, genetic predisposition, increased estrogen/testosterone ratios, obesity and physical inactivity, and exogenous administration of androgens are potential contributing factors. The largest study by Swerdlow et al. [2001] included 646 patients between 1959 and 1990 where two cases of death in breast cancer was found. The data was compared to the expected rates in the National population in UK and resulted in a standardized mortality rate (SMR) of 61.7 (95% CI 7.5–222.7). In another cohort study by Swerdlow et al. [2005b] with 3,518 men with KS in the UK, five patients had died from breast cancer and four had ongoing disease resulting in SMR of 57.8 (95% CI 18.8–135.0) and SIR 19.2 (95% CI 5.2–49.2).

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Long-standing gynecomastia, genetic predisposition, increased estrogen/testosterone ratios, obesity and physical inactivity, and exogenous administration of androgens are potential contributing factors.

OTHER MORBIDITIES AND MORTALITY

Bojesen et al. [2006a] found a significantly higher frequency of mediastinal tumors, anemia, hypothyroidism, cardiovascular, pulmonary, gastrointestinal, rheumatologic, skin, and vascular diseases in a cohort of 832 patients with XXY. An increased risk of autoimmune diseases was also reported in patients with XXY. In particular, the risk of systemic lupus erythematosus, in comparison to the general male population, has been reported to be 14-fold higher, that is, similar to women's risk, suggesting a gene dose effect of the X chromosome [Rovensky, 2006; Sawalha et al., 2009]. In a recent case–control study, a shift towards lower levels of free thyroxine with no compensatory increase in serum TSH was reported in 75 patients with XXY, thus suggesting a decrease of the set point of TSH control of thyroid function [Bjorn et al., 2009].

In general the increased morbidity in KS patients is believed to be related not only to hypogonadism but also to the effect of non-inactivated genes on the extra X chromosome and/or learning disabilities as well as to the lower socioeconomic status which are often related to the syndrome [Bojesen et al., 2011].

Bojesen et al. [2004] also reported a increased mortality risk (hazard ratio 1.40; CI 1.13–1.74) corresponding to a lower median survival of 2.1 years in comparison to same age peers. The increased mortality was due to infectious, neurological, pulmonary, and urinary tract diseases. These figures were confirmed by a British study based on 3,518 KS patients diagnosed since 1959 and followed to 2003. This study reported a SMR of 1.5 (CI 1.4–1.7) due to malignancies (SMR 1.2), cardiovascular (SMR 1.3), neurological (SMR 2.1), and respiratory (SMR 2.3) diseases [Swerdlow et al., 2005a]. Within more specific categories the risk of death was particularly increased for diabetes (SMR 5.8), epilepsy (SMR 5.2), pulmonary embolism (SMR 5.7), peripheral vascular disease (SMR 7.9), and vascular insufficiency of the intestine (SMR 12.3), cardiovascular congenital anomalies (SMR 7.3), and femoral fractures (SMR 39.). With regards to malignancies, the increased risk of mortality was due to lung and breast cancers and non-Hodgkin lymphoma, whereas a reduced risk of prostate cancer mortality was observed.

LEARNING IMPAIRMEMTS AND PSYCHOSOCIAL ASPECTS OF KS

KS boys are known to have increased risk for psychosocial problems [Ratcliffe, 1999; Van et al., 2006], and may present with impaired motor development, decreased verbal abilities, and they are more likely than other boys to require extra educational help or speech therapy [Cohen and Durham, 1985; Nielsen and Pelsen, 1987; Nielsen, 1990; Sorensen, 1992; Rovet et al., 1995; Rovet et al., 1996; Ross et al., 2008; Van et al., 2008b; Girardin et al., 2009]. The cognitive phenotype of KS is generally characterized by impaired performance on measures of language development, attention, and academic abilities. In younger boys delays in speech milestones may be observed, whereas significant deficits

in higher aspects of expressive language are common in older patients. In addition, it has been shown that KS is associated with more difficulties in identifying and verbalizing emotions [Van et al., 2007], and patients with KS are more easily emotionally aroused [Van et al., 2006].

In a recent register-based study from Denmark it was shown that KS patients had significantly fewer partnerships, fewer fatherhoods, lower educational level, lower income, and they retired at an earlier age as compared with age-matched controls [Bojesen et al., 2011]. In addition, a significantly increased crime rate for selected crimes has recently been found, whereas traffic offenses and drug-related crime were significantly decreased [Stochholm et al., 2012]. However, it is equally important to note that when socioeconomic status was taken into account no significant increase in the crime rate of patients with KS was identified.

MEDICAL MANAGEMENT IN XXY (KS)

The medical management of patients with XXY is a multidisciplinary task that may involve pediatric endocrinologists, endocrinologists/andrologists, urologists, infertility specialists, clinical geneticists, speech and language pathologists, physiotherapists, and psychologists, occupational therapists with ancillary health specialists, and educational personnel as needed. The medical management should be organized according to the age-specific challenges and problems the patient with XXY is faced with, as listed in Table I.

DIAGNOSING XXY (KS)

No specific abnormalities of XXY have been identified on prenatal ultrasound and a prenatal diagnosis of XXY is an incidental finding in pregnancies where a chorion villus sample is performed because of increased maternal age and/or an increased risk of autosomal trisomy. In our clinic 20% (30 of 166 cases) were diagnosed prenatally [Aksglaede et al., 2011b].

Newborns with 47,XXY (KS) generally present with a normal male phenotype. The attentive surgeon may suspect XXY (KS) in a child with bilateral cryptorchidism, but otherwise no specific signs or symptoms lead to the diagnosis at this stage of life. During childhood, developmental delay, speech disturbance, behavioral disturbances or

TABLE I. Age-Specific Recommendations for Medical Management

Infancy (0–2 years)	Confirmation of karyotype on blood if prenatal diagnosis
	Measurement of T, LH, FSH, inhibin B, and AMH at 3 months of age
	Treatment of cryptorchidism and micropenis if present
	Genetic counseling and psychological support to parents
Childhood (3–10 years)	Annual measurement of height and sitting height
	Bone age every 2–3 years
	DXA scan (1–2 times during childhood if the child cooperates)
	Special focus on nutrition and exercise
	Physiotherapy when needed
	Speech therapy and social training when needed
	Monitoring learning disabilities yearly- communication with school for support
	Psychological support
Puberty	Consider mild androgen supplementation in early or midpuberty if eunuchoid, tall stature, hypogonadal appearance, gynecomastia (and when LH increases to supranormal levels)
	Semen collection and cryopreservation if motile sperm in the ejaculate
	Exercise and lifestyle recommendations
	DXA scan for bone mineralization and body composition every 2–3 years
	Supplementation with calcium/vitamin D if needed
Adulthood	Consider adult androgen supplementation; transdermal or depot injections
	Monitor hematocrite, liver parameters, PSA, nadir T during treatment
	DXA scan for bone mineralization and body composition every 2–3 years
	Monitor HbA1C, calcium and vitamin D
	Lifestyle recommendations
	Counseling concerning fertility issues
	Semen collection and cryopreservation if motile sperm in the ejaculate
	Consider microdissection of testicles in case of fertility wish and previous semen cryopreservation failed (provided current azoospermia)
	If very low serum T, preoperation hormonal therapy may be considered
	Awareness of increased risk of breast cancer, cardiovascular, autoimmune, and metabolic disease
	Psychological support

excessive growth may lead to a suspicion of a genetic disorder, however it has been shown that only approximately 10% of cases are identified prior to puberty [Bojesen et al., 2003]. In peripubertal boys the diagnosis may be made because of delayed or poor pubertal development, gynecomastia, and small testes or as in earlier stages of life behavioral or growth disturbances. The majority of patients with XXY are identified in adulthood during diagnostic workup for infertility, or because of hypogonadism or gynecomastia [Aksglaede et al., 2011b]. In our clinic mean age at diagnosis during childhood and adolescence was 14 years (range 0.25–17 years), whereas mean age in adulthood was 29 years (range 18–57 years) [Aksglaede et al., 2011b].

Decreased awareness of this syndrome among health professionals and a general perception that all patients with XXY exhibit the classic textbook phenotype results in a highly under- and late diagnosed condition with up to 75% of the patients left undiagnosed.

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Early detection of this syndrome is recommended in order to offer treatment and intervention at the appropriate ages and stages of development for the purpose of preventing some of the complications associated with this phenotype, for example, hypogonadism, osteopenia/osteoporosis, metabolic syndrome, and minimizing neurodevelopmental and psychosocial dysfunction.

SCREENING FOR 47,XXY (KLINEFELTER SYNDROME)?

Herlihy et al. [2010, 2011] discussed the medical and psychosocial impacts of postnatal population-based screening for XXY at different ages. The major concern is the currently undiagnosed majority of men with KS does their phenotype differ significantly from the phenotype of the diagnosed men in order to justify the introduction of a screening program? Does awareness of the diagnosis have short - and long- term medical benefits, and does it improve quality of life in the majority of men with KS? What is the appropriate age for screening?

We recently validated a qPCR-based method for population-based screening for KS using the dried blood spot samples already being collected for the national newborn screening program [Aksglaede et al., 2012]. In addition, Inaba et al. [2012] have shown that the newborn screening test for fragile X syndrome (the fragile X-related epigenetic element 2 *FMR1* methylation test) may be used to also screen for sex chromosome aneupolidy by including a *SRY* marker. These methods open a possibility for conducting large population-based screening studies and thereby to identify the best surveillance and treatment to the KS patients. However, social, legal and ethical issues, and the potential consequences of diagnosis, positive and negative, should be considered thoroughly before such a study can be performed.

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