Klinefelter Syndrome: Identifying, characterizing and managing an underdiagnosed condition with serious consequences

A CME course from AXYS, the Association for X&Y Variations

Course Directors:
Hooman Sadri, MD, PhD
Stuart Howards, MD

Reviewed by the AXYS Clinic & Research Consortium (ACRC)

ABSTRACT

Klinefelter Syndrome (KS), the most common sex chromosome disorder, occurs in approximately 1 out of every 600 male births. It’s estimated that 60 - 75% of those with KS will remain undiagnosed throughout their lifetimes. While currently many are diagnosed prenatally, adults often are diagnosed during a fertility workup. The phenotypic variability in KS is a challenge to diagnosis.

Individuals with KS are more likely to have cardiovascular disease, type 2 diabetes, infertility, Autism Spectrum Disorder, anxiety and depression than those without KS. This article describes the signs, both physical and mental that may lead to a KS diagnosis and suggestions for care for adults with KS.
# TABLE OF CONTENTS

Introduction                                                                                                           1

Course Overview                                                                                                        2

History, Prevalence, and Etiology                                                                                      2

Impact Of KS On Lives                                                                                                  3

The Pathway to a Klinefelter Diagnosis in Adults                                                                     4

Understanding the Physical Comorbidities of KS                                                                       7

Mental Health Comorbidities                                                                                           9

A Person-Focused, Multidisciplinary Approach to Treatment                                                           11

  Recommended preventive and management schedule for adults with KS                                                  12

  FDA-approved testosterone treatments for adult hypogonadism caused by KS                                          16

  Fertility evaluation                                                                                               21

  Additional management for cardiovascular and lifestyle diseases                                                   23

Questions                                                                                                              26

References                                                                                                            28
INTRODUCTION

Have you unknowingly seen someone with Klinefelter Syndrome in your practice? Chances are, you have.

Klinefelter Syndrome (KS) is the most common sex chromosome disorder, occurring in approximately 1 out of every 600 male births.¹ Yet an estimated 60 to 75% of those with KS will remain undiagnosed throughout their lifetimes.²

Why does this matter?

It matters because KS is linked to significantly higher mortality rates and a range of physical, neurocognitive, and social/behavioral comorbidities as well as a lower quality of life and socioeconomic status. Some healthcare providers believe that delayed diagnosis can increase patient morbidity.¹,²

And it matters because those with KS are getting lost in our healthcare system. Studies show that the majority of individuals with KS report being dissatisfied with their care. In addition, many with KS and their families find that their providers have outdated information about the condition, or little information at all.³

By learning more about the many facets of KS, providers across the healthcare system can work together to better treat and support those with this condition and their families.
COURSE OVERVIEW

Audience

We created this course for healthcare providers who may be involved in the diagnosis and/or care of adults with Klinefelter Syndrome. This includes primary care providers, mental health providers, cardiologists, urologists, endocrinologists, fertility specialists, and others.

Course objective

This course aims to provide healthcare providers with the skills necessary to identify and effectively manage adults with Klinefelter Syndrome.

Learning objectives

Upon completion of this course, you should be able to:

1. Describe the basic history, prevalence, and etiology of Klinefelter Syndrome
2. Identify the wide range of symptoms of Klinefelter Syndrome in adults, and the different pathways to diagnosis
3. Identify and discuss the physical and mental health comorbidities of adults living with Klinefelter Syndrome
4. Discuss the importance of a multidisciplinary approach to managing the overall health and wellbeing of individuals with Klinefelter Syndrome
5. Discuss the recommended approach to fertility treatment for those with Klinefelter Syndrome and their partners

HISTORY, PREVALENCE, AND ETIOLOGY

Klinefelter Syndrome first appeared in medical literature in 1942 in a paper by Harry F. Klinefelter, Edward C. Reifenstein, and Fuller Albright. It was further defined as the 47,XXY karyotype by Patricia A. Jacobs and John A. Strong in 1959.2

Prevalence and demographics

As noted above, current estimates place KS prevalence at approximately 1 out of every 600 male births.1 Studies have shown a potential connection between increased incidence of KS and ethnicity.2,4

However, the available data are far too small to make any conclusions. Gravholt et al call for population-based studies, ideally via neonatal screening, to better establish prevalence and to fully determine the impact of ethnicity on KS risk.2

The only risk for having a baby with KS that researchers have identified to date is increasing maternal age.2 Recent studies propose that poor sperm quality related to increased hyperploidy of the sperm may also be a factor.4 Children resulting from reproductive technology using the sperm from KS males show a small increase in the prevalence of KS, though not enough to make conclusions.4

Etiology and phenotypic expression

KS is caused by nondisjunction during cell division:2

- 50% caused by paternal nondisjunction during 1st meiosis
- 50% caused by maternal nondisjunction in the 1st or 2nd meiosis or post-zygotic division

The etiology of KS and its wide variety of clinical features and phenotypic severity, which we will discuss in more detail further on in this course, are not well understood. Possible genetic mechanisms include:2,6

- Paternal origin of the supernumerary X chromosome
- Skewed inactivation of the X chromosomes
- Androgen receptor CAG repeat length
- Overexpression of genes located on the extra X chromosome
- Differential expression or non-coding RNA expression
- DNA methylation alterations of the genome
- Differential protein-protein interaction

However, research is not conclusive for any of these potential genetic mechanisms. To date, researchers have only made a strong connection between the SHOX gene and tall stature in KS males. More studies are clearly needed, and researchers are beginning to focus on changes in the epigenome and transcriptome.2
IMPACT OF KS ON LIVES

The burden of KS is vast. Adults with KS face a range of physical comorbidities that increase mortality, including a twofold risk of cardio- and cerebrovascular disease and a four- to sixfold higher risk of type 2 diabetes.²

In addition, more than 95% of adults with KS are azoospermic, significantly impacting their ability to father biological children.²

Individuals with KS further face a range of neurocognitive, psychiatric, and behavioral issues including Autism Spectrum Disorder, anxiety and depression—that can affect their and their families’ lives in ways large and small. In fact, KS negatively impacts their socioeconomic status (SES) and overall quality of life (QOL).²,⁷

A recent study revealed that adults with KS, in comparison to their non-KS peers:²,⁸

- Are less likely to achieve higher education (less than 10%)
- Retire an average of 15 years earlier
- Are more likely to live alone

As a result of these factors, they have a lower annual income throughout their lives. This lower SES also contributes to their morbidity.

In addition, KS decreases quality of life for many—with many reports tying decreased QOL to factors that also affect SES, such as having a lower income and living alone without a partner.²,⁸

A population-based sample of 87 adults with KS showed noticeably poorer QOL outcomes than the general male population across all evaluated domains, including:⁷

- Subjective well-being
- Self esteem
- Body image
- Mental health
- General health

In this study, KS phenotypic severity score was the most consistent factor in lowered QOL outcomes. However, contrary to previous belief that later diagnosis correlates with less severe phenotype, this study showed that those diagnosed later in life had equally prevalent issues such as learning and behavioral difficulties—and were significantly less likely to have received treatment.⁷
Understanding the patient perspective

“I would like for [healthcare providers] to acknowledge that [KS] is something that causes challenges and that it shouldn’t be ignored or brushed under the rug.”

Adults with KS report that some of their biggest challenges are:

- The lack of a long-term relationship and feeling unloved
- Feeling misunderstood all their lives
- Struggling to stay employed
- Shame of their feminized features and diagnosis
- Struggling to fit in socially

THE PATHWAY TO A KLINEFELTER DIAGNOSIS IN ADULTS

While the majority those with KS are not diagnosed, those who are may receive a diagnosis during the prenatal, adolescent, or adult periods. As noted in the overview, this course will focus on diagnosis and treatment in adults.

In adulthood, KS is typically diagnosed during evaluation for infertility, as most with KS have non-obstructive azoospermia. However, there is some speculation that many may remain undiagnosed through this common diagnostic pathway because they are not forming stable partnerships, potentially due to a combination of the psychological effects of KS and effects of low testosterone, such as fatigue, low libido, poor concentration, and depression. Therefore, the medical community must strive to identify KS in the overall population.
Providers must look beyond visible characteristics to find KS

Diagnosis proves challenging, however, because of the high phenotypic variability and the fact that KS does not always result in an explicit clinical manifestation. In fact, the typical description of a tall, thin individual with a eunuchoid body structure is inadequate—and it is nearly impossible to identify KS by visual observation alone. This may be one of the reasons the condition is so highly underdiagnosed.7

For this reason, Gravholt et al recommend incorporating scrotal palpation as a more routine procedure and a simple KS screening tool in the general population.2 More than 95% of adults with KS have decreased bitesticular testis volume.

Providers across specialties can play a key role in identifying suspected KS

Healthcare providers across specialties can further help to identify potential signs of KS by understanding the different ways in which it may manifest.

For example, KS is linked to certain cardiovascular abnormalities as well as recurrent leg ulcers. Salzano et al recommend that when a cardiac patient presents with these symptoms, the cardiologist should review the clinical history for other symptoms of KS and, if present, refer to an endocrinologist for follow-up.9

---

### Potential clinical manifestations of Klinefelter Syndrome in adults1,2,4,8

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Manifestation</th>
</tr>
</thead>
</table>
| Visibly noticeable physical symptoms | • Slightly taller than average stature  
• Decreased facial and/or pubic hair  
• Gynecomastia  
• Narrow shoulders and/or broad hips  
• Small depression in the chest  
• Difficulty straightening out the elbows (radio-ulnar synostosis)  
• Curved little finger (fifth finger clinodactyly)  
• Flat feet (pes planus) |
| Body composition                 | • Increased abdominal fat mass (adiposity)  
• Decreased muscle mass and strength  
• Decreased bone density |
| Gonadal symptoms                 | • Small, firm testes  
• Undescended testes (cryptorchidism)  
• Decreased bitesticular testis volume (4-8 mL) |
| Cardiovascular symptoms | • Abnormalities in left ventricular function  
• Chronotropic incompetence or reduced cardiopulmonary performance  
• Recurrent leg ulcers or vein insufficiency  
• Thrombotic events (deep vein thrombosis or pulmonary embolism) |
| Endocrinological symptoms | • Azoospermia and resulting infertility  
• Increased gonadotropin levels  
• Decreased testosterone levels (hypogonadism)  
• Presence of diabetes or metabolic syndrome |
| Cognitive and psychiatric symptoms (may be subtle) | • Slightly lower IQ  
• Executive functioning impairments  
• Social development delays  
• Speech, language or auditory processing impairments  
• Learning disabilities or memory issues  
• Autism spectrum disorder  
• Attention deficit/hyperactivity disorders (ADD, ADHD)  
• Psychiatric disturbances  
• Anxiety and/or depression |

**Recognize the Klinefelter personality**

*A personality profile of KS adults, according to Gravholt et al.*

“Reserved, passive, unassertive, less talkative, less energetic, tendency to experience negative feelings, emotional arousal, impulsiveness, difficulties in approaches to new events, less organized, less self discipline, helpful, friendly”

**Karyotyping confirms KS diagnosis**

To confirm the presence of an extra chromosome and properly diagnose Klinefelter Syndrome, the provider must take a blood or skin sample for karyotype testing.

**Karyotypes that confirm a KS diagnosis include:**

- **47,XXY**: This is the classic, and by far the most common, karyotype—comprising 80 to 90% of those diagnosed.
  - Mosaicism (46,XY/47,XXY): Mosaicism makes up approximately 7% of KS cases.
    - People with this karyotype have a mix of cell lines within the body that nest together in a mosaic-like pattern.

  For example, some may have one cell line with 46 chromosomes including a single X and single Y chromosome and the presence of a second line with two X and a single Y chromosome (46,XY/47,XXY). Mosaicism can be quite variable, with multiple cell lines that vary in the number of X and Y chromosomes.

  **Important note**: 47,XYY is often incorrectly associated as a variant of 47,XXY. However, it is a distinctly different sex chromosome aneuploidy. A key differentiation is that those with 47,XYY do not have the medical or infertility issues of those with 47,XXY. Individuals with 47,XYY may have behavioral difficulties and learning disabilities. People with the 47,XYY karyotype have normal sized testes.

- **Other related karyotypes (48,XXXX; 48,XXYY; and 49,XXXXY)**: These forms of aneuploidies are less common than KS. Scientists once classified these karyotypes as variants of KS. However, although they share some symptoms with KS, these conditions have their own distinct characteristics. Symptoms are often more numerous and severe, and may require special treatment and management.
UNDERSTANDING THE PHYSICAL COMORBIDITIES OF KS

Cardiovascular and metabolic diseases

According to data from epidemiological studies, people with KS have a twofold overall risk of cardiovascular and cerebrovascular disease (CVD)—making CVD a significant driver of the increased mortality seen in KS.² Specifically, those with KS have an increased risk of the following conditions.

Metabolic diseases and related factors

People with KS have a greater risk of metabolic diseases and factors that are linked to increased mortality risk,¹⁰ including a four- to sixfold higher risk of type 2 diabetes.² In fact, up to 50% of those with KS have metabolic syndrome (at least 3 of these 5 symptoms: hypertension, low HDL, elevated triglycerides, abdominal obesity, and glucose intolerance) and 20% have type 2 diabetes, with the increased risk likely beginning in childhood.¹³ Several studies have shown that adults with KS have an increased incidence of;¹⁰,¹³

- Metabolic syndrome
- Hyperlipidemia (especially hypertriglyceridemia)
- Insulin resistance
- Hyperinsulinemia
- Type 2 diabetes
- Fatty liver disease

Given that the National Cholesterol Education Program considers abdominal obesity a significant risk factor for metabolic syndrome,¹⁴ and based on recent studies in the KS population,¹⁰ the increased risk for this syndrome and related conditions is likely linked, in large part, to the increased prevalence of obesity, and truncal fat in particular, in those with KS.

Individuals with KS often have an increased:²

- Weight
- Hip and waist circumference
- Total and abdominal fat mass
- Total fat percentage

However, scientists are not clear on the underlying cause of abdominal obesity or increased insulin resistance and related metabolic issues. And it is important to note that even thin and normal weight individuals with KS may develop metabolic syndrome.¹³

The link between low serum testosterone levels with abdominal obesity and metabolic syndrome is well established in males independent of KS—and is believed to play a role in these conditions in those with KS.¹⁰

Low testosterone level has been linked to abdominal obesity in those with and without KS. However, since abdominal adiposity in KS begins at puberty, researchers believe other factors also likely contribute in this population. Potential genetic abnormalities that may be involved in increased abdominal fat mass in those with KS include:¹⁰

- Over-expression of X-linked genes
- Skewed X chromosome inactivation
- Transcriptional dysregulation of the apoptosis cascade
- Glucose metabolism and inflammation genes
- CAG repeat polymorphism within the androgen receptor gene
- Abnormal production of the chemokine CCL2 related to inflammation

In addition, insulin resistance in KS is related to factors beyond obesity, including:¹⁰,¹⁵

- Gene dosage of the CSF2RA gene on the X and Y chromosomes
- Higher leptin levels
- Overproduction of the chemokine CCL2 related to inflammation
- Methylation and RNA expression changes in the male KS genome
- Increased platelet reactivity

Testosterone replacement therapy (TRT) reduces fat mass, increases lean mass, and improves glycemic and insulin sensitivity in hypogonadal individuals, though studies have not found conclusive evidence in those with KS.¹⁰

A recent randomized, double-blind, placebo-controlled study of 20 adults with KS demonstrated that 6 months of testosterone therapy reduced abdominal fat mass and total body fat. TRT did not affect glucose homeostasis or other measures of intermediate
Impaired exercise performance

The cardiac abnormalities discussed above can lead to decreased cardiopulmonary performance in KS adults.\textsuperscript{10}

Those with KS typically have lower than typical muscle mass. Studies have linked this to reduced peak oxygen uptake (VO\textsubscript{2} max) as well as chronotropic incompetence (lower proportion of predicted maximum heart rate and lower increase in heart rate from baseline to exercise). CI causes exercise intolerance that has a big impact on quality of life and is a predictor of major cardiovascular disease. It’s also linked to reduced diameters of brachial, common carotid, common femoral arteries, and abdominal aorta arteries.\textsuperscript{10}

Cancer

While adults with KS do not have a higher overall risk of cancer than the general population, they do have an increased risk of the following types of cancer:

- Breast cancer: KS is the strongest independent risk factor for breast cancer in males\textsuperscript{4} and males with KS have an up to 30-fold higher risk of breast cancer.\textsuperscript{1,4} They also appear to be diagnosed younger\textsuperscript{4}.
- Extragonadal Germ Cell Tumors (GCT): Both epidemiological and pathology-based studies have shown a markedly increased occurrence of these rare tumors that develop in the midline in those with KS.\textsuperscript{4}

Evidence of a link between KS and other cancers, such as leukemia and non-Hodgkin lymphoma, exists. However, data have not been clear enough to establish a direct association.\textsuperscript{4}
Bone disease

Those with KS have an 8-fold higher incidence of osteoporosis and osteopenia than males with a normal karotype.\(^4\) Epidemiological data have also shown an overall higher incidence of fractures and mortality associated with femur fractures in the KS population.\(^4\)

This may be the result of reduced bone mineral density in the lumbar spine, femoral neck, and total hip in those with KS. Historically, reduced BMD in the KS population has been explained by hypogonadism, which leads to a reduced capacity for physical exercise and decreased muscle mass and points to testosterone therapy as a treatment.\(^8\)

However, testosterone therapy may not ameliorate all of these issues in those with KS, leading to the theory that this reduced BMD may occur independently of hypogonadism in KS.\(^1\)

Immune disorders

Adults with KS have an increased risk of immune disorders. Registry studies from the UK and Denmark showed that those with KS have an increased prevalence of the following autoimmune conditions:\(^2\)

- Addison disease
- Type 1 diabetes
- Hypothyroidism
- Rheumatoid arthritis
- Sjögren syndrome
- Systemic lupus erythematosus

Researchers have not identified a specific gene or genetic mechanism that causes this increased risk of autoimmune diseases in KS, but the belief is that it is likely linked to genes on the extra X chromosome.\(^2\)

Dental issues

Adults with KS have a significantly increased incidence of taurodontism, a rare disorder consisting of an enlarged pulp and thinning surface of the tooth that causes premature tooth decay. While rare among the general population (<3% incidence), this condition affects more than 40% of those with KS. The disorder becomes more pronounced as the number of extra X chromosomes increases.\(^16\)

MENTAL HEALTH COMORBIDITIES

Adults with KS have a higher incidence of mental health problems, and are 3 times more likely than the general population to be hospitalized with a psychiatric disorder (hazard ratio = 3.65).\(^19\)

Though more research is needed into the pathology, those with 47,XXY, in comparison to 46,XY karyotype, appear to have smaller total:\(^2\)

- Brain volume
- Gray matter volume
- White matter volume

Those with KS also have a “distinct pattern of large volumetric differences” in the ventral and central parts of the brain.\(^2\) In addition, the results of functional imaging studies of activation patterns and cerebral perfusion during verbal tasks point to the hypothesis that the “functional lateralisation of language-related ability to the left hemisphere” in typical brain development may be absent in KS.\(^5\)

Neurodevelopmental and psychotic disorders

Individuals with KS have an increased incidence of Autism spectrum disorder (ASD), Attention deficit hyperactivity disorder (ADHD), and psychotic disorders.\(^20\)

In a screening of hospital discharges of 860 adults with XXY that compared the diagnostic incidence of these disorders to the typical XY pattern, those with XXY were diagnosed:\(^20\)

- 6.2 times more often with ASD
- 5.6 times more often with ADHD
- 7.4 times more often with psychotic disorders (schizophrenia or bipolar disorder)

Language dysfunction is extremely common in KS, with up to 80% meeting the criteria for a learning disorder, most often related to language. Evidence consistently shows those with KS to have deficits in encoding of verbal information, auditory processing, comprehension, and processing speed.\(^5\) Two studies have shown a direct association between decreased language functioning and higher levels of ASD symptoms in people of all ages with KS.\(^20\)
Social, emotional, and cognitive issues

Individuals with KS have higher levels of neuroticism and lower levels of extraversion, conscientiousness, and openness to experience. They also often have difficulties with attention switching, imagination, communication, and social skills.19

A recent study showed no difference in the levels of these characteristics between adults with KS who had received testosterone therapy and those who remained untreated.19

Clinically, however, there is an impression that testosterone treatment leads to better neurocognitive functioning, but future studies should clarify this point.

Anxiety and depression

Anxiety and depression are common symptoms among those with KS. Data show that generalized anxiety affects approximately 18% of this population. More than two-thirds of those with KS report having depressive symptoms, with 19 to 24% diagnosed with clinical depression.19

A 2018 study conducted in Denmark examined the relationship between personality traits, social engagement, and anxiety and depression symptoms among 69 adults with KS vs. 69 controls matched for age and years of education. The study showed that neuroticism (defined by measure of 12 items on the Revised NEO Personality Inventory short form) was the strongest and most consistent mediator between KS and both anxiety and depression and may play a central role in these mental health issues. Neuroticism was a mediator of KS patients’ deficits in attention switching, which is related to cognitive control processes that are essential to making decisions, and engaging in physical and social activities.19

Though the researchers note that the study has limitations, including sample size, the results point to neuroticism as a potential marker for identifying and treating adults with KS who may be at high risk for anxiety, depression, or attention switching. Studies suggest that people may be able to lower their levels of neuroticism through experience and/or training.19
A PERSON-FOCUSED, MULTIDISCIPLINARY APPROACH TO TREATMENT

Due to the many intertwined comorbidities that increased morbidity and mortality risk for those with KS, they need continued specialized medical management throughout their lives. There is a growing call for a multidisciplinary approach to care for adults with KS. Gravholt et al call specifically for creating multidisciplinary clinics worldwide to care for KS individuals throughout their lives.

Understanding the KS adult perspective

"[Having Klinefelter Syndrome] has allowed me to see the world differently. It has allowed me to assist others and to change the focus of my life since my diagnosis occurred." Adults with KS report that their healthcare providers have negative assumptions about KS. They want their providers to understand the personal impact of living with KS, and acknowledge the challenges. But they also want their providers to acknowledge the positives which may include:

- Increased empathy
- New life perspective and meaning
- Becoming a stronger person
- Strengthened relationships
- Restored values
- Personal growth

The AXYS Clinic and Research Consortium helps independent multidisciplinary clinics dedicated to treating people with X and Y chromosome variations across the US to collaborate, share resources, meet to discuss important topics, and explore opportunities to participate in joint research projects. Learn more about the consortium and participating clinics.
A 2018 review article from the Department of Urology, Yamaguchi University School of Medicine in Ube, Japan, also stressed the importance for infertility specialists to understand the pathophysiology and previous histories of KS adults and to engage multidisciplinary providers in discussion for how to properly treat these individuals.21

Further, we need a more person-centered approach, with providers understanding and acknowledging the full impact of KS on people’s lives.3

Although there currently exist no standardized guidelines for follow-up care for adults with KS, we offer the following recommendations from recent literature.

<table>
<thead>
<tr>
<th>Recommended preventive and management schedule for adults with KS8</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Diagnosis</strong></td>
</tr>
<tr>
<td><strong>Physical examination</strong></td>
</tr>
<tr>
<td>• Blood pressure</td>
</tr>
<tr>
<td>• Height and weight</td>
</tr>
<tr>
<td>• Waist circumference</td>
</tr>
<tr>
<td>• Evaluation of testes</td>
</tr>
<tr>
<td>• Evaluation for presence of gynecomastia and palpation of breast tissue for potential malignancy13</td>
</tr>
<tr>
<td>• Evaluation for presence of varicose veins</td>
</tr>
<tr>
<td>• BMI</td>
</tr>
<tr>
<td><strong>Medical and mental health discussion</strong></td>
</tr>
<tr>
<td>• Overall-wellbeing</td>
</tr>
<tr>
<td>• Physical activity and energy level (if fatigue is present, screen for sleep apnea, other sleep disorders, iron-deficiency anemia, systemic illness, and hypogonadism)13</td>
</tr>
<tr>
<td>• Thorough history to identify symptoms of autoimmune disorders (with appropriate evaluation as needed)13</td>
</tr>
<tr>
<td>• Sexual activity and libido</td>
</tr>
<tr>
<td>• Socioeconomic situation</td>
</tr>
<tr>
<td>• PHQ-9 to screen for depression</td>
</tr>
<tr>
<td><strong>Baseline lab tests</strong></td>
</tr>
<tr>
<td>• Confirmation of karyotype (if necessary)</td>
</tr>
<tr>
<td>• Sex hormones (testosterone, estrogen, SHBG, FSH, LH)</td>
</tr>
<tr>
<td>• Fasting glucose, lipids, AST/ALT13, HbA1c</td>
</tr>
<tr>
<td>• Thyroid status</td>
</tr>
<tr>
<td>• Hemoglobin and hematocrit</td>
</tr>
<tr>
<td>• Vitamin D status</td>
</tr>
<tr>
<td>• Iron levels (if fatigue is present)13</td>
</tr>
<tr>
<td><strong>Additional tests</strong></td>
</tr>
<tr>
<td>• Bone densitometry (DEXA scan)</td>
</tr>
<tr>
<td>• Echocardiography (if deemed necessary)</td>
</tr>
</tbody>
</table>
### Discussion of KS and its management, including potential for TRT

- Discussion of TRT and treatment options (injections, transdermal, intranasal or oral) and initiation for most\(^2\) (see section below for more details)
- Information about KS as well as supportive resources and peer groups\(^2\)
- Counseling around venous disease (if needed)\(^1\)\(^6\)
- Counseling around nutrition and exercise, with recommendation of a diabetes prevention program or weight management program (as needed)\(^10\),\(^16\)
- Counseling around smoking cessation

### Potential referrals (as needed)

- Fertility clinic
- Plastic surgeon for correction of gynecomastia
- Psychologist
- Cardiologist
- Endocrinologist
- Urologist
- Genetic counselor
- Dentist
- Dietitian
- Social worker
- Diabetes prevention or weight management program\(^10\),\(^16\)
- Physical therapist or orthopedist (if flat feet, elbow differences, hyperextensibility, or joint instability are causing pain, limiting activities, or affecting motor coordination)\(^13\)
- Sleep specialists (to rule out sleep apnea and other disorders if fatigue is present)\(^13\)

### Every 3 months, then annually after first year

#### Physical examination

- Blood pressure
- Height and weight
- Waist circumference
- Evaluation for presence of gynecomastia and palpation of breast tissue for potential malignancy

#### Medical and mental health discussion

- Overall wellbeing
- Physical activity and energy level (if fatigue is present, screen for sleep apnea, other sleep disorders, iron-deficiency anemia, systemic illness, and hypogonadism)\(^13\)
- Thorough history to identify symptoms of autoimmune disorders (with appropriate evaluation as needed)\(^13\)
- Sexual activity and libido
- Socioeconomic situation
- Information about support groups and resources\(^2\)
- Counseling around venous disease (if needed)\(^1\)\(^6\)
- Counseling around nutrition and exercise, with recommendation of a diabetes prevention program or weight management program (as needed)\(^10\),\(^16\)

#### Lab tests

- Sex hormone nadir values (testosterone, estrogen, SHBG, FSH, LH)
- Fasting glucose, lipids, AST/ALT\(^13\), HbA1c
- Thyroid status
- Hemoglobin and hematocrit
- Iron levels (if fatigue is present)\(^13\)
<table>
<thead>
<tr>
<th>Potential referrals (as needed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fertility clinic</td>
</tr>
<tr>
<td>Plastic surgeon for correction of gynecomastia</td>
</tr>
<tr>
<td>Psychologist</td>
</tr>
<tr>
<td>Cardiologist</td>
</tr>
<tr>
<td>Endocrinologist</td>
</tr>
<tr>
<td>Urologist</td>
</tr>
<tr>
<td>Gastroenterologist</td>
</tr>
<tr>
<td>Genetic counselor</td>
</tr>
<tr>
<td>Dentist</td>
</tr>
<tr>
<td>Dietitian</td>
</tr>
<tr>
<td>Social worker</td>
</tr>
<tr>
<td>Occupational therapy</td>
</tr>
<tr>
<td>Vocational rehab</td>
</tr>
<tr>
<td>Psychiatrist</td>
</tr>
<tr>
<td>Diabetes prevention or weight manageent program [10,16]</td>
</tr>
<tr>
<td>Physical therapist or orthopedist (if flat feet, elbow differences, hyperextensibility, or joint instability are causing pain, limiting activities, or affecting motor coordination) [13]</td>
</tr>
<tr>
<td>Sleep specialists (to rule out sleep apnea and other disorders if fatigue is present) [13]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Every 2nd year or up to every 10th year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tests</td>
</tr>
<tr>
<td>Bone densitometry (DEXA scan)</td>
</tr>
<tr>
<td>Vitamin D status</td>
</tr>
<tr>
<td>Echocardiography (if deemed necessary)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regular throughout life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dental care</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>More about testosterone replacement therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gravholt et al call testosterone replacement therapy (TRT) &quot;a cornerstone of proper treatment&quot; for KS adults. These experts call for lifelong TRT to prevent comorbid conditions such as diabetes, metabolic syndrome, and osteoporosis, despite the lack of clear evidence of efficacy in adults with KS. They also caution, however, that large, observational, randomized, controlled studies are required to evaluate the efficacy and safety of TRT throughout life stages, and particularly during middle age and beyond. [2]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>In addition providers must consider each person’s medical history and the risks of TRT in regards to the factors below: [29-31]</th>
</tr>
</thead>
<tbody>
<tr>
<td>High blood pressure and other cardiovascular disease risk factors. TRT may increase blood pressure, which can lead to an increased risk of major cardiovascular events. In fact, FDA now requires all testosterone product manufacturers to include warnings about the possible increased risk of heart attacks and strokes associated with TRT, and to conduct post marketing trials to further evaluate risks of high blood pressure, heart attack, or stroke.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment considerations and goals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before initiating TRT, providers should consider: [1,2]</td>
</tr>
<tr>
<td>Screening for thrombophilia</td>
</tr>
<tr>
<td>A diagnostic echocardiogram to check for cardiac structural abnormalities</td>
</tr>
<tr>
<td>Referral to a urologist or fertility specialist for testicular sperm extraction (TESE), if the patient wants or may want the potential to produce biological children in the future</td>
</tr>
</tbody>
</table>

Given the increased cardiovascular risk with KS, this consideration becomes even more important. Obtain the baseline blood pressure and, if needed, ensure adequate control prior to initiating treatment. Con-
continue monitoring blood pressure and other cardiovascular risks (including lipid levels) and adjust treatment as needed throughout the course of therapy.

- **Venous thromboembolism (VTE).** VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE) have been reported in people using testosterone products. The increased risk of VTE in KS adds to the concern.

Throughout the course of therapy, monitor for symptoms of acute shortness of breath (a sign of PE) or pain, edema, warmth, and erythema in the lower extremities (signs of DVT). Evaluate symptoms as they arise and, if DVT or PE is suspected, discontinue TRT to further diagnose and manage the DVT or PE.

- **Polycythemia.** TRT may increase hematocrit, which may increase the risk of thromboembolic events. TRT is contraindicated with a hematocrit level of >50%.29 Evaluate hematocrit levels throughout the course of treatment, per medication-specific instructions.

- **Breast and prostate cancer.** TRT may increase the risk of prostate cancer. It is contraindicated in breast cancer and prostate cancer, a prostate nodule or induration, or a prostate-specific antigen (PSA) above 4 ng/mL or above 3 ng/mL in those at high risk for prostate cancer.29 Screen for prostate cancer prior to starting TRT, and continue monitoring PSA throughout the course of treatment.

- **Benign prostatic hyperplasia:** TRT increases the risk of worsening signs and symptoms of BPH. Monitor for symptoms of BPH throughout the course of TRT.

- **Cardiac, renal, or hepatic disease.** TRT can cause sodium and water retention, which can lead to serious complications for those with these pre-existing conditions. If edema is found, discontinue TRT and consider diuretic therapy.

- **Sleep disorders and related risk factors.** TRT can increase the risk or severity of sleep apnea in some, especially those with risk factors like obesity or chronic lung disease. It is contraindicated with severe obstructive and untreated sleep apnea.29


Gravholt et al note that during TRT, they aim to:2

- Normalize LH and FSH levels
- Avoid elevated hemoglobin and hematocrit

Groth et al recommend normalizing LH and testosterone levels in the mid-normal range because many individuals are undertreated. They also note that providers should pay attention not only to LH levels, which may be difficult to normalize due to elevated hematocrit, but also to the self-reported symptoms. This is especially true with injection therapy, in which a high testosterone level can cause discomfort.8

Further, TRT may help to normalize other androgen-responsive tissues, including fat and muscle mass.8 Providers may estimate fat and muscle mass with a whole-body DEXA scan and work to assess changes in libido and energy with self-reported outcomes measures.

**Dosage and administration**

Scientists first isolated and then synthesized testosterone for clinical use in 1935.25 TRT was first introduced in the form of subcutaneous testosterone pellets in the 1940s. The 1950s brought intramuscular injections of testosterone esters, followed by oral testosterone undecanoate in the 1980s (not available in the US), transdermal patches in the 1990s, topical gels, buccal tablets, and a long-acting intramuscular formulation in the 2000s. More recent additions include an intranasal gel in 2016 and a new testosterone undecanoate soft gel formulation for hypogonadism in 2019.26

While all formulations show clinical response, providers typically choose therapies based on:26

- Patient preference
- Pharmacokinetic profile
- Treatment burden (and patient’s ability to comply with treatment)
- Cost
The below table outlines FDA-approved TRT options for adult male patients with hypogonadism, including that caused by KS.

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Medication</th>
<th>Dosing forms and strengths</th>
<th>Adult dosing</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| Oral capsule            | Testosterone undecanoate (Jatenzo®) | 158 mg, 198 mg, 237 mg      | Starting dose: 237 mg orally, twice daily (morning and evening) with food    | • Less invasive administration                  | • Potential for poor adherence (twice daily dosing)  
• Can cause blood pressure increases that can increase the risk of major adverse cardiovascular events, requiring adequate blood pressure control prior to initiation and continued monitoring and control as well as CV risk assessment prior to treatment and continued monitoring and overall risk-benefit analysis  
• Reports of depression and suicidal ideation in clinical trials  
• Most common adverse reactions (incidence >2%): polycythemia, diarrhea, dyspepsia, eructation, peripheral edema, nausea, increased hematocrit, headache, prostatomegaly, and hypertension  
• 32.6% of subjects experienced gingivitis in long-term extension study  
• Patients must regularly inspect their gums where they apply Striant  
• Most expensive option (avg. monthly cost of $724.77, calculated from common dose) |
| Buccal tablet32         | Buccal testosterone system (Striant®) | 30 mg per buccal system     | 1 buccal system, applied to the gum region twice daily, morning and evening (about 12 hours apart)  
Monitor serum testosterone concentrations to ensure proper dosing, per instructions | • Normalizes levels in 24 hours  
• Less invasive administration | • Potential for poor adherence (twice daily dosing)  
• Most common adverse events (incidence >1%): gum or mouth irritation, bitter taste, gum pain, gum tenderness, headache, gum edema, taste perversion  
• 32.6% of subjects experienced gingivitis in long-term extension study  
• Patients must regularly inspect their gums where they apply Striant  
• Most expensive option (avg. monthly cost of $724.77, calculated from common dose) |
| InTRANASAL GEL | TESTOSTERONE NASAL GEL (NATESTO®) | Metered dose pump (5.5 mg delivered with 1 pump actuation) | 2 pump actuations (1 per nostril), 3 times per day | • Less invasive administration  
• Less risk of unintentional transfer to women and children | • Potential for poor adherence (3 times daily dosing)  
• Not recommended for use in patients with chronic nasal conditions or alterations in nasal anatomy  
• Most common adverse events (incidence >3%): increased PSA, headache, rhinorrhea, epistaxis, nasal discomfort, nasopharyngitis, bronchitis, upper respiratory tract infection, sinusitis, nasal scab  
• Expensive (avg. monthly cost of $699.20, calculated from common dose) |

| Transdermal gel | Transdermal testosterone gels | Testim® 1% testosterone gel: Topical formulation in 5 g (50 mg) and 10 g (100 mg) gel tubes  
VogelxoTM 1% testosterone gel:  
AndroGel® 1% testosterone gel: Topical formulation available in 25 mg or 50 mg packets  
AndroGel® 1.62% testosterone gel: Metered-dose pump (20.25 mg of testosterone delivered with each pump actuation in 1.25 g of gel); unit dose packet with 20.25 mg of testosterone in 1.25 g of gel; or unit dose packet with 40.5 mg of testosterone in 2.5 g of gel  
Fortesta® 2% testosterone gel: | Applied to clean, dry, intact skin that can be covered fully by patient’s clothing.  
Testim®: Apply only to: shoulders and upper arms  
Starting dose: 5 g of gel (1 tube), once daily (preferably in the morning)  
Adjust dose: up to 10 g, depending on serum testosterone concentration monitoring per instructions  
VogelxoTM 1% testosterone gel: Apply only to: shoulders and upper arms  
Starting dose: 50 mg of testosterone (1 tube, 1 packet, or 4 pump actuations) once daily at same time of day  
Adjust dose: up to 100 mg (2 tubes, 2 packets, or 8 pump actuations) once daily, depending on serum testosterone | • Mimics circadian variations in testosterone levels  
• Good clinical response  
• No visible patch  
• Gel dries quickly  
• Good compliance  
• Ease of dose titration | • Normal serum testosterone levels not achieved in all hypogonadal males  
• Risk of secondary exposure to testosterone in children, leading to risk of virilization; providers must advise patients to strictly adhere to recommended instructions for use and ensure children avoid contact with product as well as with unwashed or unclothed application sites in adults using product  
• Requires careful application and attention to precautions in storage, application, application site coverage, hand washing, and product disposal  
• Restrictions on bathing and swimming  
• Testim® 1% testosterone gel most common adverse reactions (incidence >1%): application site reactions, increased hematocrit/hemoglobin  
• VogelxoTM 1% testosterone gel most common side effects: skin irritation at application site, increased red blood cell count, headache, increased blood pressure  
• AndroGel® 1% most common adverse events: acne, skin irritation at application site, lab test changes, increased PSA |
<table>
<thead>
<tr>
<th>Transdermal gel (cont.)</th>
<th>Transdermal testosterone gels (cont.)</th>
<th>2 pump actuations (1 per nostril), 3 times per day</th>
<th>concentration monitoring per instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>AndroGel® 1%:</td>
<td></td>
<td></td>
<td>AndroGel® 1%: Apply only to: Upper arms and/or abdomen. Starting dose: two 25 mg packets or one 50 mg packet, once daily (preferably in the morning). Adjust dose: using 50 mg, 75 mg, or 100 mg of testosterone based on serum testosterone concentration monitoring, per instructions.</td>
</tr>
<tr>
<td>AndroGel® 1.62%:</td>
<td></td>
<td></td>
<td>AndroGel® 1.62%: Apply only to: Shoulders and upper arms. Starting dose: 40.5 mg (2 pump actuations or a single 40.5 mg packet). Adjust dose: within 20.25 mg - 81 mg range based on serum testosterone concentration monitoring, per instructions.</td>
</tr>
<tr>
<td>Fortesta®</td>
<td></td>
<td></td>
<td>Fortesta® Apply only to: Thighs. Starting dose: 40 mg (4 pump actuations) once daily, in the morning. Adjust dose: within 10 mg - 70 mg range based on serum testosterone concentration monitoring, per instructions.</td>
</tr>
</tbody>
</table>

- AndroGel® 1.62% most common adverse event: increased PSA, mood swings, high blood pressure, increased red blood cell count, skin irritation at application site
- Fortesta® most common adverse reactions (incidence >1%): skin reaction, PSA increase, abnormal dreams
| Transdermal solution | Transdermal patch | Metered dose pump (delivering 30 mg of testosterone per either pump or twist) | Starting dose: 60 mg (2 pump or 2 twist actuations) applied once daily to the axilla, preferably at the same time each morning, to clean, dry, intact skin | Adjust dose based on serum testosterone concentration monitoring, per instructions | • Mimics circadian variations in testosterone levels  
• Good clinical response  
• No visible patch  
• Good compliance  
• Ease of dose titration | • Risk of secondary exposure to testosterone in children, leading to risk of virilization; providers must advise patients to strictly adhere to recommended instructions for use and ensure children avoid contact with product as well as with unwashed or unclothed application sites in adults using product  
• Risk of exposure to testosterone in pregnant or nursing mothers, with risk of fetal harm or serious adverse reactions in nursing infants  
• Requires careful application and attention to precautions in storage, application, and disposal  
• Common adverse events (incidence >4%) include: application site irritation, application site erythema, headache, increased hematocrit, diarrhea, vomiting, increased PSA  
• Postmarketing adverse reactions include: myocardial infarction, stroke, venous thromboembolism  
• Most expensive of the transdermal gels/solutions (avg. monthly cost of $630.78, calculated from common dose) |
| Transdermal solution | Testosterone transdermal system (2 mg/day or 4 mg/day) | 1 patch (2 mg or 4 mg) applied nightly for 24 hours to dry, intact skin of the back, abdomen, upper thighs, or arm (rotating application site with interval of 7 days for each site) | 1 patch (2 mg or 4 mg) applied nightly for 24 hours to dry, intact skin of the back, abdomen, upper thighs, or arm (rotating application site with interval of 7 days for each site) | 1 patch (2 mg or 4 mg) applied nightly for 24 hours to dry, intact skin of the back, abdomen, upper thighs, or arm (rotating application site with interval of 7 days for each site) | • Mimics circadian variations in testosterone levels  
• More affordable than all options except intramuscular injections (avg. monthly cost of $195.03, calculated from common dose) | • Most common adverse reactions (incidence >3%); application site reactions, skin pain  
• Potential for skin burns at application site during magnetic resonance imaging (MRI)  
• Potential for poor adherence |
<table>
<thead>
<tr>
<th>Intramuscular injections</th>
<th>Testosterone cypionate (Depo-Testosterone®)</th>
<th>Testosterone enanthate (Delatestryl®)</th>
<th>Injected deep into gluteal muscle (thighs or buttocks)</th>
<th>50-400 mg every 2-3 weeks; adjust dose depending on patient’s response and appearance of adverse reactions</th>
<th>Long-acting(^2) (twice monthly dosing)</th>
<th>Ease of administration(^8)</th>
<th>Most affordable option (avg. monthly cost of $18.45 to 98.07, calculated from common dose)</th>
<th>Risk of local side effects (including pain, erythema, inflammatory reaction, sterile abscess)</th>
<th>Rare risk of anaphylaxis upon injection with Delatestryl®</th>
<th>Additional common side effects include: gynecomastia, mood disturbances</th>
<th>Risk of priapism in patients with sickle cell disease</th>
<th>Longer duration of effect for testosterone enanthate than propionate</th>
<th>Fluctuations in testosterone levels between injections</th>
<th>Delatestryl® can be difficult to obtain due to being in short supply</th>
<th>Need for regular injections can negatively affect patient compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone undecanoate (Aveed®)</td>
<td>750 mg/3mL (250 mg/mL) testosterone undecanoate sterile injection solution single-use vials</td>
<td>Injected into gluteal medius only 750 mg every 10 weeks or 1,000 mg every 10-14 weeks</td>
<td>Stable testosterone levels</td>
<td>Local pain</td>
<td>Injection-associated pulmonary oil microembolism (POME)</td>
<td>Restricted access in U.S.</td>
<td>Trochar needed for extra-long acting esters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcutaneous pellet implants</td>
<td>Testosterone implant pellets (Testopel®)</td>
<td>75 mg testosterone pellets 2 - 6 pellets (150 -450 mg) Implant-ed subcutaneously under hips, every 3 to 6 months</td>
<td>Long-acting</td>
<td>Requires incision</td>
<td>Risk of pellet extrusion, infection, fibrosis at or near implantation site</td>
<td>No available information on optimal dosing, and less flexibility for dosage adjustment than other methods</td>
<td>Risk of blood clots in the legs or lungs</td>
<td>Possible increased risk of heart attack, stroke, or death</td>
<td>Risk of increased swelling of ankles, feet, or body, with or without heart failure, in patients who have heart, kidney, or liver disease</td>
<td>Risk of gynecomastia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Understanding concerns**

"[A challenge of living with KS has been] Getting testosterone levels to work for me. Different doctors have different opinions on what’s the right amount for my desired outcome."\(^3\)

Adults with KS have reported that challenges with TRT include:\(^3\)

- Cost/insurance coverage
- Trouble finding the right form and level
- Concerns about self-administration
- Lack of consensus of ideal administration to optimize efficacy and minimize side effects
More about fertility treatment

As noted previously, infertility is a significant concern with KS, and is often the pathway to diagnosis. Though controversy exists regarding timing and approach, fertility preservation and treatment is a key area of consideration in KS. The good news is that some with KS can have biological children without chromosomal abnormalities, with the help of sperm retrieval and intracytoplasmic sperm injection (ICSI). Experts recommend a consultation with a reproductive urologist to discuss their options.6

Providers should also acknowledge the significant emotional impact that infertility can have on the individual, their partner, and their broader family. Providers must conduct evaluation, diagnosis, and treatment with sensitivity, emphasizing the fact that infertility does not imply anything about one’s gender identity, sexual orientation, or sexual function.3

The AXYS Clinical and Research Consortium recently released a document regarding issues of fertility in KS adults. A summary of the guidelines is below.

Evaluation
The initial fertility evaluation should include the following.22

<table>
<thead>
<tr>
<th>Fertility evaluation22</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical history</strong></td>
</tr>
<tr>
<td>• Comprehensive fertility history of the person and their partner</td>
</tr>
<tr>
<td>• Review of past medical and surgical history</td>
</tr>
<tr>
<td>• Medication history, particularly endocrine disruptors</td>
</tr>
<tr>
<td>• Lifestyle factors such as smoking, recreational drugs, weight loss, and exercise</td>
</tr>
<tr>
<td>• Environmental and work-related exposures</td>
</tr>
<tr>
<td><strong>Physical examination</strong></td>
</tr>
<tr>
<td>• General status and body habitus</td>
</tr>
<tr>
<td>• Presence of gynecomastia</td>
</tr>
<tr>
<td>• Secondary sexual characteristics and masculinization such as facial hair, muscular development, penile and testes</td>
</tr>
<tr>
<td><strong>Lab tests</strong></td>
</tr>
<tr>
<td>• 2 semen analyses with extended search following centrifugation</td>
</tr>
<tr>
<td>• Hormone profile consisting of an early morning (8 to 10 am) testosterone, estradiol, follicle stimulating hormone (FSH), and luteinizing hormone (LH)</td>
</tr>
<tr>
<td>• Y-chromosome microdeletion testing</td>
</tr>
</tbody>
</table>

Note: Individuals with KS do not have a higher incidence of Y-chromosome microdeletions than the general male population. However, Y-chromosome microdeletion testing can help to detect the level of potential mosaicism to help determine the likelihood of sperm retrieval prior to invasive fertility preservation methods.

Treatment

Advances in sperm retrieval methods are making it more possible for those with KS males to produce biological children through sperm retrieval followed by intracytoplasmic sperm injection (ICSI). Recent studies have shown a:22

- 43% to 45% sperm retrieval rate
- 43% pregnancy rate using ICSI
- 43% live birth rate of those patients who use ICSI

Those with mosaicism with a 46,XY cell line may be more likely to have success with TESE, while those over 30 years of age may be less likely to have success. However, findings on predictive factors are not consistent.6
Steps to fertility treatment for KS adults and their partners

**Normalization of testosterone levels**

Normalizing testosterone levels is critical to enhance sperm development in preparation for retrieval. Non-steroidal aromatase inhibitors are most likely to improve intratesticular testosterone levels and normalize the testosterone/estradiol balance, which may improve surgical recovery rate.

**Sperm retrieval**

Due to the focal nature of spermatogenesis with KS, microdissection testicular sperm extraction (mTESE) is best for extracting focally dilated seminiferous tubules while identifying and minimizing damage to intratesticular blood vessels. A urologist and IVF team with expertise in sperm retrieval and tissue processing can optimize recovery of extremely rare sperm.

**Intracytoplasmic sperm injection (ICSI)**

A reproductive endocrinologist should provide a female fertility evaluation and coordinate oocyte retrieval for the KS patient’s partner. Oocyte retrieval may be coordinated to occur prior to sperm retrieval (with cryopreservation of oocyte and thawing on day of sperm retrieval), the day after sperm retrieval, or further after sperm retrieval (with cryopreservation of sperm). Studies have shown no evidence of variation in results.

**Additional considerations for infertility**

- **Expert opinion on genetic testing:** Perform preimplantation genetic diagnosis (PGD) or, if PGD is not available, noninvasive prenatal testing (NIPT). While those with KS can produce normal offspring, studies do show an increase of sex chromosomal and autosomal abnormalities in the embryos of couples in which the father has KS.

- **Expert opinion on long-term testosterone replacement therapy (TRT):** Caution patients about the uncertainty of successful sperm recovery after long-term TRT use. There are too few studies demonstrating the safety of TRT in the midst of fertility therapy. In addition, at present, TRT is considered a contraindication for those actively seeking fertility treatment within 6 months, although strategies, such as concomitant hCG therapy, do exist to maintain spermatogenesis.

**Understanding the KS perspective**

“The worst moment was when the doctor explained the infertility aspect. My thoughts and dreams ended at a full stop. I have become a fatalist.”

Male infertility has been linked to feelings of:

- Distress
- Stigmatization
- Loss of control
- Low self-esteem
- Guilt
- Anxiety
Additional management for cardiovascular and lifestyle diseases

Salzano et al recommend a full cardiac workup of adults with KS to assess risk for metabolic syndrome and thromboembolic disease as well as echocardiography.9

In addition, adults with KS should receive:

- Monitoring of, and counseling around, venous diseases.

  Suggest they reduce their risk of venous disorder by avoiding sitting or standing in one position for long periods of time as well as to maintain a healthy weight through diet and exercise. For those with active venous diseases, compression socks, elevation, and/or blood thinning consider medication.13,16

- Screenings for metabolic syndrome and diabetes throughout life.

  This may include a screening for dyslipidemia with a fasting lipid panel for early identification of metabolic syndrome or its features.10

  Adults with KS should receive a fasting blood glucose (FBG) test. If obesity is present, screening should include alanine aminotransferase and hemoglobin A1c.13,16 For those who develop metabolic syndrome or prediabetes, consider recommending a diabetes prevention program.10
Normal Blood Glucose

- FBG: 70 to 99 mg/dL
- OGT: Less than 140 mg/dL
- HbA1c: 4 to 5.6%

Prediabetes

- FBG: 100 to 125 mg/dL
- OGT: 140 and 199 mg/dL
- HbA1c: 5.7 to 6.4%

Diabetes Mellitus

- FBG: 126 mg/dL or higher
- OGT: 200 mg/dL or higher
- HbA1c: 6.5% or higher

- Counseling on the importance of nutrition and regular exercise.\(^{10}\)
- If obesity is present, consider referral to a weight management program.\(^{16}\) To note, when evaluating for obesity, consider BMI carefully. Adults with KS have been shown to have a lower lean body mass and increased truncal fat percentage for any given BMI.\(^2\)
- Supplements or other medications.
- Consider recommending fish oil to help lower triglyceride concentrations as well as prescribing medications to lower cholesterol or increase insulin sensitivity, as needed. Follow accepted treatment guidelines for metabolic syndrome, dyslipidemia, diabetes, and hypertension. No specific treatment recommendations for adults with KS exist at this time.\(^{13}\)

Additional management for mental health

Researchers recommend neurocognitive treatment for adults with KS.\(^2\) As noted above, individuals may be able to lower their levels of neuroticism, which is linked to anxiety, depression, and attention problems, through training.\(^{19}\)

A recent study by Van Rijn and Swaab in 26 adults with 47,XXY evaluated whether language and executive functioning deficits in KS contribute to emotion regulation problems and related symptoms of psychopathology. The study found that, in a portion of those with KS, emotion regulation was atypical.\(^{23}\)

Results suggested that when an adult with KS responded to stress, they were significantly more likely than their non-KS peers to react with:\(^{23}\)
- An expression of emotions (an outburst like showing frustration or anger)
- Avoiding (letting things take their course)
- Seeking distraction (such as smoking, drinking, or going out)
- Passively coping (such as isolating themselves, focusing on past worries, or escaping into fantasies)

However, those with KS were also significantly more likely to seek social support, which could indicate good potential for treatment.\(^{23}\)

This study showed that executive functioning abilities were linked to the ability to regulate emotions. In addition, emotion regulation issues such as passive coping and avoiding were linked to mental health problems like anxiety and depression. Therefore, the authors recommend that clinicians focus on both executive function and emotion regulation in their assessment and treatment.\(^{23}\)

The authors recommend the following for clinical screening of executive function (EF) in adults with KS who exhibit signs of difficulty regulating emotion:\(^{23}\)
- Computerized neuropsychological testing for EF
- Assessment of specific executive functions
- Use of sensitive measures of EF to detect subtle deficits
- Inclusion of EF screening within a more complete neuropsychological assessment

For treatment, Van Rijn et al recommend both:\(^{23}\)
- Training and/or intervention programs, and
- Psychoeducation to help those with KS understand their strengths and weaknesses in order to better manage their individual challenges

Van Rijn et al, as well as other researchers, call for ongoing studies to continue building knowledge around the emotion regulation, executive dysfunction, and other neurocognitive issues that individuals with KS face.\(^{23}\)

Gender identity

The issue of gender identity in adults with KS has not been extensively explored. Evidence suggests that
some with KS report feeling and looking neither masculine or feminine.²⁴ However, it should be noted that a portion of biological males who do not have KS also identify as female, nonbinary, or intersex.

As part of a multidisciplinary approach to care, healthcare providers can screen for signs of distress due to gender identity or other issues and, when necessary, discuss appropriate options for referrals and other support.

More about social work and other supportive services

Transition to adult independence typically takes longer for those with KS than for young adults without X and Y chromosome variations, and there is a significant variation among individuals. Many with KS need support in higher education and many need help with assessing their strengths and their deficits in order to establish a successful career.

Adults with KS and their families need information about the services they may need to help them live as independently as possible. These may include information about and connection to:

- Vocational rehabilitation services
- Social skills training programs
- Speech, occupational, and physical therapy services
- Life skills training and financial literacy programs
- Mental health professionals for family and/or individual therapy
- Independent living centers
- Special needs life coaches

They also need information about how to navigate the government benefits they may be entitled to, including:

- Supplemental Security Income (SSI)
- Social Security Disability Insurance (SSDI)
- State Vocational Rehabilitation services
- Medicaid and Medicaid waiver services (for housing, life skills training, and other sources of support)
- SNAP (food stamps)
- Housing assistance (Section 8)
- Temporary general assistance

For more information: Watch a video presentation on government benefits for adults by Virginia Cover, MSW at the 2017 AXYS Family Conference. See also the chapter “Transitioning from School to Adult Services” in Cover, V. Living with Klinefelter Syndrome, Trisomy X, and 47,XXY: A guide for families and individuals affected by X and Y chromosome variations. New York, NY 2012.

AXYS offers a wealth of additional resources for adults with KS and their families, including information about clinical trials, legal help, support groups, and more.

Find AXYS resources
5. What percentage of those with KS have been shown to have metabolic syndrome? Please select one of the answers below.

- 20%
- 30%
- 40%
- 50%
- 60%

6. Which of the following professionals should be included in the multidisciplinary care of individuals with KS? Please check all that apply.

- General practitioners
- Specialists such as cardiologists, endocrinologists, and urologists
- Infertility specialists
- Mental health professionals
- Dietitians and social workers

7. What are 3 considerations a provider should make before initiating testosterone replacement therapy (TRT) in a man with KS?

1. _________________________
2. _________________________
3. _________________________

8. According to recent studies, what is the sperm retrieval rate in individuals with KS?

- 23 to 25%
- 33 to 35%
- 43 to 45%
- 53 to 55%
- 63 to 65%

9. What lab tests should a man with KS receive every 3 months throughout his life? Please check all that apply.

- Thyroid status
- Fasting glucose, lipids, AST/ALT, HbA1c
- Hemoglobin and hematocrit
- Iron levels (if fatigue is present)
- Sex hormone nadir values (testosterone, estrogen, SHBG, FSH, LH)
10. How will you change your current practice based on what you’ve learned in this course?


37. Axiron [package insert]. Indianapolis, IN. Lilly USA, LLC.


