Skrevet av Daniela Knutsen.

4th International Workshop on Klinefelter Syndrome

The 4th International Workshop on Klinefelter Syndrome and Other Sex Chromosome Abnormalities was held in Padua, Italy, from October 8–10, 2025. The conference brought together researchers, clinicians, and representatives from patient and advocacy organizations across Europe and the United States to share the latest knowledge about Klinefelter syndrome (47,XXY) and related conditions such as Trisomy X (47,XXX) and XYY syndrome.

This conference continued the tradition of previous international workshops:

- The 1st Workshop - held in Copenhagen, Denmark (May 6–8, 2010).
- The 2nd Workshop - held in Münster, Germany (March 10–12, 2016).
- The 3rd Workshop - held in Leiden, the Netherlands (September 12–14, 2022).

The 2025 workshop in Padua focused particularly on fertility and male hormone regulation, as well as the early detection and comprehensive care of individuals with Klinefelter syndrome. Additional sessions addressed the genetic mechanisms underlying sex chromosome aneuploidies, the psychological aspects of genetic counselling, and the public health challenges related to underdiagnosis. Across three days of presentations and discussions, several major themes emerged:

- Improved early detection: Research shows that a majority of individuals with KS remain undiagnosed. Advances in prenatal and neonatal genetic screening may allow earlier and more precise identification.
- Fertility and hormonal health:New data confirm that sperm retrieval is possible in roughly one-third of non-mosaic KS men. Early hormonal assessment and individualized testosterone therapy can improve physical and metabolic outcomes.
- Neurodevelopment and mental health: Presentations highlighted the increased risk of cognitive, social, and psychiatric difficulties in KS, emphasizing the need for early psychological and educational support.
- Ethical and social aspects: Counselling and communication strategies must be improved for families receiving a prenatal diagnosis. Studies show that better information and peer support reduce parental anxiety and promote positive adjustment.
- Collaboration and advocacy: The workshop strengthened cooperation among clinicians, researchers, and patient organizations from Italy, Spain, the Netherlands, Belgium, and the United States. Continued international collaboration will be essential for improving care standards and advancing research.

Overall, the Padua workshop underscored significant progress in understanding the biological, medical, and psychosocial dimensions of Klinefelter syndrome. It also reaffirmed the need for early detection, coordinated multidisciplinary care, and active involvement of patient associations in shaping future research and policy initiatives.

"Do We Really Know the Incidence and Prevalence of Klinefelter Syndrome?"

Speaker: Dr. Andres Ingason (Denmark)

Dr. Ingason opened the session with a discussion on how little we still know about the true prevalence of Klinefelter syndrome (KS).

In 1965, early studies reported an incidence far lower than what we now believe to be accurate. By 2006, registry-based studies in Denmark revealed that only around 20% of individuals with KS are ever diagnosed. In 2021, Dr. Ingason's team received a grant to further investigate this topic using Denmark's national registries, which collect detailed information about citizens' health and genetics.

Prevalence: When comparing data from different populations, it appears that KS remains significantly underdetected. One possible explanation is incomplete detection from newborn screening (such as PKU testing), which does not identify chromosomal anomalies. Increasing use of prenatal screening may also alter prevalence statistics, as pregnancies may be terminated after a prenatal KS diagnosis.

Psychiatric Risk: Dr. Ingason's data broadly confirm a two- to fivefold increased risk of psychiatric disorders among individuals with KS. The risk appears somewhat lower for depression but comparable to that seen in individuals with Triple X (47,XXX).

Why It Matters: He connected this to a recent review of the genetics of schizophrenia, showing that as the genetic load for certain disorders decreases, the associated risk also drops slightly. However, sex chromosome aneuploidies such as KS stand out for having particularly high relative risks compared to other genetic variants.
The risk profiles across KS and related disorders remain similar overall.

Audience Question:
What first drew Dr. Ingason to investigate the connection between KS and schizophrenia?
He explained that several years ago, he attended a schizophrenia research conference near Venice, where leading professors repeatedly referred to KS in their discussions. This sparked his interest in exploring the overlap between these conditions.

"Insights on Novel Genetic and Molecular Events at the Origin of KS"

Speaker: Dr. Marco Barchi (Italy)

Dr. Barchi discussed the origins of Klinefelter syndrome at the molecular level, focusing on how errors during meiosislead to the presence of an extra X chromosome.
He reviewed the stages of meiosis — leptotene, zygotene, pachytene, and diplotene — emphasizing that in males, pairing and crossover of the sex chromosomes occur during the pachytene stage. The enzyme SPO11 plays a critical role in initiating these crossovers.

His team's research uses gene-by-gene analysis across the genome and exome to identify disease-causing variants without prior assumptions. Studies in male mice with KS-like chromosomal patterns have shown aneuploid sperm productionand structural differences in chromosomal loops.

Question from the audience:
If parents carry certain genetic variants, are siblings of KS individuals more likely to have KS as well?
Dr. Barchi answered that while theoretically possible, there is no strong evidence that KS clusters within families. Environmental factors, including maternal age, appear to play a more significant role. Older maternal age is associated with a slightly higher risk, while paternal age shows no consistent correlation.

"15-Year Trends in U.S. Pediatric Sex Chromosome Trisomies"

Speaker: Dr. Shanlee Davis (USA)

Dr. Shanlee presented data from the United States showing significant changes in how sex chromosome trisomies are diagnosed over the past 15 years.
Klinefelter syndrome remains one of the most underdiagnosed genetic conditions, but the introduction of prenatal cell-free DNA (cfDNA) screening — also known as NIPT — has begun to shift this trend.

Previously, such testing was offered only to high-risk pregnancies. Now, recommendations increasingly suggest that screening should be offered to all pregnancies, regardless of risk. Recent data show a significant increase in annual diagnoses, particularly in infants, indicating that earlier detection is becoming more common.

Discussion Points:

- Cognitive outcomes may correlate with age at diagnosis, similar to findings in autism research.

- Although NIPT is recommended for all pregnancies in the U.S., many providers exclude sex chromosome analysis due to cost, technical issues, or uncertainty about follow-up procedures.

Prevalence and Diagnosis:
Recent studies conducted before the widespread use of genetic testing found an unexpectedly high KS prevalence — up to 0.9%, though this may reflect a special group (e.g., couples undergoing IVF). Postnatal prevalence estimates are lower.

During the panel discussion, Italian researcher Prof. Ferlin asked:

> "What do we tell patients — that KS is 1 in 600 or 1 in a million?"

Another physician responded:

> "I simply tell my patients it's very common."

Accurately determining true prevalence requires understanding how much remains undiagnosed. In U.S. military screening data, KS occurs in about 1 in 600 men. However, termination rates following prenatal diagnosis (around 15% in Denmark) may influence observed prevalence.

Ethical and Practical Variations Between Countries:

- Italy: Testing is not covered by the national system; couples pay privately, and only high-risk pregnancies are routinely offered screening.
- Denmark: All pregnant women receive ultrasound scans at 12 and 20 weeks. Based on risk assessment, some are offered invasive tests.
- Netherlands: Screening is available to all, but sex chromosome analysis is often excluded.

Panelists also discussed the ethical responsibility to follow up with children and families after NIPT results, which is not yet systematically done in many countries.

Structure and features of the supernumerary X chromosome and the role of epigenetics – a stem cell perspective

Speaker: Dr. Antonio Adamo (Saudi Arabia)

Dr. Adamo presented findings on the genetic complexity of sex chromosome aneuploidies, focusing on the genes located in the PAR1 and PAR2 regions — the pseudoautosomal regions shared between the X and Y chromosomes.

He compared Klinefelter syndrome (47,XXY) with Jacob's syndrome (47,XYY), explaining that while the genetic mechanisms differ, both share several overlapping clinical features due to gene dosage effects.
In Klinefelter syndrome, the extra X chromosome undergoes partial inactivation, while in Jacob's syndrome, the extra Y chromosome remains active. Understanding how these differences influence gene expression during neurodevelopment can help explain why symptoms vary across the sex chromosome trisomies.

Adamo's team also explored the shared transcriptomic signatures of sex chromosome aneuploidies during brain development. Their work aims to identify how extra copies of sex-linked genes impact neural pathways, potentially leading to cognitive and behavioral differences.

Audience question:
What happens to the Y chromosome that is sometimes lost in men after age 60?
Dr. Adamo explained that much remains unknown. Researchers rely on simplified cellular models to study this, but age-related chromosomal loss is an area that still needs more investigation.

Genetic Counselling in Sex Chromosome Trisomies: Insights from Parental Experience

Speaker: Dr. Susan Howell (USA)

Dr. Howell discussed the psychological and informational challenges families face when receiving a prenatal diagnosis of a sex chromosome trisomy, such as Klinefelter syndrome, Triple X, or XYY.

She began by defining genetic counselling as "the process of helping individuals and families understand and adapt to the medical, psychological, and familial implications of genetic conditions". Approaches and Key Findings:

Prenatal screening:
Cell-free DNA testing (cfDNA or NIPT) is increasingly used, but its positive predictive value (PPV) for sex chromosome conditions is still relatively low. Many parents receive the test as part of a "gender test," often without fully understanding that it screens for chromosomal differences.

If a test result is positive, confirmation through diagnostic testing (such as amniocentesis) is essential. Howell emphasized the importance of anticipatory guidance — preparing families for what to expect after diagnosis, including potential medical issues during the first year of life and developmental milestones to monitor.

Families are advised to:

- Have hormone levels checked after birth.
- Learn about early development and available interventions.
- Connect with reliable educational and support resources.

Parental Experiences and Emotions

Dr. Howell's ongoing research with the "Extraordinary Babies" project has identified four main themes among families following a prenatal SCT diagnosis:

1. Negative diagnostic experiences – often due to insufficient or poorly delivered information.
2. Hope in early childhood – families typically report increased optimism as their child grows and develops.
3. Emotional adjustment over time – initial anxiety decreases as families receive more information and support.
4. Value of connection – linking with other parents and professionals is crucial for emotional well-being.

Data show a large increase in parental hope and a decrease in worry between the time of the NIPT result and the postnatal diagnosis.

Dr. Howell highlighted several reputable sources of information and peer support, including:

- AXYS (genetic.org)
- Living with XXY (community and education initiative)
- Facebook parent support groups
- "Living with KS: A Guide for Families" (booklet)
- "What You Need to Know When You're Expecting" (educational guide for families facing a prenatal diagnosis)

Her presentation also introduced tools for parent advocacy, helping families better communicate with healthcare providers and navigate early intervention systems.

"Congenital Malformations in Klinefelter Syndrome"

Speaker: Dr. Inger Dorf (Denmark)

Dr. Dorf presented results from a large-scale Danish registry study investigating congenital malformations among individuals with Klinefelter syndrome.
Until now, few studies have systematically explored this area.

Key Findings

- Individuals with KS have a significantly increased risk of congenital malformations affecting the nervous system, heart, musculoskeletal system, and genitals.
- Genital malformations were the most common, affecting nearly 10% of cases, including undescended or ectopic testes.
- Musculoskeletal malformations were found in around 3% of cases, most frequently flat feet or clubfoot.
- Nervous system malformations, including microcephaly, were rare but notable (five reported cases).

Study Limitations

Because the data excluded terminated pregnancies diagnosed prenatally with KS, the results likely underestimate the true frequency of congenital malformations.
Additionally, the researchers could not report categories with fewer than three affected individuals to protect anonymity.

Discussion and Next Steps

Several questions were raised about whether malformations lead to earlier KS detection, or whether KS itself contributes to a higher risk of these malformations. Dr. Dorf noted that this question will be the focus of the next research phase at Aarhus University Hospital.

She also observed that prenatal diagnoses show a higher rate of detected malformations than postnatal ones, possibly due to more detailed early examinations.
Older studies (e.g., from 2005) reported increased mortality associated with congenital malformations but did not specify types. Danish data confirm that many recorded heart malformations remain unspecified in the registry.

When asked about pregnancy termination rates, Dr. Dorf reported that around 60% of KS fetuses in Denmark are terminated following a prenatal diagnosis, although the reasons (KS itself versus the presence of a malformation) are often unclear.

A related discussion emerged about clinical practice:
Roughly one-third of KS patients present with cryptorchidism (undescended testes). In such cases, Danish doctors typically recommend genetic testing, increasing the likelihood of diagnosis.

Is universal screening a solution? Improving Diagnosis: Towards Newborn and Early Screening

Speaker: Claus Gravholt (Denmark)

Several talks focused on how to improve the rate and timing of diagnosis.
Currently, most individuals with KS remain undiagnosed well into adulthood, often only after fertility problems or hypogonadism appear.

Neonatal Genetic Screening

Discussions explored the potential for newborn genetic screening, including the use of whole-exome or whole-genome sequencing as part of future standard screening programs.

Pros:

- Early diagnosis would allow better monitoring, early support for neurodevelopment, and prevention of later comorbidities.

Cons:

- Ethical and psychological concerns about diagnosing infants with a condition that varies greatly in severity.
- The healthcare system may not yet be equipped to handle the volume of follow-up required.

Knowledge, information and correct application of testing indications

Speaker: Giovanni Corona (Italy)

Dr. Giovanni Corona (Italy) presented findings from a 2017 Italian study (Bonomi et al., J. Endocrinol Invest. 2017) showing that only the “tip of the iceberg” of KS patients are diagnosed — probably fewer than half.
Similar results were reported from Australia, and the European Academy of Andrology confirmed in 2021 (Zitzmann et al., Andrology) that roughly 50% of KS cases remain undiagnosed across Europe.

Early and Late Diagnosis. Studies show that certain early signs should raise clinical suspicion:

- Bilateral cryptorchidism (undescended testes) — strong association with KS; should trigger testing.
- Delayed or atypical pubertal development.
- Reading, language, or cognitive difficulties.

Later in life, symptoms such as hypogonadism, reduced libido, or erectile dysfunction often lead to diagnosis — but these occur after years of missed opportunities for earlier support.

Speakers stressed that general practitioners and school nurses must receive better education on KS indicators. Simple heel-prick (newborn blood) tests and appropriate use of genetic panels could be effective, provided there are systems in place for informed consent and follow-up.

The Cost of Not Diagnosing.

Researchers from Denmark presented an analysis of the economic and social costs of late diagnosis. They are also performing a study analysing this topic of how much more it actually cots the danish society when not diagnosing. Men who remain undiagnosed often require more healthcare, experience reduced work participation, and have higher overall public healthcare costs.

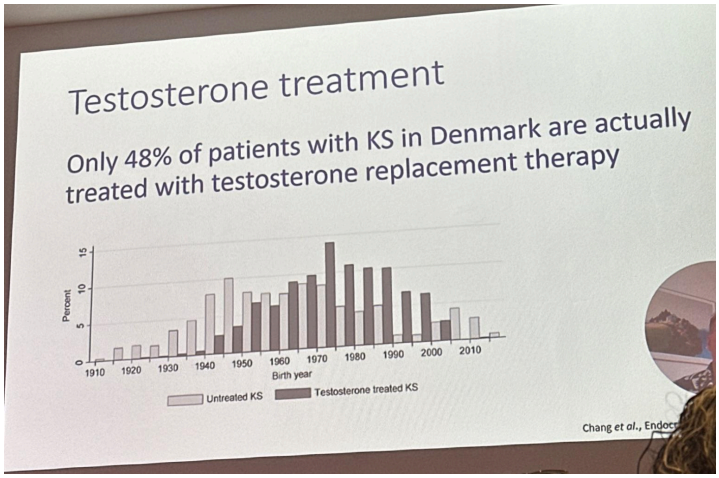
Italian representatives added that KS has only recently been recognized as a formal disease category in Italy, affecting access to treatment and insurance coverage.
The group agreed that as genetic testing becomes more accessible worldwide, countries must prepare for both ethical implications and practical implementation — ensuring that results are understood and acted upon responsibly.

When to Start Testosterone Therapy in KS

Speaker: Dr. Lise Aksglaede (Denmark)

This highly anticipated session tackled one of the most debated clinical questions: When should testosterone therapy begin in boys with Klinefelter syndrome?

Dr. Aksglæde reviewed the existing evidence and the ongoing Danish “TIPY Study” (Rigshospitalet), which involves four national centers following boys aged 10–14 years with non-mosaic 47,XXY karyotype.



Key Points

- There is no clear international consensus on when to start testosterone treatment.
- Many specialists have differing opinions based on clinical experience rather than research evidence.
- About 60% of boys and men with KS show signs of compensated hypogonadism — normal testosterone levels but elevated LH, suggesting the body is working harder to maintain balance.

Findings from Current Studies

- Body composition: Untreated boys often have higher body fat percentages; studies suggest that testosterone therapy may reduce fat mass.
- Blood pressure: No significant differences before and after treatment have been observed.
- Bone health: Bone mineral density tends to be normal, though it varies with height and weight adjustments.

Dr. Aksglæde presented real patient cases she is following and invited the audience to discuss how they would manage testosterone treatment for these cases. There was no generall agreement among the participants. She then reviewed her own approach to treatment (noted in parentheses):

- 14-year-old with normal development (Dr. Aksglæde recommended that no testosterone treatment be started for now).
- Teenager slightly behind peers, with lower testosterone levels and higher body fat (Dr. Aksglæde considers that the patient should start testosterone treatment).
- 26-year-old, overweight and symptomatic (Dr. Aksglæde advised the patient to start treatment; the patient has begun therapy with good results).
- 30-year-old who stopped treatment due to lack of perceived effect (Dr. Aksglæde is monitoring the patient’s hormone levels and lets the patient decide independently).

These cases show the need for individualized treatment. Some patients feel better on therapy, others do not.

The main challenge for ongoing studies is finding suitable placebo formulations and recruiting participants, as many patients already receive testosterone before entering trials.

Conclusions from the Danish Study

- All boys show elevated LH from mid-puberty onward.
- Each case requires individual assessment — therapy should not be automatic.
- Testosterone can improve metabolic health but is not a universal solution for all KS-related difficulties.

In adolescents, doctors often start with low-dose gels and gradually adjust. Some patients prefer injections; others dislike handling gels. The choice is guided by patient comfort and practical considerations.

Managing Fertility in Klinefelter Syndrome

Speaker: Dr. Andrea Garolla (Padua, Italy)

Dr. Garolla presented the latest research on fertility and sperm retrieval in Klinefelter syndrome.

He began with an unusual case study: the skeleton of an adult male from ancient remains (reported in The Lancet, 2022) that showed clear signs of KS — demonstrating that the condition has existed for millennia.

Origin of Infertility in KS

Fertility problems begin very early, already at the fetal stage, when the presence of an extra X chromosome disrupts the development of fetal germ cells (FGCs). This overexpression of X-linked genes impairs the maturation of the male germ line.

However, some exceptions exist — for example, a 43-year-old non-mosaic KS man with normal semen parameters who conceived naturally. Such cases show that KS is not equivalent to infertility but rather associated with reduced fertility potential.
Importantly, the genetic risk to offspring is not higher than in the general population.

Sperm Retrieval Studies

Dr. Garolla presented findings from 111 non-mosaic KS patients who underwent TESE (testicular sperm extraction)procedures:

- Sperm retrieval success rate: about 34%.
- Age correlation: slightly higher success in younger patients (average age ~30 years).
- No clear differences between conventional TESE and micro-TESE methods.

He recommended that sperm retrieval be performed before age 35, as testicular volume and germ cell activity decline with age.

Ethical Considerations

Performing TESE in adolescents remains controversial.
Although spermatogonia can sometimes be found, these procedures should be conducted only within research protocols, given the ethical and medical complexities.

Some studies suggest that androgenic stimulation (e.g., anastrozole) may improve sperm retrieval rates, but more evidence is needed.
The ongoing TIPY Study in Denmark is expected to provide further answers by 2030.

Experimental Research: Stimulating Testosterone Production

Speaker: Dr. Fariba Saadati (Germany)

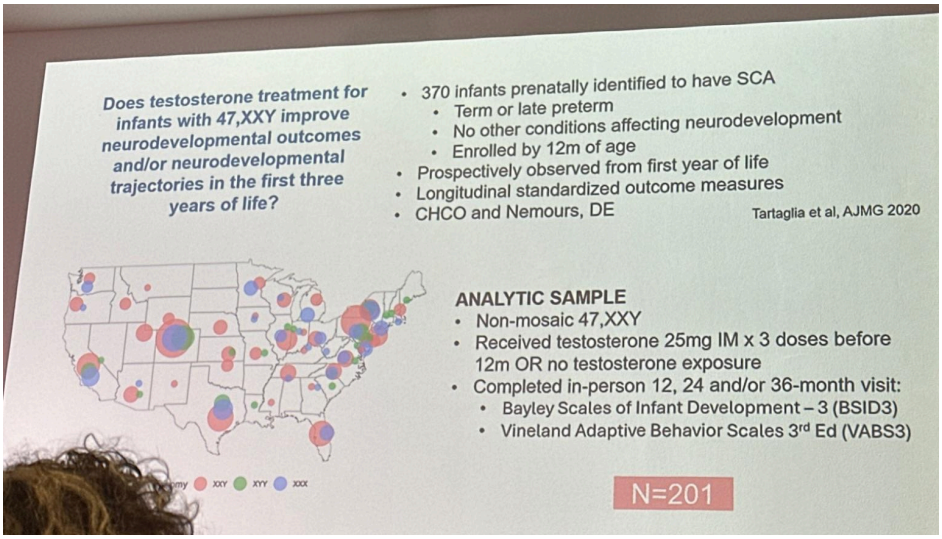
Dr. Fariba presented experimental data using XXY mouse models to explore whether stimulating the LH receptor can restore testosterone production in KS.

In KS, Leydig cells in the testes do not produce sufficient testosterone. The question remains whether this is due to defective hormone synthesis or impaired transport.
Her team tested the use of LH receptor agonists at different doses and ages, finding that stimulation could increase testosterone levels in both young and older mice.

The discussion emphasized that while animal models provide valuable insights, translating these findings to human treatment requires caution — as hormonal signaling and receptor function can differ significantly between species.

Testosterone effects on short-term physical, hormonal, and neurodevelopmental outcomes (TESTO) in infants with 47,XXY

Speaker: Dr. Shanlee Davis (USA)



Dr. Davis presented findings from the TESTO study, investigating the short-term physical, hormonal, and neurodevelopmental effects of testosterone therapy in infants with 47,XXY.

She began by describing a recent shift in parental attitudes toward early testosterone treatment. While online parent communities increasingly discuss testosterone use in infants, some parents question whether hormone therapy is necessary for babies who appear healthy and show no immediate symptoms.

Dr. Davis emphasized that testosterone is not a “cure” for Klinefelter syndrome, and that its use should be guided by medical evidence rather than social pressure or general expectations within parent groups. Family environment, parenting style, and emotional support also play important roles in child development.

In clinical practice, testosterone levels are first measured and monitored. Treatment is only considered when infants show consistently low testosterone and clinical indications of deficiency.
Parents are reassured that many infants maintain healthy hormonal levels without intervention.

Regarding testosterone therapy in adolescence, Dr. Davis noted that treatment typically continues for several years. However, extending therapy beyond the natural “mini-puberty” phase of infancy is not recommended, as it does not reflect physiological hormone patterns.

The session also referenced European practices:

- In Rome, clinicians often wait until age 17 to assess fertility and request semen samples, regardless of testosterone history. Among 180 young adult KS patients, sperm was found in 11%.
- In Denmark, clinicians evaluate each case individually.
- All agree the need for international consensus on how to manage the transition from pediatric to adult care.

Sleep Disorders in Children and Adolescents with KS

Speaker: Dr. Luigi Tarani (Italy)

Dr. Tarani discussed the high prevalence of sleep disturbances among school-aged children with Klinefelter syndrome.
Compared to neurotypical peers, KS children exhibit significantly more problems with sleep onset, restlessness, and frequent awakenings.

A particular focus was placed on Restless Legs Syndrome, which in some cases is associated with low iron levels. Monitoring and supplementation can improve symptoms.

In adults, sleep disturbances — especially sleep apnea — occur more frequently in those with KS, though the relationship between testosterone therapy and sleep quality remains complex. Testosterone may influence natural sleep cycles, and therefore requires careful monitoring.

Dr. Tarani also highlighted the safe and effective long-term use of melatonin for preschool-aged children who continue to experience persistent sleep problems.

The Role of Testosterone Therapy in Cardiometabolic Health and Mortality

Speaker: Dr. Simon Chang (Denmark)

Dr. Chang presented data on how testosterone replacement therapy (TRT) affects cardiometabolic risk and overall mortality in men with Klinefelter syndrome.

Recent epidemiological studies confirm a significant increase in mortality among men with KS, largely due to preventable conditions such as cardiovascular disease, metabolic syndrome, and mental health disorders.

Encouragingly, evidence now shows that appropriate testosterone therapy reduces, rather than increases, the risk of thrombosis and cardiovascular events.
When administered and monitored correctly, TRT contributes to improved metabolic profiles, muscle mass, and bone health, and may lower the overall mortality risk.

Experts agreed that optimal management requires:

- Early psychological and educational support beginning in childhood.
- Comprehensive medical screening for metabolic and cardiovascular risk factors.
- Lifelong follow-up within multidisciplinary endocrinology teams.

Aging and Bone Health in Klinefelter Syndrome

Speaker: Dr. Vincenzo Rochira (Italy)

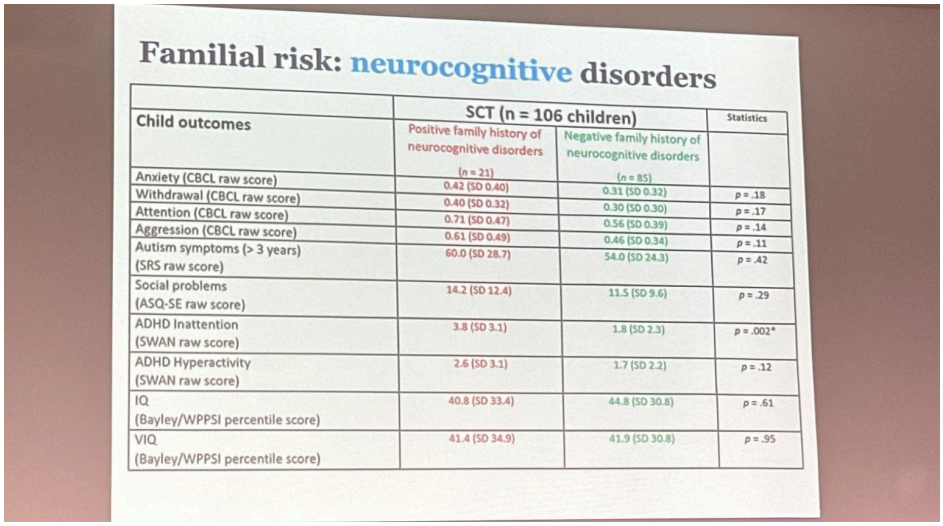
Dr. Rochira addressed the effects of aging on bone health in men with Klinefelter syndrome. While testosterone deficiency contributes to reduced bone density, other factors such as low physical activity, vitamin D deficiency, and delayed diagnosis play a major role.

He emphasized that maintaining adequate testosterone levels, engaging in regular weight-bearing exercise, and monitoring bone mineral density (BMD) are critical for preventing osteoporosis and fractures in adulthood.

The role of familial environment in behavioral and neurocognitive phenotypes

Speaker: Dr. Sophie van Rijn (The Netherlands)

Dr. van Rijn explored how family environment and parenting behaviors influence neurocognitive and behavioral outcomes in children with sex chromosome trisomies (SCTs).



Familial risk: neurocognitive disorders

Child outcomes	SCT (n = 106 children)		Statistics
	Positive family history of neurocognitive disorders (n = 21)	Negative family history of neurocognitive disorders (n = 85)	
Anxiety (CBCL raw score)	0.42 (SD 0.40)	0.31 (SD 0.32)	p = .18
Withdrawal (CBCL raw score)	0.40 (SD 0.32)	0.30 (SD 0.30)	p = .17
Attention (CBCL raw score)	0.71 (SD 0.47)	0.56 (SD 0.39)	p = .14
Aggression (CBCL raw score)	0.61 (SD 0.49)	0.46 (SD 0.34)	p = .11
Autism symptoms (> 3 years) (SRS raw score)	60.0 (SD 28.7)	54.0 (SD 24.3)	p = .42
Social problems (ASQ-SE raw score)	14.2 (SD 12.4)	11.5 (SD 9.6)	p = .29
ADHD Inattention (SWAN raw score)	3.8 (SD 3.1)	1.8 (SD 2.3)	p = .002*
ADHD Hyperactivity (SWAN raw score)	2.6 (SD 3.1)	1.7 (SD 2.2)	p = .12
IQ (Bayley/WPPSI percentile score)	40.8 (SD 33.4)	44.8 (SD 30.8)	p = .61
VIQ (Bayley/WPPSI percentile score)	41.4 (SD 34.9)	41.9 (SD 30.8)	p = .95

Her research found that early-life stress and parental anxiety did not directly predict anxiety in the children themselves, suggesting that protective family factors play a stronger role than genetics alone.

In observational studies, parent–child interactions were recorded while the children (average age 4.5 years) completed cognitive tasks. Findings showed that when parents displayed:

- Positive affect → positive emotions / happiness / good mood
- Active involvement → engagement / participation / actively involved
- Effective emotional regulation (mentalization skills) → good control of emotions / ability to understand and manage one's own and others' emotions

… their children showed fewer behavioral difficulties and better social understanding.

Conclusions

Familial risk for neuropsychiatric disorders does not 'explain' the vulnerabilities of children with SCT

↓

Effect of the extra X/Y?

Familial risk for neurocognitive disorders is associated with increased ADHD symptoms (inattention) in children with SCT

↓

Effect of the extra X/Y + familial effects ?

Parenting is very important!

Parental warmth
Responsiveness
Positive affect
Contingent interaction
Supportive guidance

→

Mental health
Emotional wellbeing
Resilience
Cognitive functioning
Quality of life

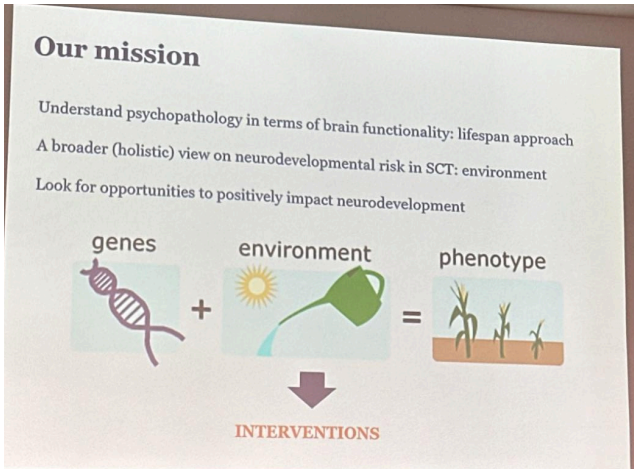
Parenting is very important!

Parental warmth
Responsiveness
Positive affect
Contingent interaction
Supportive guidance

Mental health
Emotional wellbeing
Resilience
Cognitive functioning
Quality of life

Prolonged frontal lobe maturation
Stress regulation (HPA axis)
Neural synchrony

Over time, however, social cognition challenges tended to increase in children with SCTs, highlighting the potential value of neurocognitive and social-skills training programs to support development.



The Importance of Early Diagnosis

Speaker: Dr. Alberto Ferlin (Italy)

Dr. Ferlin presented data demonstrating that age at diagnosis strongly correlates with a range of clinical outcomes in Klinefelter syndrome, including bone density, body mass index (BMI) and fertility potential.

Although meta-analyses show no statistically significant difference in sperm retrieval rates based on age, real-world data suggest that earlier diagnosis leads to better overall management and quality of life.

Interviews with patients revealed that most would have preferred an earlier diagnosis, believing that better awareness and timely support could have improved their development and well-being.

Dr. Ferlin concluded with a proposal to establish a global Klinefelter Syndrome Registry, designed to collect patient-focused data and foster international collaboration.

Concluding Remarks

Speaker: Dr. Alberto Ferlin (Italy)

In his final summary, Dr. Ferlin emphasized that lifestyle factors may be as important as testosterone therapy in determining long-term outcomes for individuals with KS. Healthy habits, physical activity, and preventive healthcare all contribute significantly to improved quality of life.

He reiterated that while testosterone therapy reduces mortality, there remain open questions about why some individuals have low hormone levels and others maintain normal ones, and why symptoms vary so widely.

Finally, he noted that in the United States, more than 50% of KS diagnoses are now made prenatally, underscoring the need for sensitive counselling and continued collaboration between clinicians, researchers, and patient organizations worldwide.