Neurodevelopment in early childhood in SCT:
There are several risks for symptoms associated with SCT that can appear throughout a child's life. Some of these risks include:

- Cognitive, language, and learning disabilities
- Attention and executive function difficulties
- Internalizing and externalizing behavioral and psychological disorders

The focus in this paper will be on unanswered questions, research findings about children ages 3-5, and neurodevelopmental disorders that can present during this time. It will look at language impairment, ASD, and motor skills deficits.

Language impairment and early social cognition:

Over 75% of children with SCTs participate in speech therapy. They're at increased risk for mild delays in language milestones, and may experience challenges with expressive language skills. Common diagnoses include Expressive language disorder and Receptive-Expressive language disorder. These diagnoses help children qualify for speech therapy. A 2018 study indicated that while there's a higher rate of language difficulties amongst children ages 5-16, one third of those children had no language impairment at all.

Other studies reported children with SCT might have delays in phonological processing (how children simplify adult speech to better understand it), oromotor skills (coordination, strength, and movement of the mouth, jaw, and muscles), articulation, and motor planning of speech [p.5]. It's important for speech therapists to identify exactly where the issues are, and how they can assist each child. Speech therapy is an important component of early intervention, as language deficits can lead to scholastic, behavioral, and social problems.

Studies have also found children with SCTs who have extra X chromosomes (such as XXY) seem to struggle with social cognition, meaning they have difficulty understanding how to pick up on cues that help them socially communicate. They can struggle interpreting social situations, reading facial expressions, and understanding tone of voice [p.6].

Autism spectrum disorder:
Results from ASD evaluations at two clinical sites showed "5%-10% of boys with XXY and up to 38% of boys with XYY in these samples met criteria for ASD" [p.6]. These rates are higher than for typical XY boys in the United States. A long term study is needed to further discover why these rates are higher, and help identify ASD predictors.

Motor deficits:

Children with SCT are at increased risk for motor delays and deficits in motor coordination, endurance, and strength. There's a lower deficiency in XYY as opposed to XXY, suggesting androgen (testosterone) deficiency can play a role in motor delays.

Neurodevelopmental disorders beyond early childhood in SCT—Learning disabilities, executive dysfunction/ADHD, and emotional disorders:
While neurodevelopmental disorders can arise in early childhood, they can also appear later in life. These disorders include "increased risk for cognitive problems and learning disabilities, including dyslexia and disorders of written expression," [p.7]. Attention problems and ADHD rates are higher in KS groups, as opposed to the general population. "Children with SCT also have increased risk for difficulties with executive function, including initiation, planning, organization, working memory, and cognitive flexibility," [p.7]. This can make things more difficult for children academically, and personally. They may be at increased risk for depression, anxiety, and mood disorders.

MEDICAL AND ENDOCRINE MANIFESTATIONS OF SCT:
Overview of testicular and ovarian function and cardiometabolic health in SCT:
The atypical sex chromosomes impact the development of a boy with KS' gonads (testes). Boys with XXY/KS don't produce normal amounts of testosterone, and require testosterone replacement therapy. As sperm production is impaired, there can be issues with fertility. Gonadal function is important to observe in infants for physical, and neurodevelopmental function. This is important to follow into adulthood, as men with XXY are at significantly higher risk for metabolic syndrome. Reports are also finding cardiometabolic disorders (insulin resistance, impaired glucose tolerance, dyslipidemia, hypertension, etc). Boys with XXY/KS are noted to have "low inhibin B, a hormone reflecting testicular function in prepubertal boys" [p.7].

Testicular function in infants with XXY:
One of the major symptoms of XXY is a lack of testicular function, which can lead to hypogonadism. However, there's limited research into the testicular function of infants and adolescents. All infants go through what's referred to as a mini-puberty in the first months of life. In studies of mice, there's been some evidence that including testosterone during this early mini-puberty can help physical and cognitive development. In humans, there's been less than 100 XXY infants studied who've gone through a mini-puberty. The largest of these studies indicated testosterone levels "fell below the median in 83% of XXY infants," [p.8]. There's been increased interest in treating infants with XXY with testosterone during the mini-puberty phase.

A study following infants given testosterone during the mini-puberty phase showed decreased body fat, as opposed to other XXY boys who didn't receive the testosterone. They also had longer penile length, and no serious adverse effects from the treatment were noted. The

eXtraordinarY Baby study will continue to explore whether motor function contributes to body fat accumulation, looking at if XXY children may have more body fat due to delayed motor function. It'll also explore if poor testicular function can contribute to body composition later in life.

Improved cognitive outcomes were indicated in children who received testosterone during the mini-puberty, as opposed to those who didn't. However, the study that indicated this did not have a blind group, or a group who did not receive the shot, nor did it test androgen (testosterone) levels prior to administering the treatment. More studies are needed to determine if the early treatment is effective.

Hormonal and genetic research considerations
It's thought "that hormonal treatments are unlikely to normalize neurodevelopmental and brain function in XXY," [p.9]. This is because there are hundreds of other genes that can impact how the brain develops and functions, not just the ones associated with the child's SCT. As the number of sex chromosomes impacted increases, so do the errors caused by the extra chromosomes.

Congenital malformations and other health problems:
SCT conditions including KS have "increased risk for other congenital malformations and medical diagnoses," [p.10]. Some of these risks include:

- Congenital cardiac and renal malformations
- Allergies
- Autoimmunity
- Eosinophilic esophagitis
- Dental problems
- Velopharyngeal insufficiency
- Elbow abnormalities
- Hypotonia (low muscle tone)
- Pes planus (flat feet)
- Tremors and seizure activity
- White matter MRI abnormalities

XXY has been associated with increased rates "of hernias, venous thrombosis, and certain malignancies such as germ cell tumors" [p.10].

CONSIDERATIONS OF NEWBORN SCREENING FOR SCT:
Newborn screening for SCTs may provide "opportunity for interventions to improve long-term outcomes" [p.10]. Recent research shows possible benefits of early hormone therapy in infants and children with XXY/KS, as it might allow for disease modifying early intervention. Some

argue SCTs shouldn't qualify for early screening due to the wide array of how children are impacted. They recommend delays should be observed before making a diagnosis.

There are also concerns that by knowing about their child's SCT before or from birth, the relationships parents have with their child may be impacted. Parents may have less expectations of their child, and the child's self-identity may be negatively impacted by being aware of the possible symptoms of their SCT. On the other hand, one could argue that by being aware of the diagnosis from birth, parents can be more prepared to raise their child, and better offer interventions and support.

CONCLUSIONS AND FUTURE DIRECTIONS:

The goal of the eXtraordinarY Babies Study is to help improve upon care for children with SCTs by utilizing past research, and answering new questions about the health, development, and care of a child with SCT. The results of the study will be utilized along with previous research to help "inform genetic counseling, guide considerations for newborn screening, improve care recommendations, and to identify targets for intervention trials" [p.11]. With ongoing research, there's hope for "improved quality of life for individuals with all types of sex chromosome disorders" [p.11].