Medical Findings in Infants Prenatally Identified With Sex Chromosome Trisomy in Year 1 of Life

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abstract

BACKGROUND AND OBJECTIVE: Sex chromosome trisomies (SCT), including XXY, XYY, and XXX syndromes, have been historically underdiagnosed. Noninvasive prenatal cell-free DNA screening has significantly increased identification, leading to a need for pediatric care for a growing population of newborns with SCT. Our goal was to analyze and compare perinatal, medical, and physical features in infants with prenatal identification of SCT through 12 months of age.

METHODS: The eXtraordinarY Babies Study is a prospective natural history study of prenatally identified children with SCT. Participants enroll prior to 12 months of age and have medical histories and examinations at 2-, 6-, and 12-month visits. Descriptive statistics were followed by comparisons between SCT groups (*t* tests, analysis of variance, Fisher exact tests). Relative risks were calculated compared to general population rates.

RESULTS: A total of 309 infants are included (XXY = 182; XXX = 76; XYY = 51). Relative risk (RR) compared to general population is elevated for breastfeeding difficulties (51.1%; RR 2.7 [CI 2.1–3.4]), positional torticollis (29.4%; RR 7.5 [5.3–10.7]), eczema (47.6%; RR 3.5 [3.1–3.9]), food allergies (19.4%; RR 2.4 [1.9–3.1]), small cardiac septal defects (7.8%; RR 17.3 [11.8–25.3]), and structural renal abnormalities (4.5%; RR 10.1 [6.0–16.8]), all $P < .001$. Comparisons between groups show more similarities than differences; however, infants with an extra X chromosome are at higher risk for lower birth weight and length, infants with XXX have higher risk for renal and cardiac malformations, and the risk of eczema is higher in boys.

DISCUSSION: Results inform care as pediatricians and families can be reassured that a prenatal diagnosis of SCT is not associated with complex medical or physical abnormalities within the first year of life, but proactive monitoring for select at-risk conditions is warranted.

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Drs Tartaglia and Davis conceptualized and designed the study, designed data collection instruments, supervised data collection, collected data, developed data analysis plan, drafted the initial manuscript, and critically reviewed and revised the manuscript. Dr Ross conceptualized and designed the study, supervised data collection, collected data, and critically reviewed and revised the manuscript. Dr Ikomi, Dr Berglund, Ms Howell, and Ms Kowal collected data and critically reviewed and revised the manuscript. Ms Bothwell conducted data analysis, generated tables and figures, and critically reviewed and revised the manuscript. Ms Nocon and Ms Reynolds participated in participant recruitment, study visit coordination, data collection and management, and critically reviewed and revised the manuscript. Mr Keene participated in data collection, data sharing, manuscript preparation, and critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

WHAT'S KNOWN ON THIS SUBJECT: One in ~500 individuals have an extra X or Y chromosome, or sex chromosome trisomy (SCT). Prenatal screening is now routinely identifying SCT; however, there are few studies to guide perinatal and infant care for these individuals.

WHAT THIS STUDY ADDS: This prospective observational study presents medical features for 309 infants with prenatally identified SCT from birth through the first year of life. Results identify where proactive screenings and/or interventions may be warranted for infants with SCT.

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INTRODUCTION

Sex chromosome trisomies (SCT) occur in approximately 1:500 births and include XXY (Klinefelter syndrome) and XYY syndrome in boys, and XXX (trisomy X) syndrome in girls.[1,2] Historically, prenatal diagnosis of SCT occurred only when chorionic villi sampling (CVS) or amniocentesis was indicated, such as due to abnormal ultrasonography findings or advanced maternal age, accounting for only 5% to 10% of all cases of SCT.[3] An additional 5% to 25% were diagnosed postnatally upon presentation of clinical symptoms; however, 65% to 90% of SCT cases remained undiagnosed.[3] The adoption of cell-free DNA (cfDNA) screening into routine prenatal care in the United States has led to a marked increase in the prenatal identification of SCT[4] resulting in a large cohort of infants with a known diagnosis. With a median of over 4000 visits annually per pediatric physician,[5] each pediatrician will have several patients with SCT in their practice.

Due to the previously low rate of diagnosis in the prenatal period, there is a paucity of research on medical features in the early years of life. Prior international newborn screening studies identified 200 infants with SCT in the 1960s. These reports suggest that most infants with SCT are born at term and are not at an increased risk of congenital malformations or medical conditions during the neonatal period.[6,7] In childhood, tall stature and mild hypotonia are commonly described in the literature, as well as reports of atopic conditions, autoimmunity, constipation, seizure disorders, tremor, and recurrent respiratory infections.[7–12] However, the preexisting literature relies on small sample sizes and selection bias and therefore may not be generalizable to the population identified through prenatal cfDNA screening. Furthermore, although the medical complexity of these children is often assumed to be low, there is no information on health care utilization such as hospitalization or surgery. Prevalence data for medical comorbidities collected prospectively are needed to guide best care practices for pediatric SCT care and provide appropriate counseling to parents.

The surge of infants with SCT being identified by prenatal cfDNA screening provides a rich opportunity for prospective study of these infants to inform the natural history of these conditions. The eXtraordinarY Babies Study collects comprehensive data on health and development for prenatally identified infants with SCT starting within the first year of life to better inform and guide counseling and care for these infants. The aim of this study is to describe the prospective physical and medical features in the perinatal period and first year of life for a large, prenatally ascertained cohort of infants with SCT and to compare features between SCT conditions and to the general population estimates.

METHODS

Parents of infants with prenatal identification of SCT were invited to participate in an institutional review board–approved natural history study called the eXtraordinarY Babies Study at 1 of 2 sites in Colorado or Delaware (ClinicalTrials.gov NCT03396562; COMIRB 17–0118; Nemours IRB No. 1151006). Descriptions of study methodology and assessment measures have been previously published and are summarized in Figure 1.[13] Participants are recruited through postings sent to genetic counselors across the nation, SCT advocacy groups, and social media sites. All participants are required to have prenatal identification of SCT through cfDNA, CVS, and/or amniocentesis. Participants with only prenatal cfDNA are required to also provide diagnostic postnatal confirmatory testing (karyotype, microarray, and/or gene sequencing). CVS and/or amniocentesis alone are considered diagnostic, and postnatal confirmatory testing is encouraged but not required for participation. Inclusion criteria include SCT with less than 20% mosaicism of a typical cell line, gestational age at or above 34 weeks at birth, and enrollment prior to 12 months of age. Following written informed consent, data were collected by medical clinicians using review of medical records and a standardized interview with the parents developed for the study that included detailed birth and medical histories. Study visits occurred at 2, 6, and/or 12 months of age depending on timing of enrollment (eg, a participant enrolled at 4 months of age would start study visits at 6 months of age; see Figure 1). Visits were

FIGURE 1.
Schematic of eXtraordinarY Babies Study visits.

conducted in person or via telehealth due to COVID-19 restrictions during the study period. This report focuses on medical and physical features identified within the first year of life.

Demographic data were collected through a standardized parent survey, and the Hollingshead 4-Factor Index was calculated as previously described.[14] Race and ethnicity were self-reported and collected as per National Institutes of Health (NIH) guidelines. Physical examinations were conducted by board-certified pediatricians at 2-, 6-, and/or 12-month visits, and sample size differences for these data are variable due to differences in enrollment age and COVID-19 restrictions preventing in-person visits for some participants. Birth weight (BW) and length (BL) measurements were converted to z-scores for gestational age and sex according to US norms.[15] Descriptive metrics (proportions, means) and estimates (95% CIs or SDs) for each outcome were calculated for the whole sample as well as stratified by SCT. Outcomes were compared between SCT groups using Fisher exact tests for low cell counts or analysis of variance followed by pairwise comparisons. Finally, when rigorous published data were available for the general pediatric population, risk ratios and 95% CIs were calculated by unconditional maximum likelihood estimation (Wald) in the epitools R package to determine whether the SCT sample proportion differed from what is expected in the general population. To explore the potential confounding of advanced maternal age (AMA), we conducted a sensitivity analysis of the findings presented in with only patients born to non-AMA mothers to compare with the pooled group. All analyses were 2-sided with a type 1 error rate set at 0.05. Data were stored and managed in the secure REDCap database and all analyses were conducted in RStudio version 2022.12.0 (Posit PBC) using R version 4.2.2 (The R Project for Statistical Computing).

RESULTS

The full sample consisted of 309 infants (XXY: n = 182; XXX: n = 76; XYY: n = 51) representing 47 US states (Figure 2) and diverse racial and ethnic backgrounds (Table 1). Four additional participants withdrew or were lost to follow-up after their initial visit, and their data were excluded from analysis. Nearly all (96.1%) were initially identified to have SCT via prenatal cfDNA screening performed either for AMA or no clinical indication (elective), whereas the minority (4.2%) had abnormal ultrasonography and/or biochemical markers prompting prenatal genetic testing (Table 2). All participants except for 3 girls with XXX were nonmosaic; the 3 mosaic cases were 47,XXX/46,XX with less than 20% 46,XX cell line in all cases. Pregnancies were largely uncomplicated, and the vast majority of the cohort was born full term via vaginal delivery at a mean gestational age 38.7 ± 1.4 weeks. Most infants (84.1%) were average for gestational age (AGA); however, infants with XXY and XXX had lower mean weight and length z-scores at birth than those with XYY.

Major congenital anomalies were identified in only 0.6% of the cohort, including cleft lip/palate (n = 1), and clubfoot (n = 1), which is not different from general population estimates (up to 3%) (Table 3).[16] Common minor congenital anomalies (Figure 3) were fifth-digit clinodactyly (49.1%),

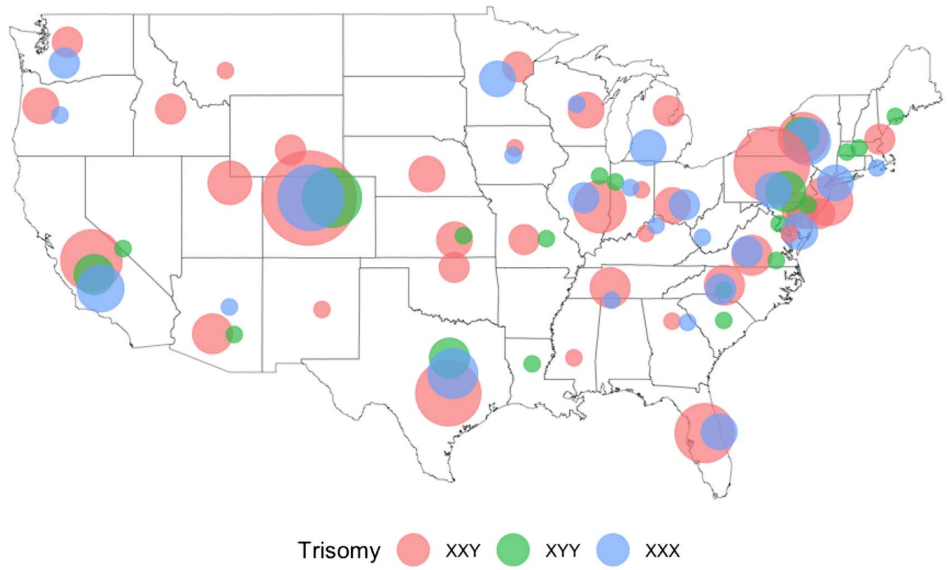

FIGURE 2.
Participant US regional representation. Point sizes range from N = 1 to N = 38. Hawaii and Alaska are both represented by N = 1. N = 9 patients are international.

TABLE 1. Participant Demographics

	Overall	XXX	XXY	XYY	ANOVA or Fisher Exact Test (*P* Value)
n	309	76	182	51	
Enrollment site (%)					.953
Colorado	236 (76.4)	57 (75.0)	140 (76.9)	39 (76.5)	
Nemours	73 (23.6)	19 (25.0)	42 (23.1)	12 (23.5)	
Enrollment age, months (median [IQR])	5.5 (1.3, 29.1)	6.3 (1.41, 16.3)	3.0 (1.3, 20.2)	6.8 (1.7, 29.1)	.002[a]
Enrollment visit window (%)					<.001[a,b]
2 mos	149 (48.2)	27 (35.5)	107 (58.8)	15 (29.4)	
6 mos	83 (26.9)	29 (38.2)	35 (19.2)	19 (37.3)	
12 mos	74 (23.9)	20 (26.3)	38 (20.9)	16 (31.4)	
Other	3 (1.0)	0 (0)	2 (1.1)	1 (2.0)	
Race (%)[c]					.344
Asian	10 (3.2)	4 (5.3)	6 (3.3)	0	
African American or Black	7 (2.3)	1 (1.3)	3 (1.6)	3 (5.9)	
More than 1 race	32 (10.4)	6 (7.9)	20 (11.0)	6 (11.8)	
Caucasian or White	258 (83.5)	65 (85.5)	151 (83.0)	42 (82.4)	
Unreported	2 (0.6)	0 (0.0)	2 (1.1)	0 (0.0)	
Ethnicity (%)[c]					.912
Hispanic/Latino	45 (14.6)	10 (13.2)	28 (15.4)	7 (13.7)	
Not Hispanic/Latino	264 (85.4)	66 (86.8)	154 (84.6)	44 (86.3)	
Hollingshead					.523
4-factor index mean (SD)	53.6 (9.1)	54.3 (7.9)	53.6 (9.2)	52.3 (10.3)	
Annual household income (%)					.678
< $75 000	31 (10.0)	8 (10.5)	16 (8.8)	7 (13.7)	
$75 000–150 000	110 (35.6)	26 (34.2)	63 (34.6)	21 (41.2)	
$150 000–250 000	76 (24.6)	22 (28.9)	45 (24.7)	9 (17.6)	
>$250 000	90 (29.1)	19 (25.0)	57 (31.3)	14 (27.5)	
Did not report	2 (0.6)	1 (1.3)	1 (0.5)	0	
Region (US Census Bureau) (%)					.141
International	7 (2.3)	0	3 (1.6)	4 (7.8)	
Midwest	44 (14.2)	12 (15.8)	29 (15.9)	3 (5.9)	
Northeast	64 (20.7)	15 (19.7)	35 (19.2)	14 (27.5)	
South	83 (26.9)	22 (28.9)	50 (27.5)	11 (21.6)	
West	111 (35.9)	27 (35.5)	65 (35.7)	19 (37.3)	

Abbreviation: ANOVA, analysis of variance.

Categorical data are represented as n (%), and continuous data are mean (standard deviation).

[a] $P < .05$.

[b] Pairwise comparison analysis: 2-month visit XXY > XXX, XYY.

[c] Race and ethnicity were self-reported by parents/guardians. Additional race categories collected were Native Hawaiian or Other Pacific Islander and Native American or Alaska Native, although no one identified as single race in these categories. All parents/guardians who identified their child as "More than one race" marked White/Caucasian with Native Hawaiian or Other Pacific Islander (n = 1), Native Hawaiian or Other Pacific Islander and Asian (n = 1), African American or Black (n = 11), African American or Black and Native American or Alaska Native (n = 1), Asian (n = 15), and Native American or Alaska Native (n = 3). Race/ethnicity reporting are required by NIH guidelines.

epicanthal folds (45.3%), torticollis (29.4%), plagiocephaly (24.9%), umbilical hernia (12.6%), and preauricular tags (6.0%). Overall mean z-score for intercanthal distance was nearly a full SD higher than norms (z-score −0.73 (95% CI: [−1.33, 2.79]); however, only 3.0% met criteria for hypertelorism (z-score >2.0). There were very few differences in the rates of physical findings between SCT groups. Male infants with XXY had lower stretched penile length compared to XYY at 2 months ($P < .001$); however, mean length in the XXY group was only a quarter of an SD below the mean for the general population, and only 9 (9.0%) met criteria for short penis length (stretch penile

TABLE 2. Prenatal and Perinatal History

	Overall	XXX	XXY	XYY	ANOVA or Fisher Exact Test *P* Value
n	309	76	182	51	
Initial genetic test					
Cell-free DNA screening	297 (96.1)	72 (94.7)	176 (96.7)	49 (96.1)	.706
CVS or amniocentesis	35 (11.3)	6 (7.9)	20 (11.0)	9 (17.6)	.250
Reason for prenatal test					.607
Abnormal ultrasonography or serum test	13 (4.2)	5 (6.6)	5 (2.7)	3 (5.9)	
AMA	161 (52.1)	35 (46.1)	101 (55.5)	25 (49.0)	
Routine/elective	118 (38.2)	31 (40.8)	67 (36.8)	20 (39.2)	
Other[a]	17 (5.5)	5 (6.6)	9 (4.9)	3 (5.9)	
Parental age at birth					
Maternal age (yrs), mean (SD)	35.1 (4.9)	35.8 (4.9)	35.0 (4.9)	34.2 (4.6)	.159
Paternal age (yrs), mean (SD)	36.8 (5.8)	37.3 (5.7)	36.6 (6.0)	37.0 (5.5)	.672
Gestational diabetes	28 (9.1)	12 (15.8)	12 (6.6)	4 (7.8)	.080
Delivery method					.829
Cesarean section	105 (34.0)	26 (34.2)	60 (33.0)	19 (37.3)	
Gestational age (wks), mean (SD)	38.7 (1.4)	38.6 (1.5)	38.7 (1.4)	38.8 (1.4)	.711
Gestational age category[b]					.764
Preterm (34–36 wks)	24 (7.8)	5 (6.6)	14 (7.7)	5 (9.8)	
Full term (≥37.0 wks)	285 (92.2)	71 (93.4)	168 (92.3)	46 (90.2)	
Growth parameters at birth[c]					
Birth weight (grams), mean (SD)	3230 (553)	3140 (553)	3220 (533)	3430 (587)	.015[d,e]
Birth weight z-score mean (SD)	−0.24 (0.88)	−0.19 (0.92)	−0.33 (0.83)	0.05 (0.93)	.022[d,e,f]
Birth length (cm), mean (SD)	50.4 (2.9)	49.5 (2.6)	50.5 (3.0)	51.6 (2.8)	.001[d,e]
Birth length z-score, mean (SD)	0.02 (1.0)	−0.1 (0.9)	−0.02 (1.0)	0.38 (0.88)	.028[d,e,g]
Birth size category					.128[f]
Small for gestational age	34 (11.0)	6 (7.9)	25 (13.7)	3 (5.9)	
Average for gestational age	260 (84.1)	64 (84.2)	153 (84.1)	43 (84.3)	
Large for gestational age	12 (3.9)	4 (5.3)	4 (2.2)	4 (7.8)	
Neonatal medical course					
Intubation and/or ventilation	14 (4.5)	4 (5.3)	7 (3.8)	3 (5.9)	.746
Hyperbilirubinemia	45 (14.6)	9 (11.8)	27 (14.8)	9 (17.6)	.662
Hypoglycemia	26 (8.4)	6 (7.9)	16 (8.8)	4 (7.8)	1.000
NICU admission[h]	34 (11.0)	10 (13.2)	19 (10.4)	5 (9.8)	.819

Abbreviations: AMA, advanced maternal age; CVS, chronic villus sampling; NICU, neonatal intensive care unit.
Categorical data are represented as n (%), and continuous data are mean (standard deviation).
[a] Other; other reasons include previous pregnancy with chromosome abnormality (n = 5), IVF pregnancy (n = 2), genetic disorder in family (n = 4), previous high-risk pregnancy (n = 3), other pregnancy complication (n = 3).
[b] Study inclusion criteria required birth ≥ 34 weeks' gestation.
[c] Based on Fenton gestational age growth curves.
[d] $P < .05$.
[e] Pairwise comparisons analysis: XXY, XXX<XYY.
[f] Pairwise comparisons analysis: XXY<XXX, XYY.
[g] Pairwise comparisons analysis: XXX<XXY, XYY.
[h] NICU admissions were for respiratory distress, hypoglycemia, and feeding difficulties.

length z-score < −2.0) in those with a study exam who had not received testosterone treatment (Table 4).

Study protocol did not include standard imaging; however, of those who had clinical postnatal echocardiograms completed (n = 116), cardiac septal defects (atrial and/or ventricular) were found in 24 (20.7%), which is 7.8% of the cohort overall. None of the infants with identified atrial septal defect or ventricular septal defect required invasive

TABLE 3. Medical Problems From Birth to 12 Months

	Overall	XXX	XXY	XYY	ANOVA or Fisher Exact *P* Value
n	309	76	182	51	
Breastfeeding problems	158 (51.1)	40 (52.6)	90 (49.5)	28 (54.9)	.984
Aspiration	13 (4.2)	5 (6.6)	6 (3.3)	2 (3.9)	.445
Allergies (any)	75 (24.3)	15 (19.7)	49 (26.9)	11 (21.6)	.433
Food/formula allergies	60 (19.4)	11 (14.5)	39 (21.4)	10 (19.6)	.452
Food allergy onset, mean age (SD)	5.9 (4.0)	4.4 (3.7)	6.5 (4.1)	4.9 (3.7)	.207
Environmental/seasonal allergies	20 (6.5)	2 (2.6)	15 (18.2)	3 (5.9)	.256
Environmental/seasonal age at onset, mean (SD)	6.9 (3.3)	8.0 (1.4)	6.8 (3.8)	7.0 (1.0)	.900
Medication allergy	6 (1.9)	3 (3.9)	3 (1.6)	0	.366
Medication allergy age at onset, mean (SD)	10.5 (4.2)	11.3 (5.0)	9.7 (4.0)	NA	.678
Eczema	147 (47.6)	24 (31.6)	97 (53.3)	26 (51.0)	.005[a,b]
Reactive airway disease	6 (1.9)	0	4 (2.2)	2 (3.9)	.194
Otitis media	67 (21.7)	12 (15.8)	42 (23.1)	13 (25.5)	.287
Bronchiolitis	40 (12.9)	7 (9.2)	23 (12.6)	10 (19.6)	.247
Pneumonia	9 (2.9)	2 (2.6)	7 (3.8)	0	.439
Croup	11 (3.6)	2 (2.6)	8 (4.4)	1 (2.0)	.686
Delayed dental eruption[c]	16 (5.2)	5 (6.6)	11 (6.0)	0	.383
1st dental eruption age, mean (SD)	8.1 (2.3)	8.5 (2.1)	8.0 (2.2)	7.8 (2.6)	.239
Gastroesophageal reflux disease	90 (29.1)	18 (23.7)	62 (34.1)	10 (19.6)	.081[d]
Constipation	104 (33.7)	34 (44.7)	56 (30.8)	14 (27.5)	.057[b]
Eosinophilic esophagitis	1 (0.3)	1 (1.3)	0	0	.303
FTT[e]	57 (18.4)	20 (26.3)	30 (16.5)	7 (13.7)	.136
FTT at age at diagnosis, mean (SD)	3.0 (3.6)	3.1 (4.0)	2.9 (3.7)	2.9 (2.5)	.985
Hearing loss	7 (2.3)	0	6 (3.3)	1 (2.0)	.289
Strabismus	22 (7.1)	6 (7.9)	13 (7.1)	3 (5.9)	.911
Cleft palate	1 (0.3)	0	1 (0.5)	0	1.000
Polydactyly	3 (1.0)	0	2 (1.1)	1 (2.0)	.548
Clubfoot	1 (0.3)	1 (1.3)	0	0	.402
Torticollis	91 (29.4)	21 (27.6)	56 (30.8)	14 (27.5)	.881
Plagiocephaly	77 (24.9)	16 (21.1)	49 (26.9)	12 (23.5)	.613
Velopharyngeal insufficiency	2 (0.6)	0	2 (1.1)	0	1.000
Cardiac ASD or VSD – entire group	24 (7.8)	12 (15.8)	9 (4.9)	3 (5.9)	.012[a,b]
Cardiac ASD or VSD – echo subset (n = 116)[f]	24 (20.7)	12 (24.0)	9 (19.1)	3 (15.8)	.751
Other cardiac finding[g] – entire group	32 (10.4)	12 (15.8)	16 (8.8)	4 (7.8)	.212
Inguinal hernia	4 (1.3)	0 (0.0)	2 (1.1)	2 (3.9)	.174
Congenital hip dislocation/dysplasia	4 (1.3)	1 (1.3)	1 (0.5)	2 (3.9)	.118
Renal malformation – entire group	14 (4.5)	10 (13.2)	3 (1.6)	1 (2.0)	<.001[a,b]
Renal malformation – renal ultrasound subset (n = 86)[h]	14 (16.3)	10 (16.7)	3 (21.4)	1 (8.3)	.740
Umbilical hernia	30 (9.7)	5 (6.6)	18 (9.9)	7 (13.7)	.384
Hypotonia	119 (38.5)	29 (38.2)	72 (39.6)	18 (35.3)	.863
Febrile seizure	1 (0.3)	0	1 (0.5)	0	1.000
GU anomaly (% male infants; n = 265)	21 (7.9)	NA	19 (11.6)	2 (2.0)	.178
Hypospadias[i]	2 (0.8)	NA	1 (0.6)	1 (1.0)	.391
Penile chordee or webbing	12 (4.5)	NA	11 (6.0)	1 (1.0)	.472

(Continued on next page)

TABLE 3. Medical Problems From Birth to 12 Months (Continued)

	Overall	XXX	XXY	XYY	ANOVA or Fisher Exact *P* Value
Hydrocele	17 (6.4)	NA	15 (9.1)	2 (3.9)	.376
Cryptorchidism	12 (5.3)	NA	11 (6.0)	1 (1.0)	.472
Any hospitalization (excludes NICU)	40 (12.9)	9 (11.8)	22 (12.1)	9 (17.6)	.576
Hospitalization for respiratory infection	23 (57.5)	5 (55.6)	13 (59.1)	5 (55.6)	1.000
Age (mos) of first hospitalization	6.1 (3.8)	4.7 (4.1)	7.8 (3.6)	5.4 (3.8)	.347
Any surgery (1 or more surgeries)	33 (10.7)	6 (7.9)	18 (9.9)	9 (17.6)	.215
Ear PE tubes	7 (2.3)	1 (1.3)	5 (2.7)	1 (2.0)	.864
Tonsillectomy/adenoidectomy	2 (0.6)	0	2 (1.1)	0	1.000
GU surgery (excludes circumcision)[j]	11 (3.6)	1 (1.3)	6 (3.3)	4 (7.8)	.158
Other surgery[k]	13 (4.4)	3 (4.2)	6 (3.3)	4 (8.9)	.232
Age (mos) of first surgery	8.2 (3.5)	10.6 (1.6)	8.8 (3.1)	6.0 (4.1)	.103
Frenotomy (frenulectomy) procedure[l]	40 (12.9)	3 (3.9)	23 (12.6)	14 (27.5)	<.002[a,b,m]

Abbreviations: ANOVA, analysis of variance; ASD, atrial septal defect; FTT, failure to thrive; GU, genitourinary; NICU, neonatal intensive care unit; PE, pressure equalization; VSD, ventricular septal defect.

Participants who have completed their 12-month study visit are included. Categorical data are represented as n (%), and continuous data are mean (standard deviation). All ages are in months.

[a] $P < .05$.

[b] Pairwise comparisons analysis: XXX ≠ XXY, XYY.

[c] Delayed dental eruption defined as lack of eruption by 12 months of age.

[d] Pairwise comparisons analysis: XXY ≠ XXX, XYY.

[e] Failure to Thrive defined as medical evaluation and intervention required due to inadequate weight gain, also called growth faltering or inadequate weight gain.

[f] Echocardiogram group total n = 116 (50 XXX, 47 XXY, 19 XYY).

[g] Other cardiac findings included (some participants had more than 1 finding): Patent Ductus Arteriosus (n = 4), Pulmonic stenosis (n = 5), Situs inversus (n = 1), Patent Foramen Ovale (n = 13), Double aortic arch & vascular ring, repair required (n = 1), Right aortic arch (n = 1), Bicuspid aortic valve (n = 1).

[h] Renal ultrasound group total n = 86 (60 XXX, 14 XXY, 12 XYY). Renal ultrasound findings included: Hydronephrosis (n = 5), Pelvic caliectasis (n = 5), Bilateral small kidneys (n = 2), Duplicated collecting system (n = 1), Nephrocalcinosis (n = 1) (1 participant had both duplicated collecting system and hydronephrosis, 1 participant had both hydronephrosis and pelvic caliectasis).

[i] All cases of hypospadias classified as subcoronal hypospadias, no surgical intervention indicated.

[j] GU surgical repairs include: Hidden penis (n = 3), penile webbing / chordee (n = 5), Bifid scrotum (n = 1), ureterocele-ectomy (n = 1), some participants had >1 finding

[k] Other surgeries included: anoplasty (n = 1), dermoid cyst removal (n = 2), ear tag or accessory digit removal (n = 4), g-tube placement (n = 1), hip dislocation repair (n = 1), supraglottoplasty (n = 2), tenotomy (n = 1), vascular ring repair (n = 1).

[l] Frenotomy not included as surgery.

[m] Pairwise comparisons analysis: XXY, XXX ≠ XYY.

cardiac procedures within the first year of life; however, 1 infant required surgery for a symptomatic vascular ring secondary to double aortic arch. Of the 86 infants who had clinical renal ultrasonography, 14 (16.3%) had a structural abnormality, which represents 4.5% of the full cohort (vs 0.46% in the general population,[17] $P < .001$). When stratified by karyotype, girls with XXX were more likely to have received an echocardiogram and/or renal ultrasonography; however, the proportion with abnormal findings among those who had imaging did not significantly differ between SCT subtypes.

Breastfeeding difficulties occurred in one-half of the cohort and equally between the 3 SCT conditions, predominantly due to difficulties with latch and/or inadequate milk transfer. Despite this, the mean duration of breast milk feeding was 8.0 ± 5.5 months with 61.1% of infants still receiving breast milk at 6 months and 43.3% at 12 months, both at or above US national statistics (58.2% and 37.6%, respectively).[18] The presence of breastfeeding difficulties was associated with receiving a frenotomy (20.9% vs 5.4%, $P < .001$), earlier age of formula introduction (3.6 ± 3.5 vs 4.7 ± 3.5 months, $P = .013$), as well as a diagnosis of failure to thrive (24.6% vs 13.1%, $P = .016$). There was no relationship between breastfeeding difficulties and hypotonia, micrognathia, high arched palate, reflux, or constipation ($P > .05$ for all). Constipation was more common in all SCT groups compared with the general population (33.7% vs 7.0%, $P < .001$)[19] and was associated with hypotonia ($P = .035$).

Atopic conditions were present in 54.7% of all infants within the first year of life. Eczema was present in 47% of all infants with SCT vs 13.7% in general population (RR 3.5 [3.1–3.9], $P < .001$),[20] and allergies (food, environmental, and/or medication) were present in 24.3% vs 10.4% in the general population (RR 2.6 [2.1–3.2], $P < .001$).[21] The risk of food allergies was, on average, 2.4 times greater in infants with SCT compared with general population estimates (19.4% vs 8.8%, 95% CI [1.9–3.1], $P < .001$),[22] with a mean age of 5.9 ± 4.0 months at diagnosis. Food allergies were more common among infants with

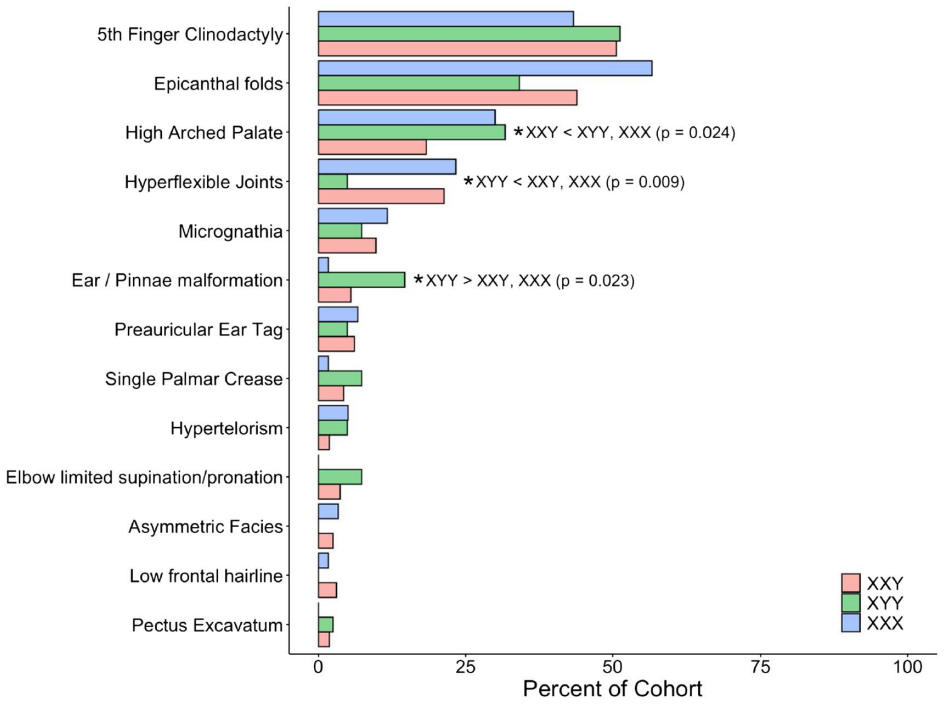

FIGURE 3.
Physical features on examination.

eczema (28.6% vs 11.2%, $P < .001$) and reflux (31.1% vs 14.7%, $P = .001$).

Acute infectious diagnoses, including otitis media (21.7%), bronchiolitis (12.9%) and pneumonia, (2.9%) were similar to estimates in the general population.[23–26] Overall, 12.9% of the cohort required inpatient hospitalization within the first year of life, with 57.5% of these hospitalizations attributable to respiratory etiologies. Surgeries occurred in 10.7% of the cohort, with the most common indication being for repair of minor genitourinary (GU) anomalies.

When comparing between SCT groups, there was sufficient evidence to conclude that rates of eczema, constipation, small cardiac septal defects, and structural renal abnormalities were statistically different in patients with XXX trisomies compared with XXY and XYY trisomies (Table 4). When subsetting to only patients with XXY and XYY syndromes, there remained evidence of a significantly higher risk of these outcomes compared with the general population. When RR differed between SCT groups, they were listed individually in Table 5. Sensitivity analysis exploring potential confounding of AMA showed that there are not meaningful differences in the risks of medical findings in children born to mothers of AMA compared with the pooled group.

Weight and weight-for-length z-scores increase in the first year of life for all SCTs, whereas length z-scores increase from birth to the first year of age for boys but not for XXX (Table 5 and Supplemental Figure 1). By 12 months of age, growth parameters in all 3 groups were within 1 SD of the mean for the general population.

DISCUSSION

This large, prospective cohort study describes the comprehensive natural history of prenatal, birth, physical findings, and medical conditions arising within the first year of life for infants prenatally identified to have SCT. Overall, major congenital anomalies and complex medical conditions were uncommon and there were minimal differences in perinatal and infant findings between SCT groups. We observed several findings warranting clinical consideration within the first year of life, including breastfeeding problems, failure to thrive, torticollis, constipation, structural cardiac and renal differences, and atopic conditions (Table 1). The results of this study directly inform pediatric care, as they reassure families and providers that a prenatal diagnosis of SCT is not associated with complex medical or physical abnormalities in the first year of life, though proactive monitoring for select at-risk conditions is recommended.

Our results indicate that pregnancies affected by SCT are generally healthy and that neither fetal nor maternal complications are obviously different from the general population. Based on these observations, standard prenatal care is appropriate, aside from genetic counseling and decisions on timing of diagnostic genetic testing.[27] However, as conditions requiring medical interventions occurred in approximately 1 out of 4 neonates in our cohort, we recommend that delivery be planned at a facility equipped to manage potential neonatal complications including hypoglycemia, hyperbilirubinemia requiring phototherapy, and respiratory

TABLE 4. Physical Examination Growth Z-Scores at 2, 6, and 12 Months[a,b]

	Overall	XXX	XXY	XYY	ANOVA or Fisher Exact *P* Value
2-month physical exam subset	135	20	108	7	
Weight z-score, mean (SD)	−0.7 (1.1)	−0.79 (1.0)	−0.76 (1.0)	0.35 (1.7)	.023[b,c]
Length z-score, mean (SD)	−0.59 (1.2)	−0.51 (1.2)	−0.71 (1.1)	1.1 (1.6)	<.001[b,c]
Weight-for-length z-score, mean (SD)	0.08 (1.1)	−0.08 (1.1)	0.09 (1.2)	0.33 (0.9)	.393
Head circumference z-score, mean (SD)	0.25 (1.1)	−0.004 (0.9)	0.17 (1.1)	0.81 (1.1)	<.001[b,c]
Stretched penile length z-score (SD) (male infants only w/o history of testosterone, n = 83; XXY = 61, XYY = 22)[d]	−0.19 (0.77)	NA	−0.40 (0.9)	0.05 (1.0)	.051
Z-score < −2.0	2 (2.4)	NA	2 (3.3)	0 (0)	1.000
6-month physical exam subset	197	43	132	22	–
Weight z-score, mean (SD)	−0.11 (1.1)	−0.34 (1.0)	−0.11 (1.1)	0.27 (1.4)	.123
Length z-score, mean (SD)	−0.18 (1.2)	−0.35 (1.0)	−0.18 (1.2)	0.20 (1.6)	.217
Weight-for-length z-score, mean (SD)	0.08 (1.1)	−0.08 (1.1)	0.09 (1.2)	0.33 (0.9)	.393
Head circumference z-score, mean (SD)	0.06 (1.2)	−0.06 (0.8)	−0.05 (1.2)	0.97 (1.4)	<.001[b,c]
Stretched penile length z-score (SD) (male infants only w/o history of testosterone, n = 83; XXY = 61, XYY = 22)[d]	−0.19 (0.77)	NA	−0.40 (0.9)	0.05 (1.0)	.051
Z-score < −2.0	2 (2.4)	NA	2 (3.3)	0 (0)	1.000
12-month physical exam subset	235	53	142	40	
Weight z-score, mean (SD)	0.28 (1.1)	−0.06 (0.8)	0.28 (1.1)	0.77 (1.2)	.001[b,c,e]
Length z-score, mean (SD)	0.07 (1.2)	−0.34 (1.0)	0.07 (1.2)	0.60 (1.5)	<.001[b,c,e]
Weight-for-length z-score, mean (SD)	0.37 (1.1)	0.15 (0.8)	0.36 (1.1)	0.67 (1.1)	.062
Head circumference z-score, mean (SD)	0.25 (1.1)	−0.004 (0.9)	0.17 (1.1)	0.81 (1.1)	<.001[b,c]
Stretched penile length z-score (SD) (male infants only w/o history of testosterone, n = 100; XXY = 60, XYY = 40)[d]	0.007 (0.9)	NA	−0.02 (1.1)	0.06 (1.0)	.708
Z-score < −2.0	9 (9.0)	NA	7 (11.7)	2 (5.0)	.309

Abbreviations: ANOVA, analysis of variance; NA, not applicable.
[a] $P < .05$.
[b] Total sample size receiving physical examination is variable due to differences in enrollment age and COVID-19 restrictions preventing in-person visits for some participants.
[c] Pairwise comparisons analysis: XXY, XXX < XYY.
[d] In XXY, those previously treated with exogenous testosterone were excluded: 2-month, n = 5 (4.6%), 6-month, n = 71 (46.1%), 12-month, n = 82 (54.9%).
[e] Pairwise comparisons analysis: XXX < XXY, XYY.

insufficiency. Furthermore, our observed prevalences of transient neonatal hypoglycemia may be low estimates, as most term, AGA infants are not routinely evaluated for hypoglycemia and neonatal hypoglycemia often does not present with overt symptoms.[28] Therefore, neonates with SCT may benefit from routine glucose screening and additional research.

Although major congenital malformations were rare, structural cardiac and renal anomalies occurred more commonly than expected, and this prevalence is likely underestimated given the minority of participants had echocardiograms or renal imaging. Indications for echocardiogram or renal imaging varied, with some performed as general screening due to a known chromosomal abnormality and others performed due to prenatal concern or postnatal exam findings such as murmur. Congenital cardiac and renal anomalies have been previously associated with XXX trisomies,[14] but these conditions in boys with SCT are primarily limited to case reports.[29–33] The high prevalence of abnormal imaging among all infants with SCT supports universal postnatal screening with echocardiogram and renal ultrasonography to identify anatomical defects; however, it is also important to acknowledge that none of the individuals required intervention within the first year of life unless symptoms were present. Longitudinal follow-up and additional studies are needed to confirm whether structural cardiac and renal imaging findings in SCT have clinical implications warranting universal imaging in asymptomatic individuals.

Interestingly, in male patients with XXY, structural cardiac and renal defects were just as common as genital abnormalities, which traditionally have been more commonly associated with XXY. Although, cumulatively, ~ 10% of the XXY cohort did have minor GU differences, which have previously been attributed to testosterone differences in XXY, penile structural abnormalities (hypospadias and chordee) were also observed in 6.6% of male infants with XYY, suggesting a possible etiology associated with the additional sex chromosome rather than a hormonal

TABLE 5. Medical Conditions at Higher Risk in Infants with Prenatal SCT Diagnosis and Guidance for Clinical Care

Feature	General Population Prevalence[a]	SCT Prevalence[b] (95% CI)	Relative Risk[b] in SCT	Considerations for Clinical Care
Infant-related breastfeeding difficulties	19%[42]	51.1% (45.6–56.7)	2.7 (2.1–3.4)	• Encourage prenatal breastfeeding classes if parent wishes to breastfeed • Proactive lactation consultation after delivery • Breast pump for expressed breast milk in case of delay with successful latch or ongoing breastfeeding challenges • Targeted history in newborn nursery and first well child checks • Evaluate for ankyloglossia and consider referral for further evaluation
Failure to thrive/ growth faltering	10%[43]	18.4% (14.1–22.8)	1.8 (1.4–2.5)	• Early feeding/breastfeeding support as above • Close follow-up for growth/weight gain in first months of life • Caloric supplementation and other medical work-up as indicated • Consideration of feeding therapy by feeding specialist, speech, or occupational therapy
Constipation (requiring intervention)	7.0%[44,45]	33.7% (28.4–38.9)	5.1 (4.2–6.2)	• Sorbitol-containing juices (eg, apple, prune, or pear) • Lactulose, polyethylene glycol, glycerin suppositories under physician supervision; referral to gastroenterology if needed
Any allergies	10.4%	24.3% (19.5–29.1)	2.6 (2.1–3.2)	• Awareness of increased risk and consideration of allergic etiology for skin, sleeping, or gastrointestinal concerns
Food/formula allergies	8.8%[46]	19.4% (15–23.8)	2.4 (1.9–3.1)	• Parent education of milk protein and food allergy symptoms, staged introduction of new foods, indications for diphenhydramine administration, and when to seek emergent care
Eczema	13.7%[20]			• Awareness of increased risk, targeted physical exam, standard pediatric eczema interventions
All SCT	–	47.6% (42–53.1)	3.5 (3.1–3.9)	
XXX only	–	31.6% (21.1–42)	2.3 (1.7–3.2)	
XXY and XYY	–	52.8% (46.4–59.2)	3.9 (3.4–4.4)	
Positional torticollis	3.9%[44,48]	29.4% (24.4–34.5)	7.5 (5.3–10.7)	• Targeted physical examination for identification • Recommend tummy time, neck stretching exercises, and positioning • Consider referral to physical therapy • Consider referral for molding helmet if associated with plagiocephaly
Male genitourinary abnormalities	–	–	–	• Targeted physical examination for cryptorchidism, hypospadias, chordee, webbing, short phallus • Referral to pediatric urology if abnormalities identified • Consider infant testosterone therapy if stretched penile length <2 cm in term infant
Cryptorchidism (XXY only)[c]	1.1%[49]	3.4% (1.4–5.5)	2.2 (1.1–4.5)	
Hypospadias	0.4%[50]	1.3% (0–2.5)	3.0 (1.0–9.4)	
Chordee	4.5%[51]	5.2% (2.7–7.6)	1.3 (0.73–2.3)	
Penis length z-score <-2.0	2.5%	3.4% (1.4–5.5)	1.7 (0.37–8.0)	
Strabismus	2.4%[52]	7.1% (4.3–10)	3.3 (2.2–5.0)	• Targeted physical examination with awareness of possible pseudostrabismus related to epicanthal folds • Referral to ophthalmology if present after 6 months of age
Cardiac septal defects	0.45%[53]	–	–	• Targeted cardiac examination • Echocardiogram and referral to cardiology if abnormal findings
All SCT	–	7.8% (4.8–10.8)	17.3 (11.8–25.3)	
XXX only	–	15.8% (7.6–24)	35 (20.9–59)	
XXY and XYY	–	5.2% (2.3–8)	11.4 (6.6–19.9)	
Renal malformations	0.46%[17]	–	–	
All SCT	–	4.5% (2.2–6.8)	10.1 (6.0–16.8)	• Renal ultrasound to evaluate for structural abnormalities • Referral to pediatric nephrology and/or urology if structural defects found
XXX only	–	13.2% (5.6–20.8)	29.2 (16.4–52.1)	
XXY and XYY	–	1.7% (0–3.4)	3.8 (1.4–10.1)	

(Continued on next page)

TABLE 5. Medical Conditions at Higher Risk in Infants with Prenatal SCT Diagnosis and Guidance for Clinical Care (Continued)

Feature	General Population Prevalence[a]	SCT Prevalence[b] (95% CI)	Relative Risk[b] in SCT	Considerations for Clinical Care
Hypotonia	8%[54]	38.5% (33.1–43.9)	3.9 (3.0–5.1)	• Close monitoring of motor development due to increased risk for delays • Referral for physical therapy if associated with delays • Further neurologic evaluation if severe or asymmetric
Other minor dysmorphologies (epicanthal folds, increased intercanthal distance, clinodactyly, ear differences)	–	–	–	• No clinical implications, reassurance to family

Abbreviation: SCT, sex chromosome trisomy.
[a] Estimated general pediatric population based on cited literature references.
[b] Reported as a single value for the pooled SCT study cohort if there were no statistically significant differences between SCT conditions. Otherwise, results reported as pooled value followed by individual percentages or RRs by SCT condition.
[c] XYY prevalence not different than the general population.

etiology. Regarding penile size, true micropenis on our examination was rare, with mean penile length z-score in XXY of −0.02 at 12 months in those not treated with testosterone. This is important, as there is a common belief that XXY is associated with short penile length. Although a thorough GU examination is advised, most babies will have typical genitalia. Subsequent analyses will evaluate serum hormone concentrations and relationship to health, physical, and developmental outcomes.

Despite a highly motivated study sample with over 90% attempting breastfeeding, breastfeeding difficulties were present in over one-half of the sample and associated with inadequate growth for a subset in the first months of life. We did not systemically evaluate quality of breastfeeding, reasons for breastfeeding challenges, or ankyloglossia, which warrant further study. We noted a high rate of frenotomy procedures with differences between karyotypes (27.5% in XYY). Ankyloglossia occurs in ∼7% of infants in the general population[34] and is a known cause of breastfeeding difficulties. Furthermore, frenotomy can be beneficial if ankyloglossia is present.[35,36] The high rate of frenotomy observed in our cohort highlights the need for additional research to identify the true prevalence and classifications of ankyloglossia in infants with SCT, the actual contribution to feeding problems, and whether frenotomy directly improves breastfeeding. Breastfeeding challenges may reflect neurodevelopmental delays in oral-motor planning and coordination, congruent with previous studies that have identified oral-motor dyspraxia in SCTs.[37–40] Other anatomical differences (such as micrognathia or high-arched palate),[41] low muscle tone, or poor endurance could also theoretically contribute to feeding difficulties; however, we did not observe a relationship between these features and feeding problems in our cohort. The relationship between early feeding problems and later developmental outcomes will be explored in future analyses as the cohort ages. From a clinical perspective, proactive support with lactation consultation may be beneficial, and it is important to appreciate that many infants with SCT were able to receive breast milk for a similar duration as the general population, either through adequate lactation support and/or expressed breast milk. Studies of the etiology of breastfeeding problems and specific interventions to support successful breastfeeding in this population are needed.

The prevalence of atopic conditions was one of the most striking medical findings occurring in the first year, with nearly one-half having eczema and 1 in 5 having a food allergy. This association has been previously reported in SCTs, although we did not expect to find such high prevalence within the first year of life. Although we did not systematically capture disease severity, eczema was, anecdotally, rarely severe and improved with age. Nevertheless, these findings suggest an altered immune system response in infants with SCT that warrants additional investigation.

We acknowledge limitations of the study, including sample size discrepancies between SCT groups, subjectivity of some of the outcomes, and reliance on published reference data for comparison to the general population. Overestimation of some findings may occur, given that a diagnosis of a genetic condition may introduce bias to search for and potentially identify abnormalities. It is also possible that our study underestimates the true prevalence of congenital anomalies in SCTs, as our study does not include fetuses that may have been spontaneously or electively terminated. There are missing data points in our physical examination data due to varying enrollment ages and COVID-19 restrictions, which may have impacted growth trajectory data. There is ascertainment bias in our sample with recruitment from family advocacy groups, social media, and genetic counseling referrals, and a high proportion of families with higher socioeconomic status and education compared to the US population. Recognizing these limitations, this study contributes vital statistics describing early phenotypic

features in SCTs and has important counseling and clinical management implications.

As this cohort ages through the toddler and school-aged years, comprehensive prospective data collection will allow for broader descriptions on the natural history of medical features into childhood. Ongoing recruitment priorities include increased racial, ethnic, and socioeconomic diversity of the study cohort and more balanced sample sizes between the 3 SCT conditions. Analyses exploring the relationships of family medical history, neurodevelopmental outcomes, reproductive hormone concentrations, and other systemic biomarkers may identify specific predictors or subpopulations most at risk for poorer health outcomes that would guide more intensive early supports, therapies, and medical follow-up.

As prenatal cfDNA screening is now routinely identifying SCT conditions and more infants are presenting to pediatricians with a prenatal diagnosis, there is an acute need for contemporary evidence on perinatal and infant comorbidities to guide counseling and care. Our results emphasize that counselors and pediatricians can reassure families that most infants have a typical perinatal course and that most medical conditions that arise are common in the general pediatric population, well known to pediatric providers, and respond to evidence-based interventions. For those medical conditions that are indeed more common and cause challenges in the first year of life, anticipatory guidance and close monitoring can facilitate appropriate interventions and timely support.

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ABBREVIATIONS

AGA: average for gestational age
AMA: advanced maternal age
ASD: atrial septal defect
BW: birth weight
BL: birth length
CDC: Centers for Disease Control and Prevention
cfDNA: cell-free DNA
COMIRB: Colorado Multiple Institutional Review Board
CVS: chorionic villus sampling
GU: genitourinary
LGA: large for gestational age
NICU: neonatal intensive care unit
NIH: National Institutes of Health
PE: pressure equalizing
RR: relative risk
SCT: sex chromosome trisomies
SGA: small for gestational age
VSD: ventricular septal defect

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