

Baseline Characteristics of Infants With Atypical Genital Development: Phenotypes, Diagnoses, and Sex of Rearing

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Purpose: Little is known about the phenotypes, diagnoses, and sex of rearing of infants with atypical genital development in the United States. As part of a multicenter study of these infants, we have provided a baseline report from US difference/disorder of sex development clinics describing the diagnoses, anatomic features, and sex of rearing. We also determined whether consensus guidelines are followed for sex designation in the United States.

Methods: Eligible participants had moderate-to-severe genital atypia, were aged <3 years, and had not undergone previous genitoplasty. Karyotype, genetic diagnosis, difference/disorder of sex development etiology, family history, and sex of rearing were collected. Standardized examinations were performed.

Results: Of 92 subjects, the karyotypes were 46,XX for 57%, 46,XY for 34%, and sex chromosome abnormality for 9%. The median age at the baseline evaluation was 8.8 months. Most 46,XX subjects (91%) had congenital adrenal hyperplasia (CAH) and most 46,XY subjects (65%) did not have a known diagnosis. Two individuals with CAH underwent a change in sex of rearing from male to female within 2 weeks of birth. The presence of a uterus and shorter phallic length were associated with female sex of rearing. The most common karyotype and diagnosis was 46,XX with CAH, followed by 46,XY with an unknown diagnosis. Phenotypically, atypical genitalia have been most commonly characterized by abnormal labioscrotal tissue, phallic length, and urethral meatus location.

Abbreviations: CAH, congenital adrenal hyperplasia; DSD, disorder of sex development; 21-OH, 21-hydroxylase; OVT, ovotesticular; PAIS, partial androgen insensitivity syndrome; SCA, sex chromosome abnormality.

Conclusions: An increased phallic length was positively associated with rearing male. Among the US centers studied, sex designation followed the Consensus Statement recommendations. Further study is needed to determine whether this results in patient satisfaction.

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Freeform/Key Words: disorder of sex development, intersex, hypospadias, ambiguous genitalia, congenital adrenal hyperplasia

Disorders of sex development (DSDs) are congenital medical conditions in which atypical chromosomal, gonadal, and/or phenotypic sex features in an individual [1]. This term encompasses a wide variety of diagnoses that can present from infancy to adulthood. The approach to DSD care has been evolving. In the 1950s, recommendations regarding intersex management included early genital surgery and confounding recommendations about both honesty and concealment of the diagnosis, leading many providers to opt for concealment [2]. The 2006 International Consensus Statement on Intersex Disorders and the 2016 Global Update have acknowledged these controversial issues and made management recommendations, including those about multidisciplinary care, sex designation, and genital surgery [1, 3]. However, concrete recommendations have been hindered by inadequate data. Although data in national and international registries are increasing, thus far, the demographic and phenotypic data about patients who present to DSD clinics have been limited and not well characterized [4–6].

Little is known about the phenotypes, diagnoses, and sex of rearing practices of infants who present with atypical genitalia to clinics in the United States. In the complicated situation requiring a choice of sex designation at birth, it has been recommended one consider the likely etiology of the DSD, the adult gender identity, sexual function, fertility, requirement for lifelong hormones, surgical options, fetal exposure to androgens, malignancy risk, and psychosocial factors [3]. The 2006 Consensus Statement changed the approach for individuals with many types of 46,XY DSDs, who would have previously been assigned a female gender, to recommend male rearing. As a result of these recommendations, the male sex designation has been increasing in Europe [7]. It is unknown, however, whether sex is being assigned according to the consensus recommendations in the United States.

As part of an ongoing, cross-sectional, observational, multicenter study assessing the medical, surgical, and psychological outcomes of children and families affected by atypical genitalia, we have provided a report on infants with atypical genitalia, as defined by the Prader [8] and Quigley [9] scale scores, in the United States. We aimed to (i) describe the diagnoses, (ii) characterize the anatomic features, (iii) determine whether US centers are following the consensus guidelines for sex designation, and (iv) report any patterns of changes in the sex of rearing. The reported data include information provided at study entry.

1. Materials and Methods

A. Participants

Participants from 12 children's hospitals in the United States specializing in DSD care were prospectively enrolled in the study from 2013 to 2017: Cook Children's Hospital, Children's Hospital Colorado, University of Oklahoma Health Sciences Center, St. Louis Children's Hospital, University of California, San Francisco, New York Presbyterian Hospital, Boston Children's Hospital, Ann and Robert H. Lurie Children's Hospital of Chicago, Women and Children's Hospital of Buffalo, Children's Hospital of Philadelphia, Children's Hospital of Michigan, and Cincinnati Children's Hospital Medical Center. The parents of the subjects

provided written informed consent, and the local institutional review boards at all sites approved the present study.

The inclusion criteria were moderate to severe genital atypia as defined by a Prader scale score of 3 to 5 in a 46,XX child or a Quigley scale score of 3 to 6 in a child with 46,XY or sex chromosome abnormality (SCA), aged <3 years, and no previous genitoplasty at enrollment. The exclusion criteria were infants and children with malformations of organ systems other than urogenital and families with a limited comprehension of either English or Spanish.

B. Clinical Information

The following data were collected for each child: prenatal and family history (immediate or extended family member) karyotype, genetic diagnosis, category of DSD, sex of rearing, and imaging study findings. The genetic evaluation varied by center and was not dictated by study protocol. The local pediatric urologist performed a standardized genital examination, assessing the stretched phallic length, presence and degree of hypospadias, gonad type (imaging, visualization, or biopsy), presence and degree of chordee, appearance of labia or scrotum, and the presence of a vagina and uterus (by imaging or cystoscopy). The Prader and/or Quigley scale scores were documented.

C. Statistical Analysis

Grouped data are described as the mean \pm SD or counts and percentages, as appropriate. Comparisons of continuous variables (*e.g.*, age, phallic length) were performed using ANOVA and the Student *t* test for the comparison of two groups. Comparisons were rechecked using nonparametric methods (*e.g.*, Mann-Whitney *U* tests). All results were consistent. Categorical measures were compared using Pearson χ^2 tests. *P* values are reported to two significant digits up to a limit of four decimal places. *P* values <0.05 were considered to indicate statistical significance. Data were analyzed using R, version 3.5.0 (2018-04-23; gmodels, version 2.16.2; R Foundation, r-project.org).

2. Results

A. Diagnosis

We enrolled 99 subjects. Of the 99 participants, 6 withdrew from the study, and 1 child did not have a documented karyotype. Thus, the findings from 92 subjects were included in the present report. The mean age at the baseline evaluation was 10 ± 7.0 months (median, 8.8; range, 0 to 29). Of the 92 children, 53 (57%) had a 46,XX karyotype, 31 (34%) had a 46,XY karyotype, and 8 (9%) had SCA. Of those with a 46,XX karyotype, the most common diagnosis was congenital adrenal hyperplasia (CAH) due to 21-hydroxylase (21-OH) deficiency (21-OH CAH; 48 of 53). Other 46,XX DSD diagnoses included 11-hydroxylase deficiency, ovotesticular (OVT) DSD, urogenital sinus, P450 oxidoreductase deficiency, and unknown DSD. Of those with 46,XY DSD, the most common diagnosis was unknown (20 of 31). Other diagnoses included partial gonadal dysgenesis, 5α -reductase deficiency, partial androgen insensitivity syndrome (PAIS), OVT, 17β -hydroxysteroid dehydrogenase deficiency, deletion of *DMRT 1* and *DMRT2*, and *NR5A1* mutation. Among those with SCA, the DSD diagnoses included mixed gonadal dysgenesis (3 of 8), partial gonadal dysgenesis, OVT, and unknown. The karyotypes are listed in [Table 1](#). Genetic evaluation beyond determination of the karyotype was performed per individual institutional practice for 22 patients. Of the 22 patients, a genetic DSD diagnosis was confirmed in 20 ([Table 2](#)).

B. Family History

Of 86 subjects, 13 (15%) had a family history of DSD (17% of those with a 46,XX karyotype and 16% with a 46,XY karyotype). Of those with a 46,XX karyotype, all had a family history of

Table 1. SCA Karyotypes and Sex Designation

Sex Designation	Karyotype
Raising female (n)	
1	45,X/46,XY
1	45,X/46,XY/47,XXY
Raising male (n)	
3	45,X/46,XY
1	45,X/46,X,idic(Y)(q11.23)
1	46,XX/48,XXYY
Undecided (n)	
1	46,XX/47,XXY

21-OH CAH (sisters and extended relatives). Of those with a 46,XY karyotype, the family history included one with PAIS (sister), one with 5 α -reductase deficiency (maternal uncle), and three who specified other (brothers and extended relatives). Ten percent of the 46,XY subjects reported a family history of hypospadias; however, none of those with 46,XX or SCA reported a family history of hypospadias.

C. Sex of Rearing

Sex of rearing was documented at study entry. Of the 92 subjects, 57 (62%) were being raised female, 34 (37%) were being raised male, and 1 was undecided. All 46,XX children were being raised female. Of the 31 children with a 46,XY karyotype, 29 (93%) were being raised male and 2 (7%) were being raised female, 1 with OVT and 1 with PAIS. Of the eight children with SCA, five (63%) were being raised male, two (35%) female, and one (12%) was undecided. Two subjects' initial sex designation had been changed from male to female within the first 2 weeks of life. Both had a diagnosis of 46,XX DSD due to 21-OH CAH.

D. Phenotype

The baseline phenotypic features are listed in Table 3. The mean stretched phallic length differed significantly among the karyotypes (ANOVA; $P = 0.0009$) when adjusted for age. Those with a 46,XY karyotype had a significantly larger mean phallic length than those with a 46,XX karyotype ($P = 0.0007$). No difference was found in the meatal location when stratified by karyotype ($P = 0.25$). Overall, most had a penoscrotal meatus (55%), followed by scrotal (23%), proximal (8%), perineal (6%), midshaft (4%), distal penile (2%), and glanular (2%). Of the subjects, 95% had partial fusion labioscrotal tissue, and no difference was found among karyotypes ($P = 0.54$). We also found a statistically significant difference in the severity of chordee among karyotype groups ($P < 0.0001$), with the 46,XY subjects having substantially more severe chordee than the 46,XX subjects ($P < 0.0001$). We also found a

Table 2. Molecular Genetic Diagnosis (Affected Gene) and Sex Designation

Karyotype and Affected Gene	Sex Designation	
	Raising Female	Raising Male
46,XX		
CYP21A2	12	0
POR	1	0
46,XY		
AR	1	
HSD17B3	0	2
SRD5A2	0	2
NR5A1	0	1
DMRT1 and DMRT2	0	1

Table 3. Baseline Phenotypic Characteristics

Cohort Characteristic (Full Cohort, n = 92)	Karyotype (%)			P Value
	46,XY	46,XX	SCA	
Sex of rearing (n = 92)				NA
Male	29 (32)	0 (0)	5 (5)	
Female	2 (2)	53 (58)	2 (2)	
Undecided	0 (0)	0 (0)	1 (1)	
Phallic length, cm (n = 89)				0.0003 ^a
Mean ± SD	3.0 ± 0.92	2.1 ± 0.89	2.9 ± 0.64	
Range	1.0–4.5	0.2–5.0	1.9–4.0	
Meatal location (n = 51)				0.25
Glanular	0 (0)	1 (2)	0 (0)	
Distal penile	0 (0)	1 (2)	0 (0)	
Midshaft	0 (0)	1 (2)	1 (2)	
Proximal penile	2 (4)	2 (4)	0 (0)	
Penoscrotal	14 (27)	10 (20)	4 (8)	
Scrotal	10 (20)	1 (2)	1 (2)	
Perineal	2 (4)	0 (0)	1 (2)	
Labiocrotal abnormality (n = 92)				0.54
Yes	30 (32.6)	49 (53.3)	8 (8.7)	
No	1 (1.1)	4 (4.3)	0 (0)	
Gonad characteristics ^b				NA
Ovary/ovary	0 (0)	52 (98)	0 (0)	
Testis/testis	26 (84)	0 (0)	3 (37.5)	
Testis/ovary	2 (6.5)	0 (0)	1 (12.5)	
Ovotestis/ovary	0 (0)	1 (2)	0 (0)	
Streak/testis	2 (6.5)	0 (0)	2 (2.5)	
Unsure/testis	1 (3)	0 (0)	1 (12.5)	
Unsure/unsure	0 (0)	0 (0)	1 (12.5)	
Presence of chordee (n = 85)				<0.0001 ^c
None	3 (3.5)	20 (23.5)	0 (0)	
Mild	0 (0)	6 (7.1)	1 (1.2)	
Moderate	8 (9.4)	15 (17.6)	5 (5.9)	
Severe	19 (22.4)	6 (7.1)	2 (2.4)	
Presence of a uterus (n = 90)				<0.0001 ^d
Yes	4 (4.4)	53 (58.9)	4 (4.4)	
No	27 (30.0)	0 (0)	2 (2.2)	
Presence of a vagina (n = 85)				<0.0001 ^e
Yes	8 (9.4)	50 (58.8)	3 (3.5)	
No	22 (25.9)	1 (1.2)	1 (1.2)	

Abbreviation: NA, not applicable.

^a $P = 0.0002$ (46,XY vs 46, XX).

^bPercentages calculated from karyotype categories.

^c $P < 0.0001$ (46,XY vs 46, XX); $P = 0.0023$ (none vs any chordee for 46,XY vs 46, XX).

^d $P < 0.0001$ (46,XY vs 46, XX).

^e $P < 0.0001$ (46,XY vs 46, XX).

statistically significant difference in the presence of a uterus among karyotype groups ($P < 0.0001$). All the 46,XX subjects had a uterus compared with only 4 of the 46,XY subjects (13%). Among the children with SCA, four had a uterus, two did not, and the presence of a uterus was unknown for two children. We also found a statistically significant difference in the presence of a vagina among the groups ($P < 0.0001$), with those with a 46,XX karyotype substantially more likely (98%) to have a vagina than those with a 46,XY karyotype (27%; $P < 0.0001$).

E. Quigley and Prader Scores

Quigley scores were reported for 28 46,XY and 4 SCA subjects. The mean Quigley score for the 46,XY subjects was 3.7 ± 0.8 (median, 3.5; range, 3 to 6.5) and 4 ± 0.8 (median, 4; range, 3 to 5)

for SCA subjects. Prader scores were reported for 2 subjects with 46,XY, 52 with 46,XX, and 4 with SCA. The Prader score for both 46,XY subjects was 4. The mean Prader score for the 46,XX subjects was 3.6 ± 0.7 (median, 3; range, 3 to 5) and for SCA subjects was 3.5 ± 0.6 (median, 3; range, 3 to 4).

F. Predictive Phenotypic Factors for Sex Designation

The presence of a vagina and/or uterus and phallic length were substantially associated with the female and male sex designation, respectively ($P = 0.0002$; Fig. 1). Of the subjects with a vagina, 98% were being raised female, of the subjects with a uterus, 97% were being reared female, and of those with both a uterus and a vagina, 98% were being raised female. Of the subjects being reared male, the mean phallic length was longer (3.0 ± 0.83 cm) than that in the subjects being reared female (2.2 ± 0.91 cm; $P < 0.0001$).

3. Discussion

The present cross-sectional, multicenter study has described the phenotypes and patterns in sex designation of infants with moderate to severe genital atypia at US centers specializing in DSDs. Most of the infants had a 46,XX karyotype and a diagnosis of 21-OH CAH, followed by 46,XY with no known diagnosis. Our results showed similarities and differences compared with other recent reports describing DSD populations. In a European population, the dsd-LIFE group studied all individuals with DSDs, of all ages, and not just those with genital ambiguity [4]. They also included patients with Turner syndrome and those with Klinefelter syndrome. When the latter diagnoses were excluded, their study population included 48% with 46,XX DSDs (89% CAH), 43% with 46,XY DSDs, and 9% with SCA. The proportion of 46,XX DSDs due to CAH was similar in our studies. Overall, however, they found a greater percentage of 46,XY DSDs, which likely resulted from the inclusion of 46,XY DSDs with no

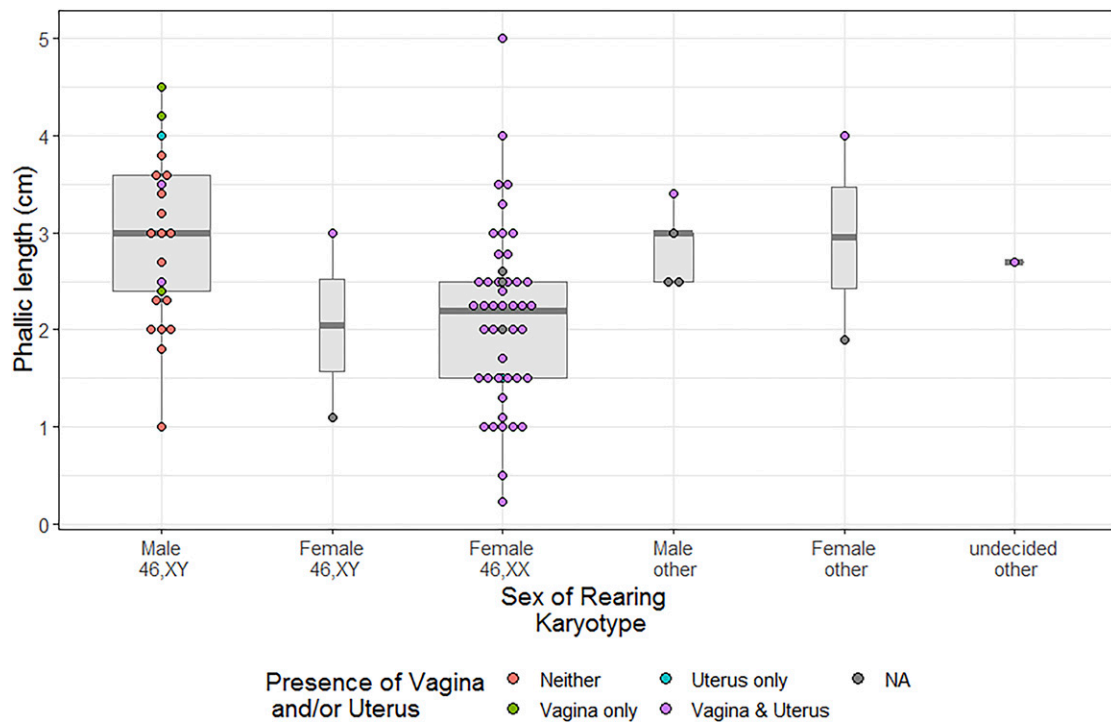


Figure 1. Predictive phenotypic factors for sex designation: phallic length and presence of vagina and uterus.

virilization (Quigley score, 7), owing to conditions such as complete androgen insensitivity syndrome (71 of 222 in their study). They also reported only 3% of 46,XY individuals with an unknown diagnosis [4]. This difference in the proportion of unknown 46,XY diagnoses might have been related to the populations studied or differences in the standard clinical evaluation. The mean age in the dsd-LIFE study was 32.4 years; thus, the lifespan to determine a diagnosis was longer, and their population might not have included individuals with proximal to perineal hypospadias increasingly being evaluated. In a Brazilian population, De Paula *et al.* [10] described individuals with DSDs that included a variety of genital phenotypes. They found more subjects with 46,XY (61%) than with 46,XX (30%) and similar proportion of mosaic subjects (8%) [10]. They also found a similar predominance of CAH among the 46,XX diagnoses (66%) and unknown diagnosis among the 46,XY subjects (41%). Finally in the United States, the DSD–Translation Research Network also reported on individuals with DSD (n = 144) and found more subjects with 46,XY (50%) than with 46,XX (36%), with 15% having sex chromosome mosaicism [5]. Again, inclusion of those without genital ambiguity likely explains the greater percentage of those with a 46,XY chromosomal complement.

Our study identified a family history of DSD in 15% of the 92 subjects and a family history of hypospadias in 10% of those with 46,XY DSD, consistent with the limited available data. Brauner *et al.* [11] reported that 22% of those with 46,XY DSDs had a family history of DSD. However, it is important to note they had included infertility as positive family history for a DSD [11]. Also, they had included all those with DSDs but not specifically ambiguous genitalia. In evaluating isolated hypospadias, which can be associated with a DSD, Ollivier *et al.* [12] recently reported that a positive family history has been underestimated in children. Although previous studies have indicated a family history in ~10% of individuals, their study found a family history in 22% [12–14]. Thus, our findings were similar to those of previous studies assessing family history.

Our study cohort included only those with moderate to severe genital ambiguity, as defined using the Prader (score, 3 to 5) and Quigley (score, 3 to 6) scales. The Quigley and Prader scores among the 46,XY and 46,XX individuals varied widely. However, the median scores on each scale were similar in the degree of atypia. The scores for those with SCA had much less variability. Within the entire cohort, we were able to specifically characterize genital ambiguity. Overall, most subjects had abnormal labioscrotal tissue, an abnormal phallic length [15], and an abnormal location of the urethral meatus. The most common meatal location was penoscrotal, regardless of the karyotype. In general, a 46,XY karyotype was more commonly coupled with a longer phallic length, more chordee with greater severity, and the lack of a uterus. Surgical management was not the focus of our analysis; however, given that this population had moderate to severe atypical genitalia, these are the patients for whom surgical genitoplasty options will usually be offered. Proposed legislation in the United States has called for a moratorium on such surgery. US providers might be increasingly caring for children who will not undergo genital surgery, and it is important to understand the anatomic features of this population.

The sex designation in the present cohort was associated with multiple factors, including diagnosis, karyotype, the presence of a uterus, and phallic size. All individuals with 21-OH CAH were ultimately assigned the female sex designation, regardless of phallic size, which ranged from 0.23 to 5.0 cm. All 46,XX individuals were being raised female, and the vast majority of 46,XY infants were being raised male. The length of the phallus was positively associated with the male sex designation. The sex designation of individuals with SCA varied more, with no clear associations with the presence of a uterus or the phallic size length. Sex redesignation was very rare and only occurred in 2 individuals with 21-OH CAH (phallic length, 3.5 cm and 5 cm) and within the first 2 weeks of life. These findings indicate that the Consensus Statement [3] recommendations for sex designations were followed at these 12 US clinics specializing in the delivery of care for DSDs.

Evidence-based recommendations regarding the management of DSD conditions have been hampered by the lack of long-term, prospective data. These participants will continue to

be followed up, and collection of participant and parent outcomes is ongoing. The present baseline analysis has shown that our study population is similar to other groups, such as the dsd-LIFE and the DSD–Translation Research Network populations; thus, our study conclusions will be broadly comparable, specifically for those born with atypical genitalia. In our analysis, the phenotypic features were associated with the sex designation. We have reported this finding; however, we do not intend this as a recommendation and the appropriateness of these choices will require assessment in the future.

The present study was limited in that it was a cross-sectional analysis of baseline data regarding the phenotype, diagnosis, and sex of rearing. Our study was not intended to provide predictive factors or management guidelines. In addition, our study did not represent all DSD conditions, only those for those individuals who had presented with moderate to severe atypical genitalia at 12 programs. We only included participants without malformations in other organ systems; thus, our results are not generalizable to children with atypical genitalia as a part of a broader syndrome affecting multiple organ systems. In addition, data were not collected qualitatively regarding parental cultural, religious, or philosophical views, which could have influenced the parents' decisions. Finally, our sample could have been biased because the participants were recruited from select DSD referral centers.

4. Conclusions

The present study has provided a description of the diagnoses and phenotypes of a population referred to national DSD centers, including atypical genitalia in infancy. Many DSD conditions present in other ways and later in life; thus, our analysis is not descriptive of the full DSD clinic population. In large populations with atypical genitalia, CAH has been the most common diagnosis, consistent with our data. We found that most individuals with a uterus are being raised female; thus, future fertility could be a factor in the decision regarding sex of rearing or surgery. The karyotype, diagnosis, and internal and external phenotypic features are associated with the sex of rearing. Finally, the sex designation at these DSD centers in the United States has been following the recommendations of the Consensus Statement.

Acknowledgments

The authors thank the parents and children who participated in our study.

Financial Support: All phases were supported by the National Institutes of Health (grant R01HD074579), under the direction of the primary investigators (A.B.W., L.L.M.).

Author Contributions: All the authors made substantial contributions to the data collection and drafting of the manuscript.

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Disclosure Summary: P.A. serves on the pediatric advisory group and is a clinical investigator for Allergan. Y.-M.C. serves on the scientific advisory board for Abbvie. D.P.P. serves on the scientific advisory board for the CARES Foundation and as cofounder and board member of Promethean Surgical Devices, Inc. None were directly involved in the funding or design of the present study. The remaining authors have nothing to disclose.

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