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Development of specific growth charts for children with Fanconi anemia

Crystal Barbus[1] | Arpana Rayannavar[1] | Bradley S. Miller[1] | Mica J. Jenkins[2,3] | O. Yaw Addo[2,3] | Ahmad Rayes[3] | Natasha Ahrweiler[1] | Alisha Olson[1] | Zachary Pohlkamp[1] | John E. Wagner[4] | Margaret L. MacMillan[4]

[1]Division of Endocrinology, Department of Pediatrics, University of Minnesota Medical School and M Health Fairview Masonic Children's Hospital, Minneapolis, Minnesota, USA

[2]Rollins School of Public Health, Emory University, Atlanta, Georgia, USA

[3]Nutrition and Health Sciences Doctoral Program, Laney Graduate School of Emory University, Atlanta, Georgia, USA

[4]Division of Blood and Marrow Transplantation & Cellular Therapy, Department of Pediatrics, University of Minnesota, Minneapolis, Minnesota, USA

Correspondence
Bradley S. Miller, Division of Endocrinology, Department of Pediatrics, University of Minnesota Medical School and MHealth Fairview Masonic Children's Hospital, Minneapolis, MN, USA.
Email: mille685@umn.edu

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Abstract

Patients with Fanconi anemia (FA) are often perceived to have poor growth when general population growth curves are utilized. We hypothesize that FA patients have unique growth and aimed to create FA-specific growth charts. Height and weight data from ages 0 to 20 years were extracted from medical records of patients treated at the Fanconi Anemia Comprehensive Care Clinic at the University of Minnesota. Height, weight, and BMI growth curves were generated and fitted to reference percentiles using the Lambda-Mu-Sigma method. FA-specific percentiles were compared to WHO standards for ages 0–2 and CDC references for ages 2–20. In FA males, the 50th height- and weight-for-age percentiles overlap with the 3rd reference percentile. In FA females, only the 50th height-for-age percentile overlaps with the 3rd reference percentile. For weight, FA females show progressive growth failure between 6 and 24 months followed by stabilization around the 50th percentile. The FA BMI-for-age percentiles show similar patterns to the weight-for-age percentiles but have different timing of onset of adiposity rebound and broader variability in females. Growth in FA patients follows a different trajectory than available normative curves. FA-specific growth charts may be useful to better guide accurate growth expectations, evaluations, and treatment.

KEYWORDS
delayed growth, disease-specific chart, Fanconi anemia, growth, hematopoietic cell transplant, LMS method

1 | INTRODUCTION

Fanconi anemia (FA) is a rare, autosomal recessive condition, estimated to occur in 1 in 130,000 live births (McReynolds et al., 2020). FA is characterized by a deficiency in DNA repair proteins that puts patients at risk of bone marrow failure at an early age and causes a later predisposition for cancer (Soulier, 2011). Known genetic variants leading to FA include changes in 23 different *FANC* genes (Mehta & Ebens, 2021) with the most common being *FANCA*, *FANCC*, *FANCG*, and *FANCD2* (Soulier, 2011).

Short stature is common in individuals with FA and is due to a combination of endocrine and non-endocrine causes (Petryk et al., 2015). Growth has been shown to be impacted as early as the pre-natal period (Auerbach, 2009). Half of all patients with FA are

small for gestational age (SGA) at birth with an average birth weight of −1.8 standard deviation scores (SDS) (Petryk et al., 2015). Due to post-natal growth failure, of those SGA patients with FA, only 25% rebound to normal height as children, compared to 90% of SGA patients without FA (Petryk et al., 2015). Adult height has been previously reported to be −2 SDS or more below the normal reference range in roughly 60% of individuals with FA (Petryk et al., 2015).

Endocrine factors contributing to short stature in FA include hormonal deficiencies due to congenital hypothalamic–pituitary abnormalities and/or acquired hormonal deficiencies inherent to FA or because of chemotherapy and radiation therapy administered before hematopoietic cell transplant (HCT). Patients with FA on average have significantly smaller pituitary volumes (Johnson-Tesch et al., 2017; Petryk et al., 2015) and can also have congenital midline central nervous system or skull base posterior fossa abnormalities, such as hypoplastic clivus, hypoplastic adenohypophysis, ectopic posterior pituitary and platybasia (Johnson-Tesch et al., 2017). Hypoplastic adenohypophysis and pituitary stalk interruption syndrome (PSIS) in FA can result in growth hormone (GH) deficiency (GHD) and thyroid stimulating hormone deficiency (TSHD) (Petryk et al., 2015). Some patients with FA found to have GHD have received GH replacement therapy (GHRT) (Forlenza et al., 2014). However, because short stature in FA is not explained by endocrine causes alone, GHRT often does not adequately normalize growth (Petryk et al., 2015). Primary hypothyroidism and central hypothyroidism/TSHD (congenital or post-HCT) may also contribute to poor growth (Petryk et al., 2015). Additionally, hypogonadism can cause deficient pubertal growth in individuals with FA, most likely due to decreased sex steroid production due to gonadal failure or gonadotropin deficiency (Petryk et al., 2015).

FA patients with normal endocrine function are often still affected by short stature, although those with endocrine dysfunction are more likely to have stunted growth (Rose et al., 2012; Wajnrajch et al., 2001). Non-endocrine causes of poor growth in FA include nutritional inadequacies (Barnum et al., 2016; Petryk et al., 2015) and skeletal abnormalities, such as scoliosis, congenital hip dysplasia, and femur malformations (Bhandari et al., 2022; Glanz & Fraser, 1982). Patients with FA are often thin as well, with an average weight of −1.26 SDS (Wajnrajch et al., 2001). Nutritional factors leading to poor growth in FA are due to a combination of insulin deficiency and/or sensitivity, increased caloric needs, and decreased oral intake (potentially due to underlying gastrointestinal issues) (Petryk et al., 2015). Low weight and BMI in FA may also be due to low muscle mass (Silva et al., 2017). However, body mass index (BMI) has been reported by Rose et al. (2012) to be −0.6 SDS for males and −0.8 SDS for females, while Giri et al. (2007) also found BMI to be normal for 51% of individuals with FA and overweight for 27%.

Despite short stature being regarded as a major characteristic of FA (Auerbach, 2009), there is currently no established method of accurately monitoring growth expectations for individuals with this condition. Use of bone age to estimate adult height is viewed as falsely inflating projected growth outcomes in FA as this assumes normal hormone production, nutrition, and puberty onset, which are not seen in FA (Petryk et al., 2015). Hormone response and duration of puberty may also be abnormal in individuals with FA. Mid-parental target height is frequently not appropriate for setting expected growth in patients with FA as the variation in adult height seen in FA exceeds the normal variation in the population estimated using mid-parental target height (Petryk et al., 2015).

Disease-specific growth charts have already been developed and implemented in the clinical setting for several other conditions, such as Down syndrome, Prader-Willi syndrome, Williams syndrome, Noonan syndrome, and Turner syndrome (Isojima et al., 2016; Malaquias et al., 2012; Martin et al., 2007; Nagai et al., 2000; Styles et al., 2002; Witt et al., 1986). Due to the differences in growth in children with FA compared to the general population, we aimed to create representative disease-specific growth curves using a cohort of patients with FA treated at the University of Minnesota.

2 | MATERIALS AND METHODS

2.1 | Editorial policies and ethical considerations

This study was approved by an ethics committee through the University of Minnesota Institutional Review Board. Informed consent was obtained from all subjects/guardians for the use of their health information in this project.

2.2 | Data collection

The Bone Marrow Transplant (BMT) Database at the University of Minnesota was used to identify patients with FA treated at the Fanconi Anemia Comprehensive Care Center at the University of Minnesota. Age, sex, height, weight, and head circumference data from birth until age 20 years old were abstracted from electronic health records (EHR) beginning in spring of 2011 when EPIC was instituted as the EHR at the FA Comprehensive Care Center. Additional data were abstracted including results of *FANC* gene variant testing and treatment data such as HCT status and use of growth hormone therapy.

2.3 | Generation of growth curves

Patient growth trajectories were visualized by plotting longitudinal anthropometric data for height, weight, and BMI serially by clinic visits for age (i.e., spaghetti plots). Prior to statistical modeling, all de-identified patient data were screened for data quality issues such as same-day anthropometric measurements, duplicate measurements, and last measurement carried-forward using a pediatric growth cleaner statistical tool (Daymont et al., 2017). The Lambda-Mu-Sigma (LMS) growth modeling method was then used to fit attained size-for-age growth functions (height-for-age, weight-for-age, and BMI-for-age) from which reference percentile ranges for children with FA were estimated. The LMS modeling technique is from the Generalized Additive Model for Location Scale and Shape (GAMLSS) family of statistical

approaches (Rigby & Stasinopoulos, 2004). It is a modeling methodology based on penalized maximum likelihood estimation with cubic splines to smooth for roughness in age-related growth channels to calculate percentiles (Cole & Green, 1992). Extensive statistical and visual diagnostics GAMLSS tools were used in selecting our final models.

To compare differences with normative growth, the FA-specific percentiles charts were then overlaid on WHO standards for ages 0–2 years old and CDC references for ages 2–20 years old.

3 | RESULTS

In total, we reviewed the charts of 260 patients with FA. One hundred twenty-two patients (57 female) had available data in the Epic EHR. Growth data from 13,110 unique clinic visits were used. Of the 122 patients with FA included in the creation of our disease-specific growth charts, 87 patients (71%) had received an HCT. Thirty-five patients (29%) had received growth hormone therapy. Of note, four patients within our cohort had limited data within their Epic EHR, so it is uncertain whether they had or had not received growth hormone treatment. The majority (56%) of patients with available data had *FANCA*. The characteristics of our study participants are provided in Table 1.

Figures 1–3 and Figures 4–6 depict the generated FA-specific growth curves overlaid on the CDC or WHO reference curves, respectively. Head circumference curves were not generated because there was only a limited number of patients (17) that had at least 1 head circumference measurement within their Epic EHR. This is most likely because the majority of patients had already surpassed the age when head circumference measurements were routinely recorded as part of clinical care when they established care at the FA Comprehensive Care Center.

Growth patterns of patients with FA varied significantly from the reference curves across the entire monitored growth period of ages 0–20 years old. Comparison of growth in regard to height shows that the 50th height-for-age percentile for children with FA overlaps the 3rd percentile for the CDC reference population for both males and females (Figure 1).

Weight-for-age was low at 6 months with some improvement between 6 and 24 months in both sexes (Figure 5). For males only, the 50th weight-for-age percentile for children with FA again overlaps the 3rd percentile for the CDC reference population (Figure 2). However, although weight-for-age percentile curves in FA males are consistently low from 6 months to 20 years (Figures 2 and 5), in FA females, there is evidence of progressive growth failure between 6 and 24 months and then subsequent stabilization of the 50th weight-for-age percentile below the 50th percentile for the CDC reference population (Figure 5). Females with FA have lower than average weight relative to the reference population, but the variation in weight at the extreme percentiles is broader than the CDC reference population (Figure 2). The 3rd percentile for weight for females with FA was below the CDC reference population, while the 97th percentile was similar between the populations.

TABLE 1 Characteristics of study cohort ($n = 122$).

Characteristic	
Male sex, *n* (%)	65 (53.3)
Received HCT, *n* (%)	87 (71.3)
Received GHRT, *n* (%)	35 (28.7)
Received both HCT and GHRT, *n* (%)	27 (22.1)
Age (mean, range), months	108.1 (0.0, 240.0)
FA complementation group	
FANCA, *n* (%)	68 (55.7)
FANCC, *n* (%)	17 (13.9)
FANCD1, *n* (%)	4 (3.3)
FANC other[a], *n* (%)	28 (23.0)
FANC unknown, *n* (%)	5 (4.1)
Anthropometric measurements	
Mean height, cm	121.3
Mean weight, kg	25.35
Mean BMI, kg/m^2	17.05
Mean height SDS[b] ($n = 3077$, mean age = 113.6 mos.)	−1.87
Mean weight SDS[b] ($n = 6224$, mean age = 102.5 mos.)	−1.65
Mean BMI SDS[a] ($n = 2879$, mean age = 114.3 mos.)	−0.73
Anthropometric indicators[c]	
Percent with BMI SDS <−2 ($n = 546$), %	18.97
Percent with BMI SDS between −2 to 0 ($n = 1378$), %	47.86
Percent with BMI SDS ≥0 ($n = 955$), %	33.17
Percent with BMI > 85th percentile ($n = 424$), %	14.73
Percent with BMI > 95th percentile ($n = 134$), %	4.65

Note: *n* is number of instances; % is percentage of participants with data available.

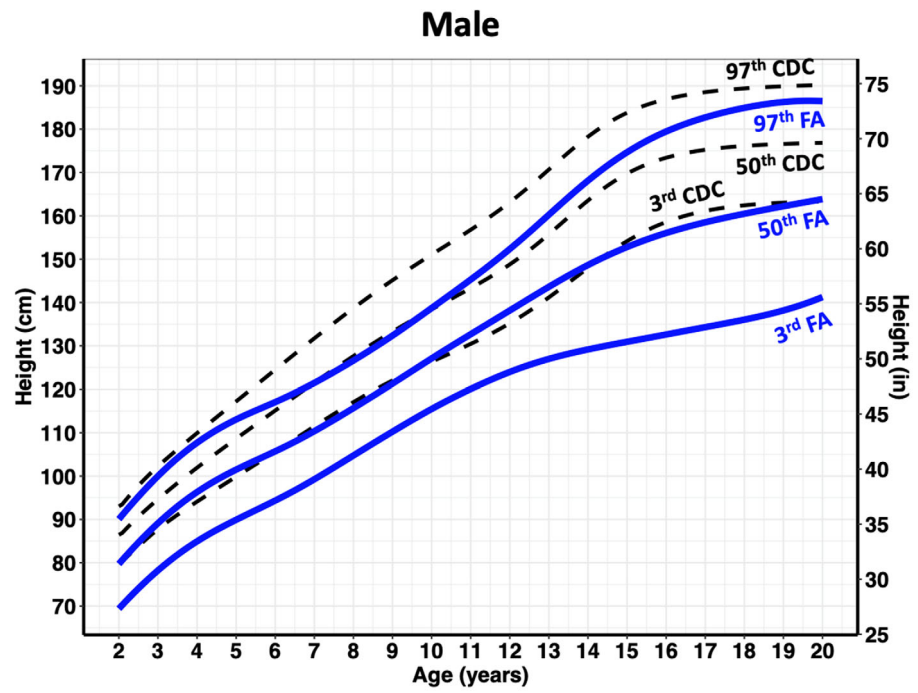
Abbreviations: BMI, body mass index; CDC, centers for disease control; FA, Fanconi Anemia; GHRT, growth hormone replacement therapy; HCT, hematopoietic cell transplant; mos, months; SDS, standard deviation scores; WHO, World Health Organization.

[a]Other *FANC* complementation groups include *FANCB*, *FANCD2*, *FANCE*, *FANCF*, *FANCG*, *FANCI*, *FANCJ/BRIP1*, *FANCL*, *FANCM*, *FANCN/PALB2*, *FANCO/RAD51C*, *FANCP/SLX4*, *FANCQ/ERCC4*, *FANCR/RAD51*, *FANCS/BRCA1*, *FANCT/UBE2T*, *FANCU/XRCC2*, *FANCV/REV7*, *FANCW/RFWD3*, and *FANCY/FAP100*.

[b]SDS based on WHO 2006 for children 0–24 months and CDC reference charts for 24–240 months.

[c]Percentages are calculated across the entire cohort of ages 0–20 years.

The BMI-for-age percentiles in children with FA show similar patterns to the weight-for-age percentiles but have different timing of onset of adiposity rebound in comparison to normative charts and have broader variability in females (Figures 3 and 6). The adiposity rebound appears delayed in males with FA and normal in females with FA compared to CDC norms (Figure 3).



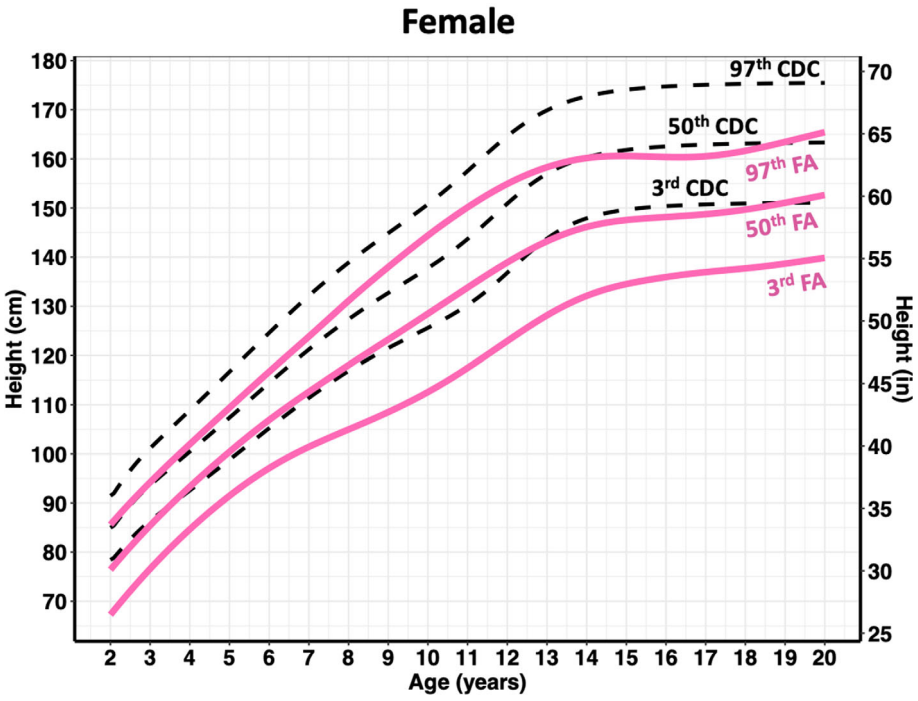


FIGURE 1 Comparison of height-for-age growth curves of male and female FA patients and CDC references for ages 2–20 years.

Table 2 illustrates a numeric comparison of estimated attained height, weight, and BMI across different timepoints of growth (at 4, 8, 12, 16, and 20 years old) between patients with FA and CDC reference data separated by gender. At first glance alone, a notable discrepancy can be seen in the median achieved adult height in patients with FA, with females being 10 cm shorter and males 13 cm shorter at age 20 years old than the CDC standards (each p-value <<0.001). Across all reported age groups, both males and females with FA showed a significant difference in estimated median height from the CDC references. This holds true for weight with FA males as well, but not for FA females. All estimates for males varied significantly from CDC reference values again for BMI, while females showed non-significant differences in BMI across all detailed age groups.

Given that roughly 1/3 of our cohort received growth hormone treatment, we performed sensitivity analyses to assess how growth patterns differ between those who had received GHRT and those who had not. Comparison of the growth charts for those who were treated with GH and those who were not yields no difference as either the percentiles and/or attained size at nodal points of growth overlaps between the two sets of curves for height, weight, and BMI across both genders. Therefore, we conclude that inclusion/exclusion of growth data from FA patients treated with growth hormone would

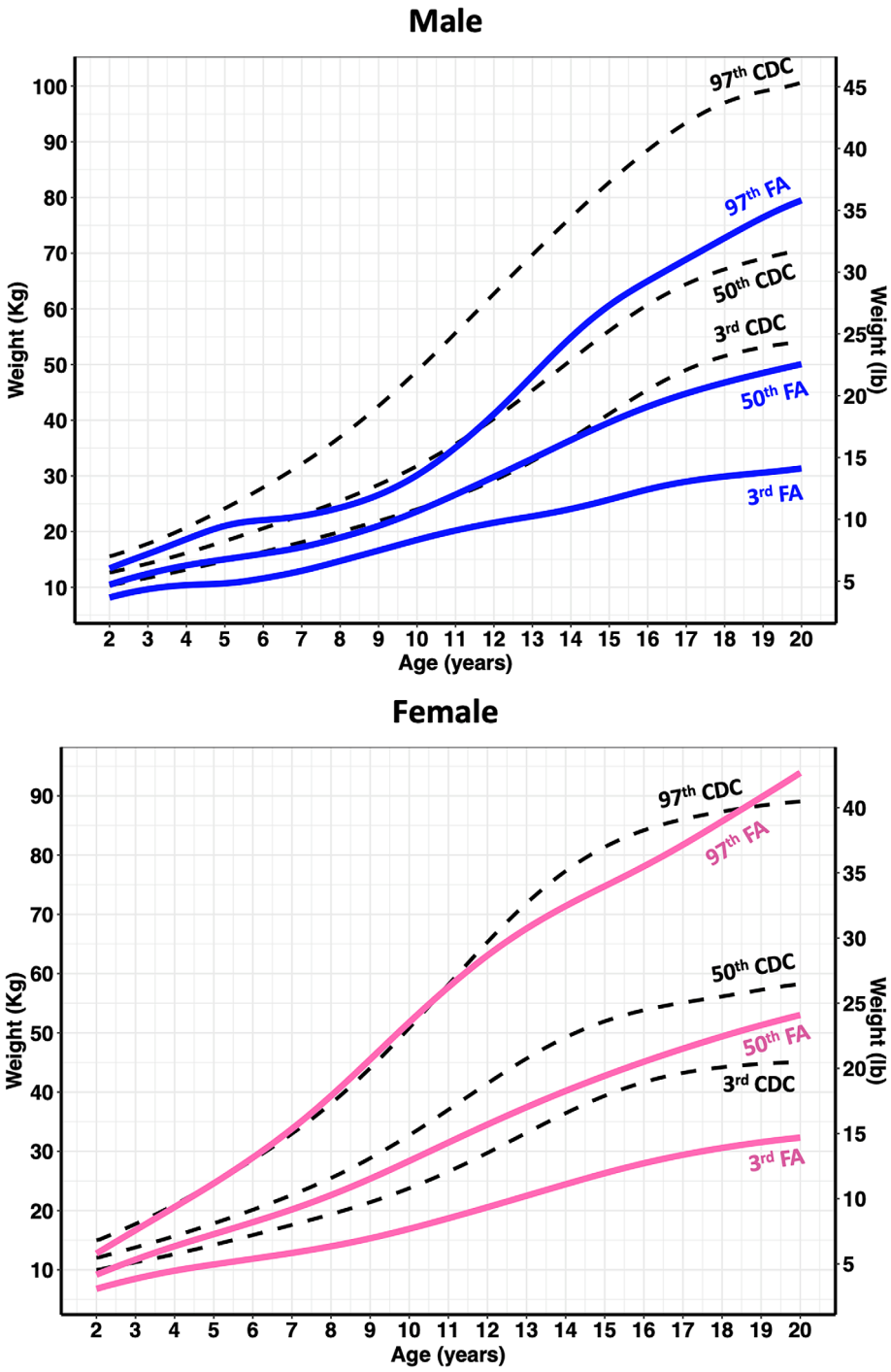


FIGURE 2 Comparison of weight-for-age growth curves of male and female FA patients and CDC references for ages 2–20 years.

not significantly alter our presented growth curves. Thus, to increase statistical power of our models, we chose to maintain curves using the whole population including those who received GHRT.

4 | DISCUSSION

In our FA cohort, delineated by gender, males with FA averaged an adult height of −1.81 SDS (164 cm), and females with FA averaged an adult height of −1.65 SDS (153 cm) (Table 2). Interestingly, our data shows that patients with FA on average gain in height between ages 16 and 20 years as individuals are on average further below the reference curve at age 16 (−2.18 SDS for males and −2.23 SDS for females) than 20 (Table 2). This could be due to continued growth after age 16 years because of pubertal delay or other reasons for delayed closure of the growth plates. Other studies aiming to characterize linear growth within patients with FA show similar results to our findings (Giri et al., 2007; Rose et al., 2012; Wajnrajch et al., 2001). However, due to the rarity of the condition, it is possible that some of the individuals in these studies overlap with our study

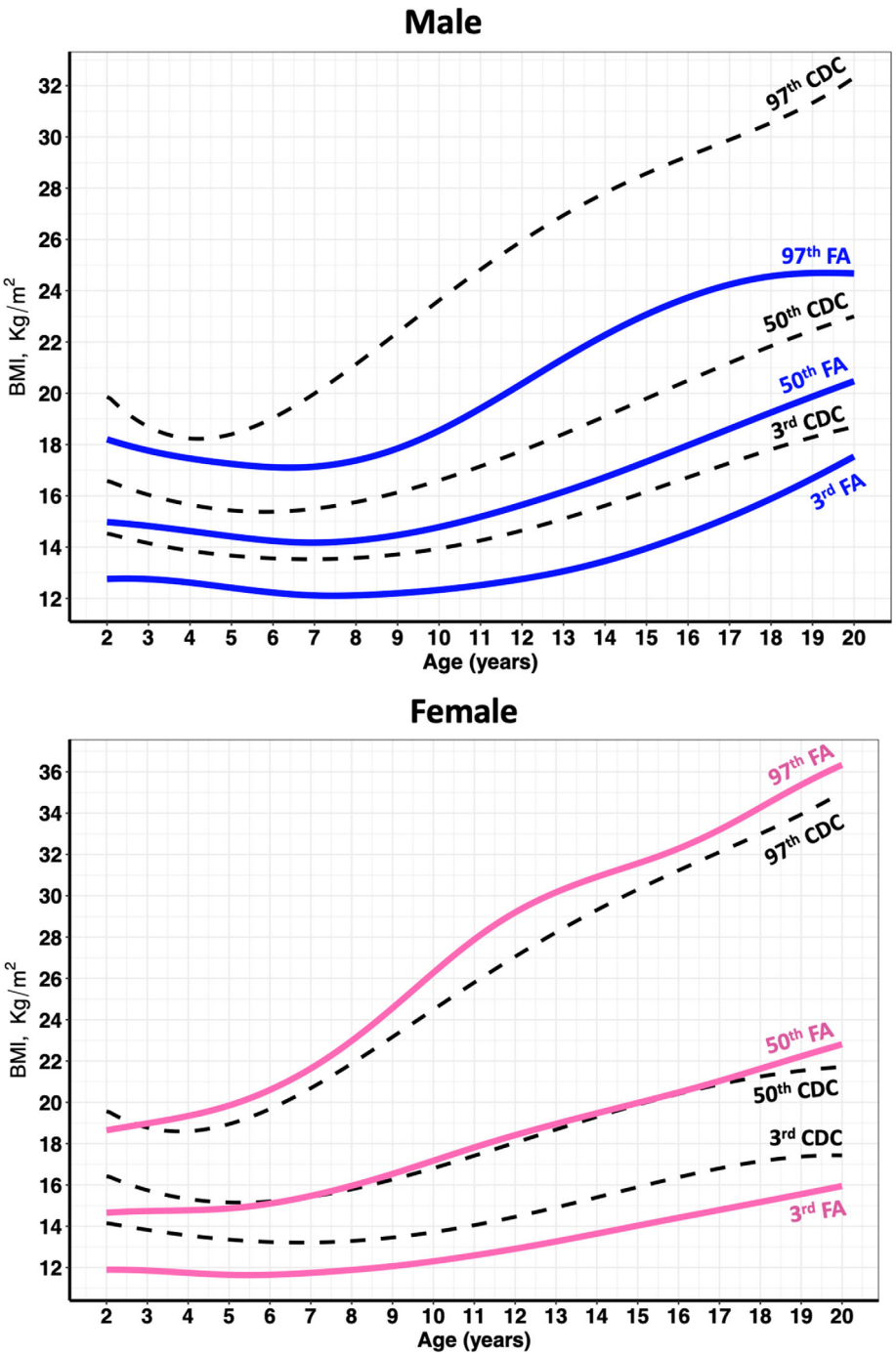


FIGURE 3 Comparison of BMI-for-age growth curves of male and female FA patients and CDC references for ages 2–20 years.

participants. It is important to note that since our earliest data points are from 2011, it is unlikely that the data used in our study were incorporated into earlier reports. Rose et al. (2012) has reported height to be an average of −2.2 SDS in males and −2.0 SDS in females. Similarly, an earlier report based on an international registry found a mean height SDS of −2.35 (Wajnrajch et al., 2001). However, these two studies analyzed across their entire cohorts that included both children and adults with median or mean age at time of assessment well before adulthood (roughly 10 (Rose et al., 2012) and 8 years (Wajnrajch et al., 2001)). Nevertheless, a study with a higher median age of 16 years also found similar results of a median height of −1.9 SDS for persons with FA (Giri et al., 2007).

In terms of adult weight, males with FA averaged −2.50 SDS (50.1 kg), and females with FA averaged −0.60 SDS (53 kg) (Table 2). This demonstrates that children with FA, especially males, can be naturally thin, although there is greater variability in weight than height (Figures 1 and 2). Low weight in individuals with FA may be due to nutritional deficits (Petryk et al., 2015), lower muscle mass (Silva et al., 2017), and lower bone mass (Giri et al., 2007); however, other studies have found normal bone mineral density (BMD) when

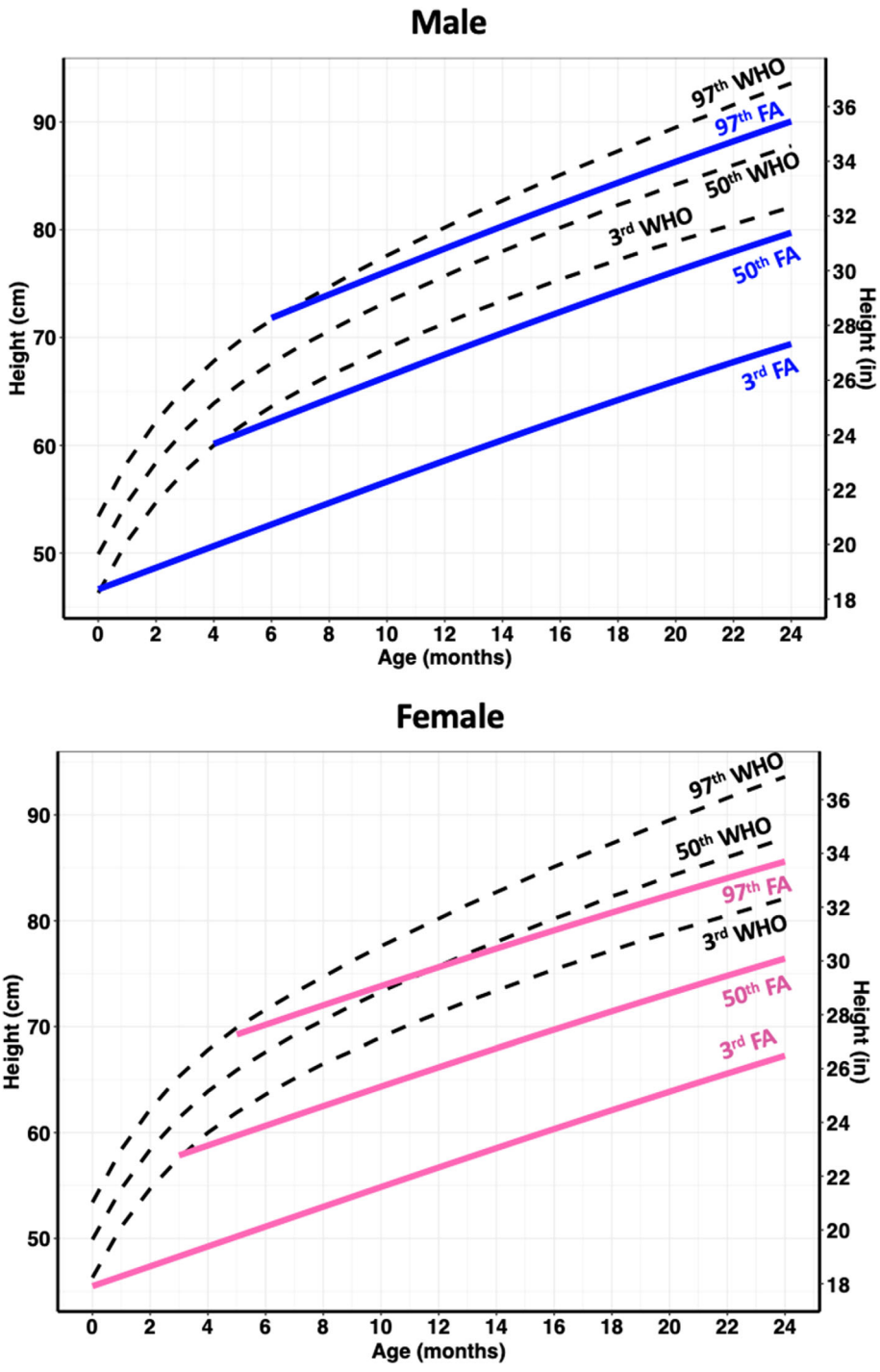


FIGURE 4 Comparison of height-for-age growth curves of male and female FA patients and WHO references for ages 0–2 years. Full range of FA percentiles were not shown due to unstable estimates at the lower ages.

adjusting for height age (Rose et al., 2012). Based upon the weight and BMI differences identified in our study and the increased risk of insulin resistance present in individuals with FA (Petryk et al., 2015), further studies characterizing lean and fat mass in FA are warranted. Previous reports detailing growth in terms of weight found an average weight of −1.26 SDS (Wajnrajch et al., 2001) when analyzing across both genders, so it is difficult to compare to our results as it is evident in our data that males and females with FA differ drastically in terms of their auxological parameters. Additionally, again, the young mean age of participants (8 years) in their cohort must be recognized.

In our cohort, males with FA averaged an adult BMI of −0.97 SDS (20.5 kg/m^2), and females with FA averaged 0.31 SDS (22.8 kg/m^2) (Table 2). Previously, median BMI has been described to be −0.6 SDS for males and −0.8 SDS for females (Rose et al., 2012). Again, this study had a median age of participants at time of analysis far before adulthood. Conversely, Giri et al. (2007) found 51% of their cohort with FA to be of normal BMI, 27% overweight, and 22% underweight. This difference is perhaps explained by the fact that Giri et al. (2007) used an older and majority female cohort, which may support our finding of the timing of adiposity rebound and non-

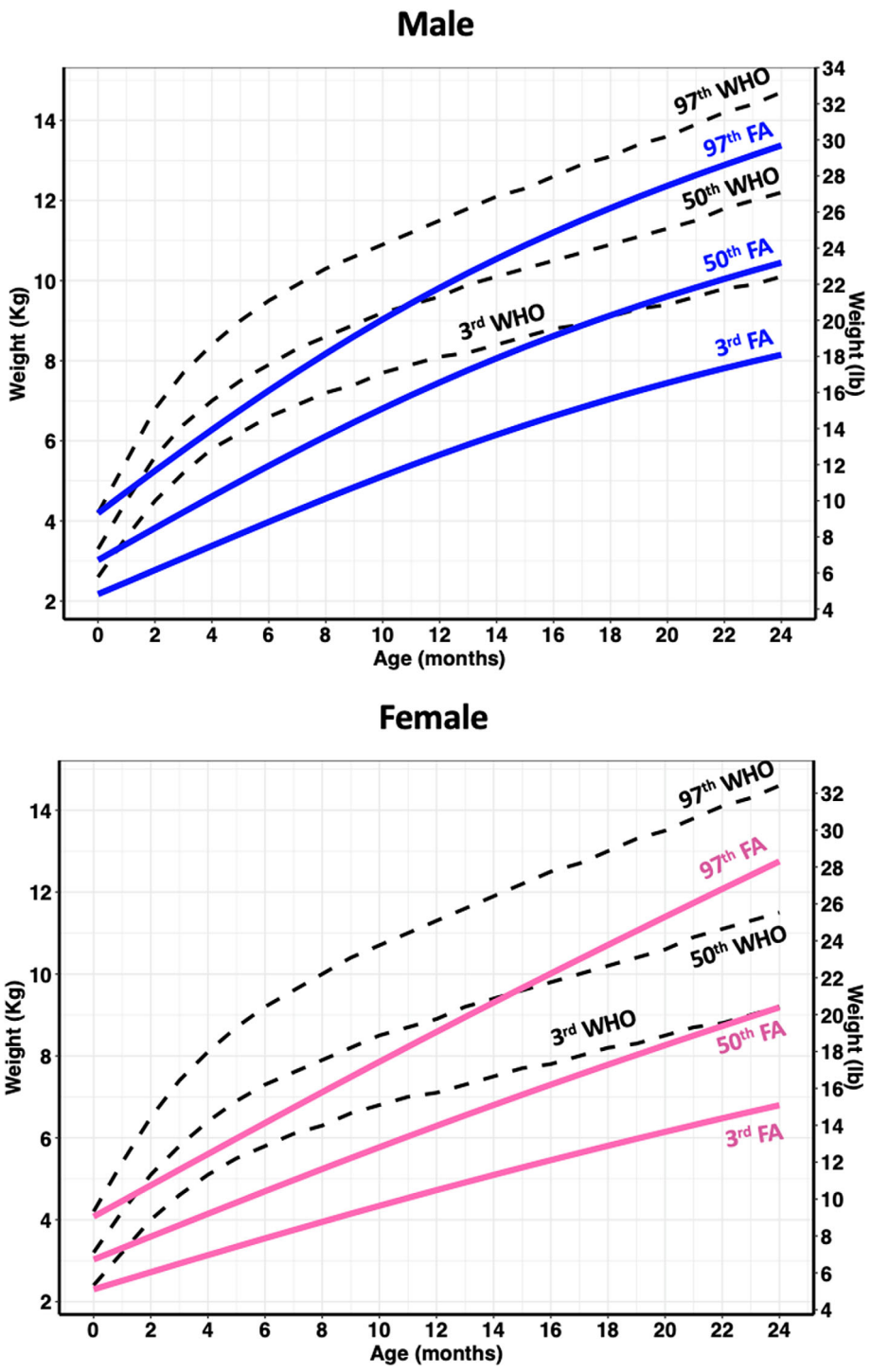


FIGURE 5 Comparison of weight-for-age growth curves of male and female FA patients and WHO references for ages 0–2 years.

significantly different BMIs for females with FA relative to normative curves. 15% of our cohort was overweight with the majority of those being female.

The ability to accurately classify persons with FA, especially females, as overweight or obese is important because FA patients can have impaired insulin secretion and an increased risk of diabetes mellitus, whether or not individuals have received a HCT (Petryk et al., 2015). A high BMI further contributes to abnormal glucose homeostasis (Giri et al., 2007). Historically, 21% of patients with FA have metabolic syndrome (overweight/obesity, dyslipidemia, and insulin resistance) and 50% have some form of metabolic dysfunction (Giri et al., 2007). Notably, our FA-specific growth charts found that females with FA have a wider range and greater variability of BMI than males, implying that they are at a greater need for monitoring for insulin deficiency and/or resistance as well as potential weight loss interventions. It is unclear why there is such variability in weight and BMI in females with FA. However, this difference was seen whether or not an HCT had occurred. Further studies to better understand

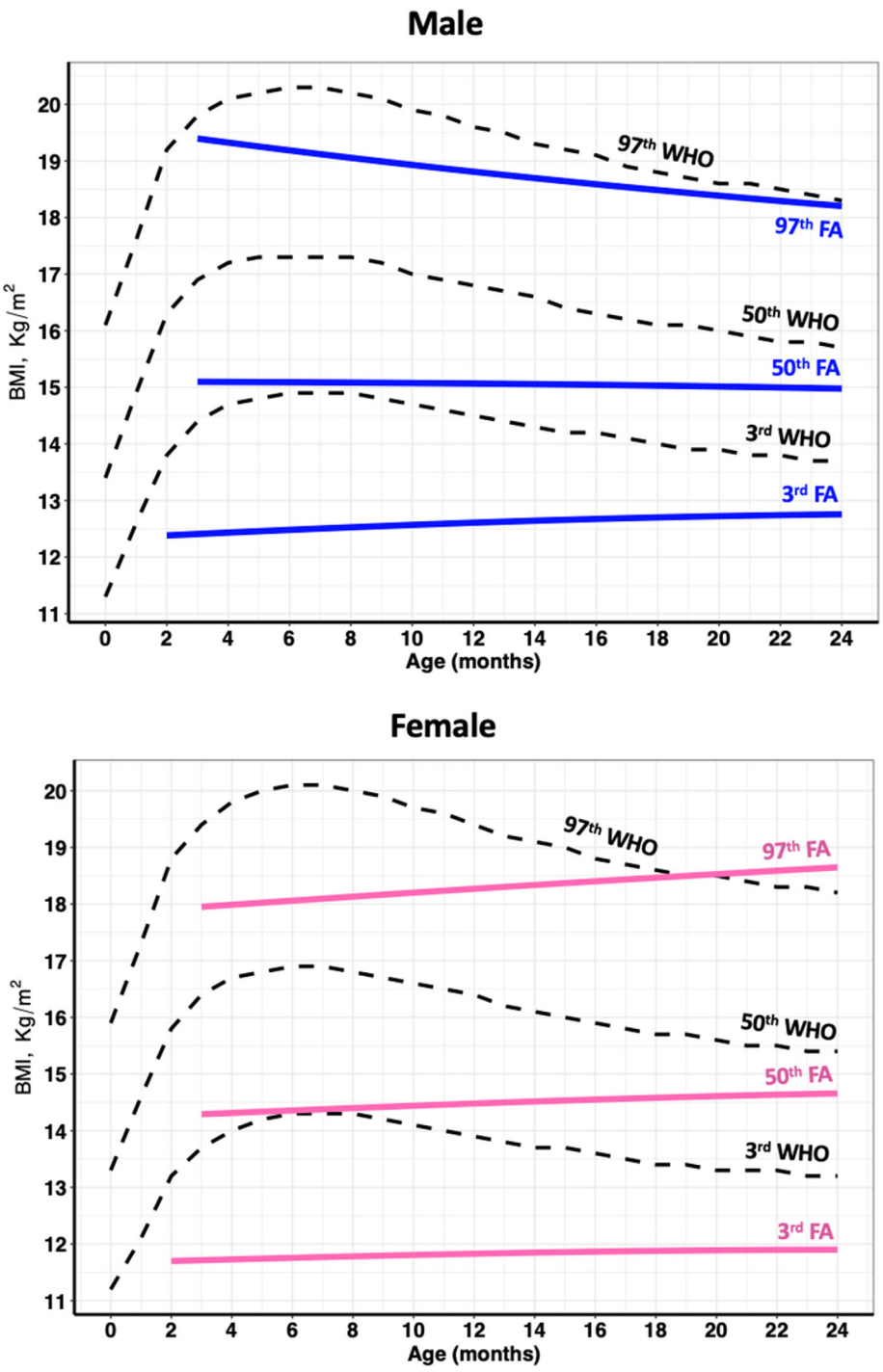


FIGURE 6 Comparison of BMI-for-age growth curves of male and female FA patients and WHO references for ages 0–2 years. Full range of FA percentiles were not shown due to unstable estimates at the lower ages.

differences in fat mass between males and females with FA and their potential impact on the development of metabolic syndrome are warranted.

Our FA-specific growth charts highlight that growth patterns of persons with FA follow vastly different trajectories relative to available normative charts. Other methods of estimating growth potential, such as bone age and mid-parental target height, do not adequately predict growth outcomes for children with FA (Petryk et al., 2015). FA-specific growth charts are needed by both parents and clinicians to provide historical reference data to set accurate growth expectations and highlight what is the expected, natural pattern of growth for this patient population. Often, parents of children with FA are compelled to increase their child's caloric intake because their weight and BMI are low relative to normative curves. This could lead to unnecessary interventions including supplemental feedings, appetite stimulants, GI evaluation, etc. FA-specific growth charts will allow clinicians to better determine which individuals may or may not need additional interventions and provide a more appropriate method of monitoring

TABLE 2 Examination of differences in cohort median attained growth at nodal points for children with FA, delineated by sex, in comparison with CDC-2000 normative charts.

	Smoothed median estimates				Smoothed median estimates			
	Females				Males			
	Height (cm)				Height (cm)			
Age (years)	CDC	FA	CDC-FA SDS	*p*-diff[a]	CDC	FA	CDC-FA SDS	*p*-diff[a]
4	100.0	93.3	−1.697	<0.00001***	102.0	96.3	−1.346	0.001374**
8	127.0	118.0	−1.659	<0.00001***	128.0	116.0	−2.133	<0.00001***
12	151.0	139.0	−1.603	<0.00001***	149.0	138.0	−1.463	<0.00001***
16	163.0	148.0	−2.226	<0.00001***	173.0	156.0	−2.182	<0.00001***
20	163.0	153.0	−1.647	0.0001621***	177.0	164.0	−1.808	<0.00001***
	Weight (kg)				Weight (kg)			
Age (years)	CDC	FA	CDC-FA-SDS	*p*-diff[a]	CDC	FA	CDC-FA-SDS	*p*-diff[a]
4	14.0	15.7	−0.948	<0.00001***	16.1	13.9	−1.324	0.0002671***
8	25.5	22.5	−0.751	<0.00001***	25.5	18.9	−2.372	<0.00001***
12	41.5	34.5	−0.974	0.1698	40.3	29.8	−1.74	<0.00001***
16	53.8	45.1	−1.21	<0.00001***	60.7	42.4	−2.394	<0.00001***
20	58.2	53.0	−0.602	0.05263	70.6	50.1	−2.501	<0.00001***
	BMI (kg/m^2)				BMI (kg/m^2)			
Age (years)	CDC	FA	CDC-FA-SDS	*p*-diff[a]	CDC	FA	CDC-FA-SDS	*p*-diff[a]
4	14.8	15.3	−0.489	0.1048	15.7	14.6	−1.002	0.001973**
8	15.8	16.0	0.091	0.2693	15.8	14.3	−1.163	<0.00001***
12	18.0	18.4	0.133	0.4061	17.8	15.6	−1.134	<0.00001***
16	20.5	20.4	0.024	0.7325	20.5	18.0	−1.125	<0.00001***
20	21.7	22.8	0.305	0.0455*	23.0	20.5	−0.966	<0.00001***

Note: *p*-values estimated from approximate one-sample quantile test of difference between CDC chart 50th percentiles relative to the FA-specific population median for each of the growth measures at ages 4, 8, 12, 16, and 20 years old.
Abbreviations: BMI, body mass index; CDC, centers for disease control; cm, centimeter; FA, Fanconi anemia; kg, kilogram; SDS, standard deviation scores.
[a]*p*-values estimated from unsmoothed FA population cohort data. *p<0.05, **p<0.01, ***p<0.00001

growth in response to treatments. As new treatment paradigms arise, FA-specific growth charts will be crucial in the interpretation of their efficacy.

4.1 | Limitations

Limitations of our study include the use of a single cohort of individuals with FA from a single center. However, our cohort is large given the rarity of FA, so it may be difficult to capture more comprehensive data. Additionally, since our cohort consisted of patients seen at FA Comprehensive Care Center, all had some medical concern that led to their diagnosis of FA and further evaluation in our center, suggesting that they could be more severely affected. Most patients (71%) included in this study received a HCT, which is known to dramatically impact growth. Alternatively, the number of individuals who did not require HCT included in this study improves the generalizability of the curves generated. We are validating our current FA-specific growth curves by analyzing how excluding data from patients after HCT impacts the curves. Some children included in the study (29%) also received growth hormone therapy. Initial analyses comparing the growth patterns of patients with FA who were treated with GH to those who were not suggests that excluding growth data from individuals who received GHRT would not significantly change the FA-specific growth curves currently presented using the full cohort data.

4.2 | Future directions

In the future, we hope to collaborate with the Fanconi Anemia Research Fund, FA registries such as the International Fanconi Anemia Registry, FA family groups, and other centers specializing in the treatment of FA to validate our growth charts with additional data. The present FA-specific growth curves are limited in that they combine data from patients of various *FANC* complementation groups, and growth patterns may differ significantly based on complementation groups or even specific FA mutations. It is already documented that the IVS4 A>T mutation of *FANCC* is associated with the most

severe short stature, with an average adult height of −4.3 SDS (Petryk et al., 2015). Within the cohort that contributed data to the generation of our growth chart, three individuals were homozygous for the IVS4 mutation, and two individuals had one copy of the variant. Going forward, we intend to analyze whether growth patterns differ significantly between complementation groups; however, these analyses may be complicated by compound heterozygosity and small numbers.

5 | CONCLUSION

Growth in individuals with FA is not well approximated by current normative curves used for monitoring their growth. To improve efficacy of clinical care and assess the success of therapies for patients, FA-specific growth curves may prove useful. They may also provide valuable information for epidemiological research and the study of novel treatments to promote growth within this patient population. Our current FA-specific growth charts can be further refined based on additional growth data as well as endocrinology and genetic information.

AUTHOR CONTRIBUTIONS

Crystal Barbus: Data collection, writing—original draft, and review and editing. **Arpana Rayannavar:** review and editing. **Bradley S. Miller:** Conceptualization, methodology, interpretation, project administration, funding acquisition, and review and editing. **Mica Jenkins:** Formal analysis. **O. Yaw Addo:** Methodology, formal analysis and interpretation, review and editing. **Ahmad Rayes:** Data collection. **Natasha Ahrweiler:** Data collection and project administration. **Alisha Olson:** Creation of database, data collection, and project administration. **Zachary Pohlkamp:** Creation of database and data collection. **John Wagner:** Conceptualization, review and editing. **Margaret MacMillan:** Conceptualization, funding acquisition, review and editing.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Data used to create the FA-specific growth charts and other additional analyses can be found at the public repository with DOI: 10.17632/84jb9r86zr.

ORCID

Crystal Barbus https://orcid.org/0000-0002-8145-7533

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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