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Research article

Modeling the distribution and progression of motor ability among children with cerebral palsy: An analysis of three reference centile sets

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A B S T R A C T

Background: Reference centiles describing gross motor function in children with cerebral palsy (CP) are used in clinical and research settings to guide treatments and evaluate interventions. However, it is unknown how existing references generalize to populations in novel settings.
Aims: The aim of this study is to evaluate the cross-sectional and longitudinal performance of three reference centiles to describe the motor function of children with CP aged 2–12 years at a large urban US pediatric hospital through a retrospective observational study.
Methods: and Procedures: We assessed cross-sectional performance by ranking our clinical population by quartile distributions described by the references. We assessed longitudinal performance by analyzing the distribution of prediction errors and correlations between predictions and observed scores.
Outcomes and Results: For cross-sectional distribution, the reference centiles by Hanna more closely described our population than those by Duran. For longitudinal progression, prediction error was less than 6 GMFM points for most records at 24-, 12-, and 6-month time scales for all three sets of reference centiles, but higher at a 48-month time scale. Prediction errors increased at younger ages and higher motor ability.
Conclusions and implications: Despite differences in cross-sectional performance, all three reference centiles achieved similar longitudinal performance and are sufficient for most clinical and research uses. Caution should be used when applying these curves to locations with different standards of care.

1. Introduction

Cerebral palsy (CP) is the most common cause of physical disability in children [1] with a prevalence of 1.5 cases per 1000 livebirths in high-income countries [2–4]. The degree of motor impairment varies greatly in individuals with CP, from mild difficulties with advanced motor skills (such as running and jumping) to full dependence on others for mobility and self-care. Motor function can be classified by the severity of physical limitation using the Gross Motor Function Classification System (GMFCS) [5] and quantified by the Gross Motor Function Measure (GMFM-66) [6].

The creation of predictive gross motor development centiles in children with CP has been useful for clinical practice and for outcomes research [7,8]. Children with CP have individual expected gross motor development based on Rosenbaum's curves which give practical information about the child's expected development and future capabilities [8]. In clinical practice, functional prognosis is important to inform family expectations, to guide clinical decisions on type and goals of treatment or adaptive equipment and

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environmental modifications, and to evaluate change in individuals. Predicting expected change is also important for the interpretation of clinical trial outcomes, particularly in young children who demonstrate the most change over time and who are increasingly a target population for intervention trials [9–11].

Several studies of reference curves describing changes in gross motor development over time in a population of children with CP from high income countries were derived to describe a specific population [8,12–14]. However, there has been little investigation into the suitability of these findings to be broadly applied to describe the distribution and progression of motor ability in other populations. Furthermore, there has been no investigation to compare the utility of the existing centiles to each other, which would guide clinicians and researchers in the selection of the most appropriate reference centile for an individual pediatric patient or a cohort.

Rosenbaum et al. first described the progression of gross motor function (GMF) in children with CP in 2002, reporting one median reference curve for each GMFCS classification level (I-V) [8]. Rosenbaum's five curves were derived from 2632 GMFM-66 scores from 657 children aged 1–13 years at 19 ambulatory rehabilitation programs in Ontario, Canada from 1996 to 2001. Hanna et al. expanded upon Rosenbaum's contribution by reporting five sets of reference centiles of GMF over time for children with CP aged 2–12 years — one set of 20 centiles (from 3rd to 97th percentile) for each of the five GMFCS levels [13]. Based on a subset of Rosenbaum's cohort and calculated using the least mean square method of Cole and Green [15], these reference centile tables are often used in clinical practice to evaluate individual children's change over time. These centiles are used in conjunction with the child's actual developmental achievement; the centiles provide information about the child's GMF in comparison to prior assessments and evaluates their abilities in comparison to others in their GMFCS level [8,13]. Marois et al. proposed an online calculator to use Rosenbaum's reference data [14]. Using a curve fitting software, Marois derived a single parameter function that replicates all five of Rosenbaum's original reference curves, and which the authors claim can represent any intermediate curve by varying the parameter. These curves are intended to describe the "expected natural evolution" of GMF in children with CP whose age at initial assessment is between 12 and 96 months. Marois defines the "GMFM Evolution Ratio" as measured GMFM score change relative to the expected GMFM score based on centile, such that a ratio of 1.0 indicates measured change equal to expected change. Ratios higher or lower than 1.0 indicate measured changes more than and less than expected change, respectively.

Duran and colleagues contributed a new set of reference centiles of GMF over time for children with CP aged 2–12 years of all GMFCS levels combined [12]. These centiles are derived from 1949 GMFM measurements from 919 children with CP from 2006 to 2016 at a single center in Germany. Duran also used the LMS method of Cole and Green [15] to calculate z-score based reference centiles. To evaluate the significance of an individual's changes over time, Duran calculated the standard deviation of change in GMFM scores over 6-month intervals This enabled the comparison of an individual's progress, relative to the expected variation found in the population.

Our objectives were to evaluate how well the existing centiles of GMF in children with CP (1) describe the *distribution* of motor ability across a US clinical population and (2) describe the *progression* of motor ability in a US clinical population.

2. Methods

2.1. Study design, setting, and participants

This study is a retrospective observational study of pediatric patients with CP at the Children's Hospital of Philadelphia (CHOP), a large urban US pediatric medical center (CHOP IRB 14–011137). Analyses were completed on a visit level. The inclusion criteria were a diagnosis of CP and at least one visit to the Children's Hospital of Philadelphia between September 2014 and June 2022 wherein the child was evaluated with the GMFM-66 (n = 2241). Records were excluded if: visits corresponded to hospital or day hospital encounters as these scores likely would not reflect baseline function (n = 43), visits that corresponded to Leukodystrophy, Neurogenetics, or Mitochondrial clinic encounters as these children may have been suspected to have progressive conditions other than CP (n = 14); visits conducted by video (n = 3); visits where less than 13 GMFM-66 items were administered [16] (n = 84); visits with a standard error of measurement >9 (n = 2); visits when children were older than 12 years(n = 347); and duplicated representations of a single visit (n = 17). During the longitudinal analysis 9 outliers were flagged for chart review; 5 were excluded as data entry errors and 4 were retained as true outliers (Appendix 1).

To analyze the distribution of motor ability, a cross-sectional subset of 1492 visits across 808 children was sampled from the study population using the methods established by Hanna et al. [13]. We created 10 age bands for 1 year intervals from 2 to 12 years, where each age band contained a maximum of 1 observation per child; if a child had multiple visits within an age band, the visit included in the analytic dataset was selected at random.

To evaluate the extent to which the Hanna, Duran, and Marois curves model the progression of GMF over time in the study population, longitudinal subsets were sampled from the study population by selecting children with pairs of visits that were 6, 12, 24, and 48 months apart (±30 % margin of time around these target durations). For each period, the earliest pair of visits that met the qualifying criteria was selected for each child (n = 154, 250, 221, 153 visit pairs respectively).

Demographic data included age, sex, race, ethnicity, GMFCS level and the Child Opportunity Index (COI). COI is a zip-code based metric that is often used to describe social, economic, educational, and health disparities. The COI has five levels, ranging from "very high" to "very low". A high COI score indicates that the child's environment supports social, economic, educational, and health opportunities; a low COI score implies the opposite [17].

Hanna percentile rank data were included in the EHR for most records and were manually annotated for the remaining 140 records (10 %) when missing. Duran z-scores were annotated by hand from the raw GMFM-66 scores for each record.

For the longitudinal analysis, a predicted score from each reference centile was derived for each pair of observed scores. For the

Hanna and Duran centiles, predicted scores at the time of the second visit were determined manually by following the centile curve from the first visit, and returning the GMFM-66 score intersecting the curve at the age of the child's second visit. For the Marois evolution ratio, predicted scores were derived by calculating the function parameter from the child's first visit to forecast the expected score at the time of the second visit.

A trained researcher completed all manual annotations (centiles and predicted scores). For each dataset, a clinical expert annotated a 10 % validation sample. Spearman's correlation statistic and rate of agreement were calculated to compare the results from the two annotators.

2.2. Statistical analysis

The distribution of motor ability in our population was evaluated with the cross-sectional dataset. Children were grouped into quartiles determined by each reference source. This distribution is reported in the overall clinical population, and by age group.

The progression of motor ability predicted by the Hanna, Marois, and Duran reference curves in the longitudinal data was compared to the observed progression in our clinical population using prediction error (ε-GMFM = observed score at t_1-predicted score at t_1).

Overall prediction performance was assessed via the distribution of ε-GMFM with skewness, mean, and standard deviation for each set of centiles and each timescale. At the 12-month timescale, the correlation between the three prediction methods and observed scores at second visits were assessed with Pearson correlation, and prediction performance was additionally assessed with mean absolute error by age and GMFCS level.

To assess prediction performance trends and demographic factors, children who progressed more than (Duran ε-GMFM $>$ 1sd), less than (Duran ε-GMFM $<$ -1sd), or similar to predicted (Duran ε-GMFM within $\pm$ 1sd) were grouped. These relationships were assessed with the appropriate statistical difference test: Fisher's exact test, Pearson's Chi-squared test, or Kruskal-Wallis rank sum test.

Table 1
Characteristics of study population.

Characteristic	N = 808[a]
Age at first encounter	4.48 (2.46, 7.39)
Sex	
Female	355 (44 %)
Male	453 (56 %)
Race	
American Indian or Alaska Native	1 (0.1 %)
Asian	27 (3.3 %)
Black or African American	242 (30 %)
Indian	10 (1.2 %)
Missing	7 (0.9 %)
Multiple Races Selected	38 (4.7 %)
Other	147 (18 %)
White	336 (42 %)
Ethnicity	
Hispanic or Latino	97 (12 %)
Not Hispanic or Latino	703 (88 %)
Unknown	8
Overall SVI	
Very Low (0.0–0.19)	160 (21 %)
Low (0.20–0.39)	143 (19 %)
Moderate (0.40–0.59)	120 (16 %)
High (0.60–0.79)	157 (21 %)
Very High (0.80–1.0)	172 (23 %)
Unknown	56
Overall COI	
Very Low (0.0–0.20)	225 (30 %)
Low (0.21–0.41)	96 (13 %)
Moderate (0.41–0.60)	108 (14 %)
High (0.61–0.80)	144 (19 %)
Very High (0.81–1.0)	179 (24 %)
Unknown	56
GMFCS Level at first visit	
I	233 (30 %)
II	141 (18 %)
III	114 (15 %)
IV	126 (16 %)
V	166 (21 %)
Unknown	28
Number of visits	2.00 (1.00, 3.00)

[a] Median (IQR); n (%).

All analyses were performed in Python version 3.9.7 and R version 4.1.3.

3. Results

3.1. Study population

Between September 2014 and June 2022, 808 children had 1726 eligible visits (Appendix 1), with a mean age of 4 years 6 months and GMFCS level at first visit, and a median of 2 visits per child (Tables 1 and 2).

3.2. Cross-sectional analysis

The Hanna centiles appropriately describe the distribution of motor ability in our population with approximately 25 % of the sample ranked in each quartile, validating the use of these centiles to describe motor ability in our population. However, our clinical population contains fewer children in the fourth quartile (higher motor function) of motor ability for their age and GMFCS level than the Hanna centiles describe.

In contrast, the Duran centiles poorly describe the distribution of motor ability in our clinical population, limiting their use for children in our setting. We observed that 44 % of the sample was scored at the 75 % centile or above. Typically, we would expect a maximum of 25 % of the population to fall within this group. This effect is more extreme for some age groups, e.g., 48 % of 8–10-year-olds ranked in the fourth quartile of motor ability with the Duran's centile rankings. This discrepancy between Duran's centile and our observed distribution of motor ability indicates another reference, i.e., Hanna, may perform better in our setting (Table 3).

3.3. Longitudinal analysis

All three reference centiles exhibit similar longitudinal performance across various timescales (Table 4). For each centile at each timescale, the prediction error (ε-GMFM) is normally distributed with a low skewness and a mean near 0. On average, all three reference sources under-predict motor development on the 6- and 12-month timescales and overpredict development on the 24- and 48-month timescales. However, in all the approaches the developmental predictions of the older children were more accurate than in younger children.

At the 12-month timescale, the predictions made from each reference are highly correlated with each other and with the true observed GMFM scores (Table 5). For each reference, we observed a lower mean absolute ε-GMFM for older children than younger children, and a lower mean absolute ε-GMFM for more severely impaired children than less severely impaired children (Table 6). For children between 1 and 2 years— for whom the Hanna and Duran comparison centiles are not available—we observed a mean absolute ε-GMFM using the Marois centiles that were within one point of the overall mean absolute ε-GMFM for any of the three centiles at this timescale. By using each of the three reference centiles when appropriate, 68 % of the CP pediatric clinical population motor development achieved an absolute prediction error of less than 6 points at the 6-month, 1-year, and 2-year time-scales.

We observed no statistically significant relationships between children's motor development trends (ε-GMFM $<$ -1SD, within $\pm$1SD, $>$1SD) and demographics, including race ($p = 0.3$), sex ($p = 0.6$), ethnicity ($p = 0.9$), GMFCS level ($p = 0.2$), or overall COI ($p = 0.2$).

4. Discussion

This is the first analysis to investigate the application of the existing CP GMF reference centile to a large urban US clinical population. Specifically, our institution functions as a pediatric tertiary care center and a community hospital for the surrounding neighborhoods in West Philadelphia. The distribution of GMFCS levels in our clinical cohort suggests that the motor function of our population is slightly lower than the US average reported by Kirby et al. [18]. Our findings confirm that the Hanna centiles most closely approximate the distribution of motor ability in our clinical population, while the Duran centiles describe our population less accurately. Furthermore, all three existing reference centiles (Hanna, Marois, Duran) sufficiently describe the progression of motor ability in the clinical population of children with CP at our institution, with 68 % of the cohort achieving an absolute prediction error of less than 6 points at the 6-month, 1-year, and 2-year time-scales. Despite this sufficiency, it is important to note that the Hanna and Marois (particularly in children between 1 and 2 years old) methods were better predictors of the cohort's motor development than Duran. As

Table 2
Distribution of CHOP population on Hanna and Duran reference curves.

	Hanna	Duran
Quartile[a]	N = 1344	N = 1325
Q1 (0.00–0.25)	342 (25 %)	369 (28 %)
Q2 (0.25–0.50)	419 (31 %)	153 (12 %)
Q3 (0.50–0.75)	369 (27 %)	214 (16 %)
Q4 (0.75–1.00)	214 (16 %)	589 (44 %)

[a] Quartiles have been ordered from lowest (Q1) to highest (Q4) gross motor function.

Table 3
Distribution of CHOP population on Hanna and Duran reference curves by age group.

Age group	[2,4), N = 361		[4,6), N = 334		[6,8), N = 284		[8,10), N = 204		[10,12], N = 161	
Method	Hanna	Duran	Hanna	Duran	Hanna	Duran	Hanna	Duran	Hanna	Duran
Quartile										
Q1	69 (19 %)	99 (29 %)	93 (28 %)	89 (27 %)	84 (30 %)	76 (27 %)	47 (23 %)	58 (28 %)	49 (30 %)	47 (29 %)
Q2	107 (30 %)	32 (9.4 %)	97 (29 %)	29 (8.7 %)	95 (33 %)	36 (13 %)	75 (37 %)	28 (14 %)	45 (28 %)	28 (17 %)
Q3	119 (33 %)	60 (18 %)	77 (23 %)	69 (21 %)	75 (26 %)	43 (15 %)	51 (25 %)	21 (10 %)	47 (29 %)	21 (13 %)
Q4	66 (18 %)	151 (44 %)	67 (20 %)	147 (44 %)	30 (11 %)	129 (45 %)	31 (15 %)	97 (48 %)	20 (12 %)	65 (40 %)
N/A	0	19[a]	0	0	0	0	0	0	0	0

[a] In nineteen cases where children were 2.0 years of age, Duran z score was not determined because the curves begin at 2.1 years of age.

Table 4
Distribution of ε-GMFM scores calculated with the Hanna, Duran, and Marois curves at 6, 12, 24, and 48 months.

	Hanna		Marois		Duran	
Months	Skew	Mean (std)	Skew	Mean (std)	Skew	Mean (std)
6	−0.09	0.34 (4.60)	−0.03	0.38 (**4.40**)	−0.02	0.32 (4.58)
12	0.19	0.32 (5.60)	0.24	0.28 (5.64)	0.28	0.07 (**5.49**)
24	0.10	−0.21 (6.02)	0.07	−0.13 (5.92)	0.11	−0.58 (**5.78**)
48	0.34	−1.06 (7.41)	0.48	−0.59 (7.74)	0.53	−1.48 (**7.30**)

Bold font indicates the method with the smallest standard deviation for each row. Note: Statistics are computed on observations starting ≥2 years old.

Table 5
Pearson correlation matrix of observed and 12-month predicted GMFM-66 scores according to the Hanna, Duran, and Marois curves.

	Observation at M12	Hanna prediction	Duran prediction	Marois prediction
Observation at M12	1.000	0.968	0.967	0.966
Hanna prediction		1.000	0.999	0.997
Duran prediction			1.000	0.997
Marois prediction				1.000

Note: Predicted scores at M12 are calculated according to each method based on the observed score at M0.

Table 6
Mean absolute ε-GMFM score for 12-month prediction calculated with the Hanna, Duran, and Marois curves.

	N	Hanna	Marois	Duran
Overall	250	**4.3**	4.4	**4.3**
by Age Group at M0				
[1,2)	38	N/A	4.9	N/A
[2,4)	85	4.6	4.7	**4.4**
[4,6)	49	4.5	4.6	**4.4**
[6,8)	40	**4.3**	**4.3**	4.5
[8,10)	27	**4.0**	**4.0**	**4.0**
[10,12]	8	1.7	**1.6**	1.7
Unknown	3	3	3	3
by GMFM Level at M0				
I	64	4.8	4.6	**4.4**
II	42	5.5	**5.2**	5.8
III	47	**3.7**	4.6	3.8
IV	43	**3.9**	4.0	4.0
V	41	3.7	3.9	**3.6**
Unknown	13	13	13	13

expected, all three approaches demonstrated better predictive accuracy in older children as expected changes in motor function are small compared to younger ages.

While the Hanna centiles [13] are routinely used in clinical practice, the utility of existing centiles to evaluate individual change to aid in the interpretation of research findings has not been reported. With an increase in intervention clinical trials, particularly in young children with CP, this work addresses an unmet need in the field. Hanna's centiles, which approximately describe our clinical population, were derived from a population that contained a similar distribution of children across GMFCS levels than our clinical cohort, with most children functioning in GMFCS level I or V. On the other hand, Duran's centiles, which struggle to appropriately describe the distribution of motor ability in our clinical population, were derived from a sample of children primarily functioning in

GMFCS levels II, III, and IV. Moreover, Duran's centiles fall short in part because they were designed specifically for the longitudinal task of assessing significance of a patient's progression over time; we found this resulted in unreliability for cross-sectional use in our setting.

As expected, we observed similar findings in the longitudinal analysis between the Hanna and Marois centiles because both centiles were derived from Rosenbaum's original dataset [13,14]. The observation that the Marois centiles performed nearly as well in predicting GMF in children 1–2 years compared to children 2–4 years is unexpected given the lack of data on GMF in this age group and the difficulty in classifying GMFCS before the age of 2 years [19]. This finding is encouraging for both clinical and research applications in children under 2 years of age, where the Hanna and Duran centiles are not available. The need for accurate prediction of future gross motor function in young children and infants will continue to grow as the diagnosis of CP is made earlier in life [20] and clinical trials in infants increase to maximize developmental neuroplasticity [9,11,21].

The observation that progression of motor function was sufficiently described by all existing centiles for different demographic groups was unexpected given known health care disparities in functional outcomes in children with CP [22,23]. It is possible that the demographic characteristics we considered – race, ethnicity and zip-code level COI – are not sufficiently sensitive to detect social disparities that may impact functional progression of CP, as the measures of neighborhood disadvantage and maternal education have been [22,23]. Nonetheless, disparities in prevalence in CP are far more studied [24,25] than the functional progression in CP and more attention is needed on the latter to fully understand functional prognosis.

Our findings suggest that different centiles may better reflect some clinical populations than others –the distribution of motor ability in our population was better described by the Hanna centiles than the Duran centiles. Nonetheless, any of the three existing centiles may be useful in predicting future function in children with CP across different populations and settings. Clinicians and researchers should choose the reference centiles most suitable for their patient or sample. For example, Duran's centiles are most appropriate for 6-month durations as the authors provide additional data for assessing significance of progression for this duration, and Marois's centiles are the only reference available for children aged 12–23 months. Hanna's and Marois's centiles are easiest to use, while the Duran centiles requiring plotting individual scores on a figure in their publication.

Caution is required in using these centiles to interpret changes in individual children. The size of observed error may exceed expected changes due to intervention, which would diminish the utility of any of the approaches to be useful in determining responder status after intervention. For example, our longitudinal results show that for 12-month predictions we expect 32 % of the population to see a predicted change in GMFM score that is that is inaccurate by least 5.5 points compared to their actual change, using any of the three reference centiles, based on the standard deviation of the prediction error we observed. Furthermore, a difference in our measurement methodology, which was a retrospective review of GMFM-66 measurements performed by several physical therapists, and the methodology of prior investigators, where GMFM-66 measurements were obtained prospectively and reliability was closely monitored in a research study, may contribute to significant variability between the samples. That said, significant measurement error was reduced by excluding patients who had scores from inpatient settings, high standard error of measurement, and insufficient item administration, as explained in our methods.

Our observations are promising for broad utility of the existing centiles to describe and predict GMF in various populations. However, all centiles extend only 12 years. While little to no increase in GMF is expected after the age of 12 years, predicting those who are likely to experience a decline in motor function during adolescence or adulthood is a challenge [26]. More work is needed on validation and extension of gross motor centiles in very young children, namely 0–2 years where robust references are not available, and 2–4 years, where the centiles tested achieve among the highest prediction errors. Finally, while our observations are encouraging for a clinical population in the US, the existing GMF centiles may not be generalizable to other settings, especially low resource settings where standard care differs or in places with large differences in health care compared to Canada, Europe and the USA.

Future work should focus on extending the existing centiles below 2-years and beyond 12-years and improving prediction performance between 2 and 4 years. Moreover, future work should investigate the impact of the care setting and socio-demographics factors on the progression of motor ability in children with CP, and how comorbidities and other confounding factors impact children's motor development. While each set of reference centiles performed remarkably similar in describing progression of motor function, suggesting the approaches will yield similar determinations of participant responder status in clinical trials, more work is needed to increase the precision of estimated change to minimize prediction error.

5. Conclusion

The reference centiles tested can be used to model the distribution and progression of motor ability in a population of children with cerebral palsy from a large urban US pediatric medical center, with some limitations. In this setting, the Hanna centiles more closely describe the distribution of motor ability in the study population than the Duran centiles. Populations that contain a distribution of GMFCS levels that do not match that of the Hanna or Duran study populations may not be well described by these centiles, as we found for our clinical population and the Duran centiles. Finally, all three centiles tested achieve sufficient performance for predicting future GMF, particularly at shorter prediction timescales. Overall, our findings confirm the utility of the reference centiles for clinical and research use, while identifying limitations and opportunities to improve their robustness.

CRediT authorship contribution statement

Rachel Sanderlin: Writing – review & editing, Visualization, Validation, Software, Investigation, Formal analysis, Data curation. **Charlotte Schluger:** Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Investigation,

Formal analysis, Data curation, Conceptualization. **Joe Wu:** Validation, Supervision, Resources, Methodology, Formal analysis. **Francis Eusebio:** Writing – review & editing. **Amy L. Roberts:** Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Laura Prosser:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Funding acquisition, Data curation, Conceptualization.

Ethics and consent

This study was reviewed and approved by The Children's Hospital of Philadelphia (CHOP) with the approval number: IRB#14–011137 on December 20th, 2023. Waiver Of Consent/Assent/HIPAA Authorization: A waiver of consent was approved per 45 CFR 46.116(d) and a waiver of HIPAA authorization had been approved per 45 CFR 164.512(i)(2)(ii). This consent was granted as the current research was a retrospective study that utilized data collected from a previous clinical trial.

Authors note

We have no conflicts of interest to disclose.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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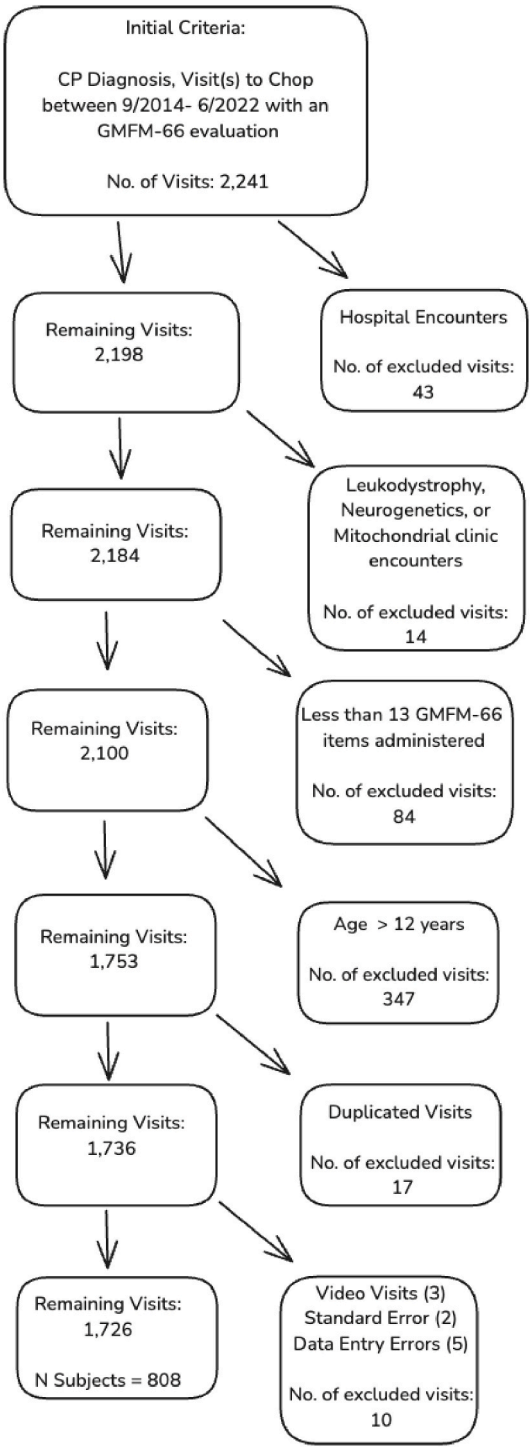
Appendix 1

Concert Chart: Exclusion and Inclusion Criteria.



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