Aberrant General Movements in Infants with and without Newborn Detectable Risks: A Preliminary Analysis

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ABSTRACT

Neurodevelopmental disorders impact 16.7% of children in the United States. It is widely accepted that early detection and treatment of such conditions (e.g., cerebral palsy) can optimize long-term outcomes for infants and their families. Alarmingly, access to time-sensitive, condition-specific interventions can be restricted until a formal diagnosis is established which may not occur until 12- to 24-months in children with cerebral palsy (CP). This is despite International Clinical Guidelines that recommend using Prechtl's General Movements Assessment (GMA) to reliably identify CP in infants less than 5-months of age. Fortunately, uptake of the GMA is increasing, particularly in specialty clinics used to monitor the development of infants with newborn detectable risks (NDR) (e.g., a history of preterm birth, neonatal asphyxia, and/or genetic variations). In contrast, the development of infants without NDR is typically assessed outside of specialty clinics using ill-fitted milestone checklists which are less sensitive for detecting early dysfunction. This is problematic as infants without NDR account for half of children with CP. Relatedly, the diagnostic accuracy of aberrant general movements (GMs) to identify CP is specific to infants with NDR; thus, it is unclear if this clinical tool is as reliable for infants without NDR. The goal of this novel dissertational work is to address this issue and determine if GMs, as a functional biomarker, could effectively screen for neuromotor dysfunction by:

1) determining the prevalence of aberrant GMs and potential barriers for administering the GMA within a more inclusive population of infants,

2) evaluating the relationships between aberrant GMs (as an immediate, or short-term outcome of interest) and other demographic or health-related features, and

3) assessing the congruence between aberrant GMs and the perceived concerns about an infant's development by a parent or non-parent caregiver.

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RELEVANT NOMENCLATURE	
Neurodevelopmental Disorders	a categorical umbrella for a variety of conditions occurring in childhood (e.g., attention-deficit disorder, autism spectrum disorder, intellectual disabilities, and cerebral palsy) impacting one out of six children in the United States and nearly 53 million children worldwide
Cerebral Palsy (CP)	the most common neuromotor disability occurring in childhood (impacting approximately 764,000 children and adults in the United States) that can affect motor, sensory, and cognitive functions.
Prechtl's General Movements Assessment (GMA)	a predictive tool used to detect neuromotor dysfunction for infants less than 6-weeks or between 9- and 20-weeks post-term age.
General Movements (GMs)	endogenously generated, age-specific patterns of movements that when categorized as aberrant can detect neuromotor dysfunction.
Newborn Detectable Risks (NDR)	problems occurring in the pre-, peri-, and/or post-natal periods (e.g., preterm birth, neonatal asphyxia, and/or congenital defects/genetic variations).
Post-Term Age (PTA)	age of an infant past their expected due date.
Nationwide Children's Hospital (NCH)	primary study site where data were collected.

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1 Introduction

This dissertational work was envisaged to investigate elements connected to a larger, multi-year project that will lead to the development of an automated detection tool to identify neurodevelopmental disorders in infants with and without newborn detectable risks (NDR). The coinciding larger project will enroll up to 6000 infants who will be followed until their 18th birthday. While the immediate, or short-term outcome of interest was the presence (or absence) or aberrant general movements (GMs), developmental outcomes will be assessed longitudinally, with any established diagnosis of a neurodevelopmental disorder documented. When available, these long-term outcomes can be used to reanalyze these dissertational results and assist in evaluating the diagnostic accuracy of aberrant GMs expressed by infants with or without NDR for identifying such conditions. Correspondingly, the analyses conducted for this dissertation uncovered some non-ideal findings related to the efficacy of data collection methods. This led to small methodological refinements, geared to optimize the efficiency for accomplishing proposed aims in the ongoing, larger project. Still, this dissertational work is unique, with objectives to:

1) determine the collective prevalence of aberrant general movements (GMs) within a more inclusive population of infants and identify obstacles encountered when collecting and analyzing these data (presented in Chapter 2)
2) evaluate the correlation between aberrant GMs (as an immediate or short-term outcome) and demographic or other health-related features included in Table 1 (presented in Chapter 3)
3) assess the congruence between aberrant GMs and perceived concerns about an infant's development by a parent or non-parent caregiver, e.g., another family member, childcare provider, or healthcare professional (presented in Chapter 4)

The importance of this dissertational work is that it adds new knowledge about the prevalence of aberrant GMs in a more inclusive population of infants and how these patterns of movements are related to other demographic or health-related features (see Table 1) as well as perceived developmental concerns by a parent or non-parent caregiver (e.g., another family member, childcare provider, or healthcare professional). This information can help address a critical and unresolved need for improving the identification of neurodevelopmental disorders in infants as young as possible. By doing so, time-sensitive, condition-specific treatments can be more readily provided to help ameliorate disability and optimize long-term outcomes for infants and their families (Herskind et al., 2015; Hirai et al., 2018; Kohli-Lynch et al., 2019; Mclntyre et al., 2011; Morgan et al., 2021; Novak et al., 2017; A. J. Spittle et al., 2008; Whitney et al., 2019). While work done in recent decades to promote early detection of such conditions has been powerful, the difficulties related to accurately identifying neurodevelopmental disorders have also been acknowledged (Lipkin & Macias, 2020; Rosenbaum et al., 2006; te Velde et al., 2019). These difficulties reflect the fact that there is no singular laboratory biomarker or assessment exists that can definitively predict clinical outcomes during infancy (Mclntyre et al., 2011; Novak et al., 2017; te Velde et al., 2019). While there is a growing trend to use Prechtl's General Movements Assessment (GMA) to assist in the identification of neurodevelopmental disorders in infants less than 5-months of age, its validity is specific to infants with NDR, which is problematic since 50% of children with cerebral palsy (CP) are those with an unremarkable pregnancy, birth, and newborn period (Novak et al., 2017; te Velde et al., 2019). Moreover, the implementation of the GMA for infants with NDR has been reported to be inconsistent (Ricci et al., 2018), with its use less well described in

infants without NDR who instead have their neuromotor competence assessed using ill-fitted milestone checklists that lack a sensitivity to detect dysfunction in infants less than 9- to 18-months of age (Hubermann et al., 2016; Noritz & Murphy, 2013; te Velde et al., 2019). Therefore, this dissertational work will serve as a first step to determine if aberrant GMs (as an immediate or short-term outcome) can be used as a functional biomarker to detect early signs of neuromotor dysfunction in infants with or without NDR.

Neurodevelopmental Disorders: CP as an Exemplar Condition

CP is defined as: "… a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain…"(Rosenbaum et al., 2006, p. 9) The cause and resultant clinical manifestation can vary, but motor, cognitive, and sensory functions can be affected, which can then lead to difficulties with moving or walking, thinking, communicating, or behaving (Centers for Disease Control and Prevention., 2020; Hirai et al., 2018; Mclntyre et al., 2011; Rosenbaum et al., 2006). Impacting 1 out of 345 infants, CP is the most common neuromotor disorder to occur in childhood (Centers for Disease Control and Prevention., 2020; Rosenbaum et al., 2006). And even though early signs of behavioral dysregulation, impaired posture, and aberrant GMs in infants less than 5-months of age have been shown to be indicative of CP, it can take 12- to 24-months for infants to receive a formal diagnosis (Mclntyre et al., 2011; Novak et al., 2017; te Velde et al., 2019).

Disconcertingly, failing to establish a formal diagnosis in infancy can obstruct implementation of time-sensitive, condition-specific interventions geared to increase independence with mobility and activities of daily living, prevent the development of

secondary complications (e.g., orthopedic deformities), help optimize educational achievements, and maximize participatory capacity within society (Herskind et al., 2015; Morgan et al., 2021; Novak et al., 2017; A. Spittle et al., 2015; Whitney et al., 2019). There have been numerous reports that have linked CP to a variety of causal indicators (including NDR); however, the science behind predicting which infants will be affected is still imprecise, as there are individualistic differences related to if and how NDR cause CP (Mclntyre et al., 2011; Novak et al., 2017; te Velde et al., 2019).

And while an eventual diagnosis of CP (or another neurodevelopmental disorder) is considered the true clinical standard or long-term outcome of interest, assessing GMs to detect neuromotor dysfunction was used as a short-term outcome, or proxy for adverse developmental outcomes for this dissertation. The link between aberrant GMs (as the immediate, or short-term outcome of interest) and other demographic or health-related features (see Table 1 for the complete list of variables) has previously not been described. Therefore, this foundational work evaluated these relationships, as a combination or triangulation of different variables may improve the accuracy for predicting neurodevelopmental disorders, thus, decreasing the age at which healthcare professionals can establish a formal diagnosis and subsequently initiate time-sensitive, condition-specific interventions.

Assessment of GMs as a Functional Biomarker

Aberrant GMs are most commonly assessed using the GMA. The GMA is a non-invasive, observational assessment that has been validated for infants 26-weeks post-menstrual age

through 5-months PTA (Einspieler & Prechtl, 2005). The sensitivity and specificity of the GMA have been reported as 98% and 96%, respectively when identifying CP in infants with NDR who present with cramped synchronized followed by absent fidgety GMs (Einspieler & Prechtl, 2005; Novak et al., 2017). Endogenous in nature, GMs can be segmented into two distinct, age-specific patterns using gestalt perception. Even though this assessment requires discernment of qualitative patterns of movements, trained assessors can accurately categorize GMs as normal or aberrant with high inter-rater reliability ($k = 0.86$) (Valentin et al., 2005).

Writhing GMs are expressed during the first age-specific period, from birth through 6-weeks PTA. The quality of normal writhing GMs is characterized by a gradual onset and offset of complex movements sequencing through the arms, neck, and trunk with an intensity that waxes and wanes (Einspieler & Prechtl, 2005; Peyton & Einspieler, 2018). Through the experience of expressing and sensing a variety of writhing movements, different parts of the brain are activated which fosters continued neural growth and refinement (Hadders-Algra, 2014). However, when the integrity of the nervous system is injured or compromised, aberrant writhing GMs may appear, which can be characterized as cramped synchronized (where movements are rigid and synchronized), poor repertoire (where movements are monotonous or repetitive), or chaotic (where movements are disorganized and jerky) (Einspieler & Prechtl, 2005; Peyton & Einspieler, 2018).

Analogously, fidgety GMs can be observed during the second age-specific period, between 9- and 20-weeks PTA. Normality is characterized as tiny, cogwheel, or multiplanar type movements within joint spaces with moderate acceleration (Einspieler & Prechtl, 2005;

Peyton & Einspieler, 2018). These movements have been theorized to be an adaptive function to recalibrate the proprioceptive system prior to the emergence of volitional, goal-directed movements (Einspieler & Prechtl, 2005; Peyton & Einspieler, 2018). Aberrant fidgety GMs can be further classified as absent (where normal fidgets are not observed), sporadic (where fidgets are present, but not consistently expressed), or abnormal (where fidgets appear overly exaggerated with an amplitude that is larger than expected) (Einspieler & Prechtl, 2005; Peyton & Einspieler, 2018). The decision to further evaluate if GMs could be used as a functional biomarker to predict neurodevelopmental disorders in infants with NDR was based on previous literature purporting its efficacy in predicting CP in infants presenting with NDR (i.e., sensitivity and specificity of 98% and 96%, respectively) (Einspieler & Prechtl, 2005; Novak et al., 2017). In addition, a recent secondary review of a collection of studies reported associations between aberrant GMs and other neurodevelopmental disorders including genetic syndromes, autism spectrum disorder, and intellectual disabilities (Peyton & Einspieler, 2018).

1.1 Statement of the Problem

The motivation for this dissertation was to address the significant impact that delayed identification of neurodevelopmental disorders can have on infants, families, and the broader society, as 1 out of 6 children in the United States are diagnosed with such conditions (Zablotsky et al., 2019). For example, even as the most common neuromotor disability, CP is frequently diagnosed late, between 12- and 24-months of age (Mclntyre et al., 2011; Novak et al., 2017; te Velde et al., 2019). This is despite International Clinical Guidelines that recommend the use of the GMA to reliably identify CP in infants with NDR during the first 5-months of life (Novak et al., 2017; te Velde et al., 2019). As it is, there

are two unresolved problems that should be scrutinized. First, there are unnecessary delays in the time it takes to receive a formal CP diagnosis, with one recent article indicating that the age when CP was formally diagnosed decreased from 18- to 13-months with the intentional integration of the GMA along with other neurological examinations in infants with NDR (Byrne et al., 2017). Yet, while there is an increasing trend for using the GMA in specialty clinics for infants with NDR (Byrne et al., 2017), this practice is inconsistent, especially in the United States (Ricci et al., 2018), which means that many infants will not have the opportunity to be screened for early signs of neuromotor dysfunction. A second problem is that the clinical effectiveness of GMs as a functional biomarker when used with infants without NDR is unknown, as previous research has disproportionately emphasized reporting the sensitivity and specificity of the GMA for infants with NDR who are eventually diagnosed with CP.

1.2 Significance of the Study

The significance of addressing these identified problems and determining if aberrant GMs can be used as a function biomarker to effectively detect neuromotor dysfunction in infants with and without NDR is that it could allow for earlier diagnosis of neurodevelopmental disorders. This can then contribute to the health of infants through improved access to time-sensitive, condition-specific interventions during a time of greatest neuroplasticity (i.e., the first 1000 days of life) which can help optimize long-term outcomes for both the child and family (Hadders-Algra, 2014; Herskind et al., 2015; Hubermann et al., 2016; Kohli-Lynch et al., 2019; Mclntyre et al., 2011; Novak et al., 2017; Whitney et al., 2019). Ultimately, this work has the potential to ameliorate disability and lessen the overall disease burden for

infants with and without NDR (Novak et al., 2017; Shahat & Greco, 2021; Whitney et al., 2019).

Moreover, according to the UN Convention on the Rights of the Child, "every child has the right to achieve their full developmental potential and must be supported in this by their caregiver, family, community, and wider society" (Kohli-Lynch et al., 2019, p. 4451). Yet, fully realizing how to best support all children is complicated. This is because the causal pathways used to identify neurodevelopmental disorders in individual infants are imprecise, with no singular laboratory biomarker or assessment in existence that can be used to rule in or out such conditions (Mclntyre et al., 2011; Novak et al., 2017; te Velde et al., 2019). Therefore, clinicians may default to waiting to see if certain key developmental milestones are achieved, including independent walking by 18-months of age, causing the establishment of a formal diagnosis and initiation of treatment to be delayed (Aravamuthan et al., 2020; Boychuck et al., 2019; Hubermann et al., 2016; Novak et al., 2017; te Velde et al., 2019; Zablotsky et al., 2019).

Finally, a delayed diagnosis of neurodevelopmental disorders can also impact the family dynamic. This is because there is an increased risk for parental stress, anxiety, and depression when a diagnosis of CP has been delayed or poorly communicated (Baird et al., 2000; Guttmann et al., 2018; Novak et al., 2017; te Velde et al., 2019). When parental concerns are inadequately addressed or dismissed, this emotional strain can negatively impact the infant-parent dyad as well as long-term outcomes for both the infant and family (Baird et al., 2000; Guttmann et al., 2018).

1.3 Specific Aims and Hypotheses

The specific aims and hypotheses for this dissertational work are as follows:

1.3.1 Specific Aim 1: Identify the prevalence of aberrant GMs for infants with and without NDR.

Hypothesis 1.1: The GMA will identify aberrant GMs in infants with or without NDR at a rate that is significantly different to the prevalence of neurodevelopment disorders which has been reported to impact ~16.7% of US children. (H_0: The incidence of aberrant GMs will occur at a rate similar the prevalence of neurodevelopmental disorders).

1.3.2 Specific Aim 2: Identify significant relationships between aberrant GMs and demographic or health-related features (see Table 1 for the complete list of variables)

Hypothesis 2.1: There will be a significant relationship between the presence of aberrant GMs and demographic and health-related features. (H_0: There will be no relationship between demographic and health-related features and the presence of aberrant GMs).

1.3.3 Specific Aim 3: Identify the degree of congruence between the presence of aberrant GMs and report of developmental concerns by the infant's parent or a non-parent caregiver (e.g., another family member, childcare provider, or healthcare professional).

Hypothesis 3.1: The proportion of infants presenting with aberrant GMs will occur at a rate that is significantly different to the proportion of parents or non-parent caregivers than reporting developmental concerns. (H_0: The presence of aberrant GMs will occur at a rate similar the proportion of parents or non-parent caregivers reporting developmental concerns).

Table 1: Complete List of Demographic and Health-Related Features

Type of Variable D=dependent I=independent	**Variable Name**	**Variable Label**	**Level of Measurement** N=nominal I-R=interval-ratio
D	**global_judgement_ for_ analysis**	**Does the infant express normal GMs?**	**N** (0 = aberrant GMs, 2 = normal GMs)
I	**pma_at_birth_calc**	**How many days was the infant born before his/her expected due date?**	**I-R** (Post-menstrual age at birth - 280 days)
I	**length of NICU stay**	**How many days did the infant spend in the NICU?**	**I-R** (In days)
I	**Sex**	**Is the infant male?**	**N** (0 = female, 1 = male)
I	**race_from_epic**	**What is the infant's race?**	**N** (0 = American Indian, 1 = Asian, 2 = black, 3 = Native Hawaiian, 4 = white, 5 = other, 6 = biracial)
I	**during_pregnancy_ __1-8**	**How many medical events were documented during pregnancy?**	**I-R** (Total number of documented medical events occurring during pregnancy)
I	**mode_of_delivery_ __3 (unplanned c-section)**	**Was an unplanned c-section required during delivery?**	**N** (0 = no, 1 = yes)
I	**birth_weight**	**Infant birth weight**	**I-R**
I	**medical_events_ since_ birth___1-7**	**How many medical events were documented during the post-natal period?**	**I-R** (Total number of documented post-natal medical events)

1.4 Research Methodology

1.4.1 Study Design

This dissertational work was interconnected to a larger project that was designed as a longitudinal, cohort study that will be continued over the next 18 years.

Chapter 2 addresses Specific Aim 1, reporting on how GMs were categorized to calculate the prevalence of aberrant GMs in a more inclusive population of infants with and without NDR. This study also evaluated data collection methods and suggested refinements for the ongoing, larger project.

Chapter 3 addresses Specific Aim 2, with the frequency and distribution of demographic information/health-related features described (see Table 1 for the complete list of variables), using mean, median, mode, and ranges, as appropriate. Correlations were also calculated to evaluate the significance of existing relationships between aberrant GMs and collected demographic/health-related features using Pearson's *r*. A binomial logistic regression and a Chi-Square Test of Independence were then used to report on the significance of a generated model to predict the occurrence of aberrant GMs based on preterm birth.

Chapter 4 addresses Specific Aim 3, reporting on the frequency, distribution, and associations between the presence of aberrant GMs and perceived developmental concerns by a parent or non-parent caregiver (e.g., another family member, childcare provider, or healthcare professional) using descriptive statistics and a Chi-Square Test of Independence.

1.4.2 Participants

In total, records of 561 infants were reviewed, however, 160 of these infants were excluded as video data were either unavailable due to technical problems (n=57) or because the GMs captured could not be accurately categorized due to the infant's behavioral state or other uncontrollable factors (n=103). Therefore, our analyses were based on a sample of 401 infants. There was a representative distribution of infants by gender, race, and ethnic background, with 128 infants presenting without a single NDR, with 188 infants enrolled in primary care offices.

Participants were recruited through Nationwide Children's Hospital's (NCH) network of clinics, including three primary care offices and eight different specialty clinics (e.g., early developmental follow-up clinic, cardiology, and therapy services). Infants were included in these studies if: (a) they were less than 7-months of age (corrected age, if born preterm), and (b) if a parent or legal guardian (*hereby inclusively referred to as parent)* was able to read English and provided written informed consent. Infants were excluded if they could not tolerate a 2-minute video recording (at minimum).

1.4.3 Instrumentation

An infant's spontaneous GMs were recorded for up to 6-minutes using a Microsoft Azure Kinect© camera and Surface tablet that captured x, y, and z coordinates of each body segment at up to 30 frames per second. These recordings (as MKV and MP4 files) were securely stored on an Azure Cloud Service tenant and were later reviewed and categorized as normal or aberrant by a specially trained assessment team (*with training procedures further described in section 1.4.4*).

Demographic and health-related features were also collected from a study-specific parental survey (see Table 1 for the complete list of variables). This survey was iteratively developed after a review of relevant literature, existing surveys, and registries used to track developmental outcomes in infants (*see more about survey construction and limitations to this instrument in section 5.2*). From this review the following constructs were deemed relevant to compare against the presence of aberrant GMs: infant gender, race, and ethnicity, as well as pregnancy history (e.g., instances of maternal infection, surgery, or maternal substance use), birth history (including birth height and weight and mode of delivery), and medical complications occurring after birth (e.g., infantile seizures, infection, or surgery). Additional questions were included to document parent or a non-parent caregiver (e.g., another family member, childcare provider, or healthcare professional) concerns.

1.4.4 Procedures

Approval for this study was received from the Institutional Review Boards of NCH (NCH IRB#12-00001) and Youngstown State University before enrolling infants or collecting data (see Appendix A for Institutional Review Board approval letters and submitted study protocol). All study staff involved in recruitment and consenting followed a standardized process that included summarizing the study purpose as well as describing the time commitment and procedures for participation. When a parent agreed to enroll their infant as a participant, they were informed of the procedures and risks of the study as well as privacy and data storage considerations included in the informed consent prior to parents giving their written consent.

Once consented, study staff distributed the survey to parents to collect demographic and health-related information in addition to asking parents to list any current diagnoses for their infant (see Appendix B for parental survey). When information was not provided by the parent, study staff completed a review of the infant's medical record. All information collected was then entered and stored into a password protected REDCap instrument designed specifically for this study.

To capture video data, infants were positioned on their back on an anti-reflective mat under a mounted Microsoft Azure Kinect© camera with GMs recorded for up to 6-minutes (see Appendix C for image of video set up for capturing GMs). Study staff also documented the infants' behavioral state at the time of recording, with additional processes employed to minimize extraneous distractions such as the parent talking to or touching the infant and discouraging use of a pacifier, as these things can influence the expression of GMs. No more than 20-minutes was required to set up the video capture system, prepare the infant participant, and record GMs. All video files were then uploaded to a secured Azure Cloud Service Tenet.

A blinded assessment team comprised of three pediatric physical therapists was responsible for categorizing GMs. All three assessors (MW, MI, & OM) received basic training through the General Movements Trust with advanced training completed by two of the three assessors (MW & MI). Prior to reviewing study videos, all assessors independently reviewed 20 videos with known classifications of GMs before discussing as a team. The videos collected from study participants were also independently reviewed and categorized

as normal or aberrant by at least two assessors, with the third assessor included in cases of disagreement. In addition, all three assessors reviewed every 25th video (n=45, 16.1%) to check and ensure ongoing inter-rater reliability which was strong (average k = 0.93; k = 0.92 for infants less than 6-weeks and k = 0.94 for infants 9-20-weeks PTA) and was greater than the inter-rater reliability (k = 0.86) reported in previous literature (Valentin et al., 2005).

All GM categorizations were entered and stored into a password protected REDCap instrument that was separate from where demographic and health-related features were stored to keep the assessors blinded of each infant's health status.

1.4.5 Data Analysis

The frequency and distribution of key demographic or health-related features, including (but not limited to) age, gender, history of preterm birth, and normal or aberrant categorization of GMs were descriptively analyzed (see Table 1 for the complete list of variables). The overall prevalence of aberrant GMs in infants with and without NDR was calculated in addition to examining how frequently different types of GMs occurred by age as well as by the clinic where the infant was enrolled.

Chi-Square Tests of Independence were used to examine associative significance between different data (e.g., the presence of normal or aberrant GMs compared to the absence or presence of perceived concerns). A bivariate correlational analysis was also used to determine which factors were associated with the presence of aberrant GMs before running

a binomial logistic regression. All analyses were completed using IBM SPSS 28.0 (IBM Corp. Armonk, NY).

Two a priori power analyses were performed using G*Power 3.1 (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany). The first was done to estimate a sample for a binomial logistic regression which yielded a minimum sample size of 342 infants (which then informed our targeted enrollment for this work). This was calculated by considering existing associations between the selected demographic and health-related features and the presence of neurodevelopmental disorders, using an odds ratio of 1.96 and alpha level of 0.05. The second a priori power analysis was used to estimate the number of participants needed to run a Chi-Square Test of Independence. This yielded a minimum sample size of 88 using a medium effect size of 0.3, power level of 0.80, and alpha level of 0.05.

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2 Democratizing access to early identification of neurodevelopmental disorders protocol: a preliminary analysis of aberrant general movements in infants

2.1 Overview

This protocol report (target journal: *Physical Therapy*) was conducted through a cross-sectional analysis of data from 279 infants less than 6-weeks PTA or between 9- and 20-weeks PTA enrolled as part of the larger, multi-year project that will continue beyond this dissertational work. This paper addressed:

> Specific Aim 1: Identify the prevalence of aberrant GMs for infants with and without NDR.

In addition to providing an appraisal of the current prevalence of aberrant GMs among a group of infants with and without NDR, this paper also described refinements made to original methodological processes for the larger ongoing project and the benefits and impact of these changes. This interim analysis, along with forthcoming data from the larger project, are particularly important as existing research related to early detection of neurodevelopmental disorders and the use of the GMA have focused on infants with NDR. Therefore, much is unknown about the clinical utility of the GMA when used for a more inclusive population of infants with or without NDR. With additional evidential support, it may be possible to use GMs as a functional biomarker to detect neuromotor dysfunction in a more inclusive population of infants. This can then lead to earlier identification and treatment of neurodevelopmental disorders, and, thus, help to optimize the function and quality of life for individuals with such conditions.

2.2 Abstract

Objective: This protocol report contains an interim analysis of data from a large, multi-year project that is still actively recruiting participants. The larger project was designed to categorize the general movements of up to 6000 infants and explore alternative mechanisms to democratize efforts for early detection of neurodevelopmental disorders. Through this initial synthesis, the feasibility and acceptability of methods being used to collect data were examined. In addition, processes that could help facilitate or impede the successful attainment of project goals were considered in terms of ongoing study viability. A secondary aim of this report was to determine the prevalence of aberrant general movements in a sample of infants who present with and without newborn detectable risks.

Methods: The larger project was designed as a longitudinal, cohort study with cross-sectional data examined for this interim report. Infants' general movements were recorded and later categorized by a specially trained team using processes established by the General Movements Trust. Demographic and health-related data were also collected through a survey given to parents. Forthcoming long-term data will include the neurodevelopmental outcomes of participants.

Impact: Three refinements related to procedural methods and data collection techniques were identified, none of which cause substantive changes to the methodology of the larger, multi-year project. The benefit for integrating these modifications now is to allow for more efficient attainment of desired data and achievement of study goals. This is the first known study to intentionally assess aberrant general movements in an inclusive population of infants which was calculated to be 45.2% based on interim data. The clinical implication of this prevalence is not clear but will be examined longitudinally over the next 18 years

with future data from the larger project helping to determine the diagnostic accuracy of the GMA to screen for neurodevelopmental disorders in all infants.

2.3 Manuscript

A large, epidemiological, multi-year project was recently launched to explore alternative mechanisms that could lead to earlier, more equitable identification of neurodevelopmental disorders in young infants. Plans are in place to recruit up to 6000 infants with their neurodevelopmental outcomes tracked for the next 18 years. This protocol report aims to describe the overall study design and acceptability of data collection methods as well as examine the prevalence of aberrant general movements (GMs) in infants who are currently enrolled in this project. Understanding the clinical utility of using aberrant GMs as a functional biomarker or proxy for adverse developmental outcomes has the potential to decrease the age when neurodevelopmental disorders are identified, which is the true clinical standard or long-term outcome of interest. This longitudinal project builds upon an assemblage of past research that has stressed the importance for early and accurate identification of neurodevelopmental disorders which can help optimize long-term functional outcomes for infants and their families.[1–8] Yet confidently establishing a diagnosis early is not without challenge, as there is no single laboratory biomarker or assessment that definitively reveals such conditions.[2,4,5] This is demonstrated by the fact that 90% of children with a variety of neurodevelopmental disorders (e.g., cerebral palsy [CP], autism, and intellectual disabilities) are not diagnosed or treated until after their third birthday.[9–11]

Delayed identification of neurodevelopmental disorders can have a significant impact on infants, families, and the broader society. In fact, one out of six children in the United States is diagnosed with such conditions which can cause limitations in function and participation as well as emotional and economic stress across one's lifetime.[12] While somewhat hard to generalize, the medical costs associated with caring for a child with CP can be up to 10 times greater than caring for a child without,[13] with reports that these expenses increase as disability becomes more severe.[14] However, there is an opportunity to minimize disease burden, ameliorate disability, and improve overall quality of life through innovative strategies that actionably advance early detection and treatment efforts.[4,6,14,15]

One fundamental reason to find alternative mechanisms to support the identification of neurodevelopmental disorders in infants as young as possible is that the initiation of interventions during the first 1000 days of life can optimize physical and cognitive competence, as this is a time of great neuroplasticity.[4,5,8,9,16,17] However, even in high-income countries, a diagnosis of CP (the most common neuromotor disability occurring in childhood) may not be established until 12-24 months of age.[2,4] Without a formal diagnosis, access to services that could ultimately improve a person's functional and participatory capacity within society may be obstructed.[11,15,16,18–20] This is problematic as without early identification and provision of time-sensitive, condition-specific treatments, there is a greater risk for more disabling secondary complications to develop, which can include orthopedic deformities, deconditioning due to immobility, and mental health disorders.[4,15,21]

This problem has been recognized by the American Academy of Pediatrics, with guidance documents disseminated that recommend screening an infant's developmental progress at 9-, 18- and 30-months.[3,10,19,20,22] This surveillance typically occurs during routine health supervision visits, with providers often relying on milestone checklists that are readily available and quick to complete as a means to detect developmental delays and dysfunction. Helpful in older-aged children, these checklists are less sensitive for identifying dysfunction in infants.[2,9,22] Furthermore, waiting to see if an infant achieves key milestones (i.e., independent sitting or walking at 9- and 18-months, respectively), may unnecessarily and regrettably delay the diagnostic process. Providers must therefore look for other markers to detect dysfunction that could indicate CP in young infants, including behavioral state dysregulation, impaired posture and balance, and aberrant general movements (GMs).[1,2]

As such, incorporating practices to assess for aberrant GMs (as a functional biomarker and proxy for adverse developmental outcomes) in infants less than 5-months of age may be warranted. Correspondingly, there is a growing trend for specialty providers (e.g., neonatologists, neurologists, and pediatric occupational and physical therapists) to administer Prechtl's General Movements Assessment (GMA) when monitoring the health and developmental progress of infants with newborn detectable risks (NDR) (i.e., those infants with a history of preterm birth, neonatal asphyxia, genetic variations, and/or congenital birth defects).[2,4,23] Yet there is inconsistent utilization of the GMA by specialty providers, especially in the United States,[24] which means that many infants with NDR will not have the opportunity to be screened for this early sign of neuromotor dysfunction.

Moreover, these practices disproportionately focus on monitoring the health and developmental progress of infants with NDR, even though infants without NDR account for half of the population of children diagnosed with CP.[4,5,9,25] As it is uncommon for infants without newborn detectable risks to have reason to see specialty providers who more likely have the training and skills to effectively assess for aberrant GMs, there is a need to consider if the GMA could be effectively and feasibly be used to screen for neuromotor dysfunction in a more inclusive population of infants with and without NDR.

The GMA is a non-invasive, observational assessment for infants 26-weeks post-menstrual age through 5-months post-term age (PTA).[23,26] Using gestalt perception, GMs are categorized according to one of two age-specific patterns: writhing (for infants less than 6-weeks PTA) and fidgety (for infants 9- to 20-weeks PTA).[23,26] Normal writhing GMs sequence through the arms, neck, and trunk, and are expressed with an intensity that waxes and wanes in a pattern that is variable and complex.[23,26] Analogously, normal fidgety GMs can be described as tiny, cogwheel or multiplanar type movements occurring with moderate acceleration within joint spaces.[23,26] GMs that are declared to be aberrant can predict risk for later neurodevelopmental disorders including identifying infants with CP with 98% sensitivity when patterns of cramped synchronized GMs are followed by absent fidgety GMs.[4,23] A secondary source has also recently recounted associations between aberrant GMs and other neurodevelopmental disorders including genetic syndromes, autism spectrum disorder, and intellectual disabilities.[26]

Therefore, the purpose of this project is to explore if and how aberrant GMs could be used as a functional biomarker or proxy for identifying neurodevelopmental disorders in infants with and without NDR. Forthcoming results could substantially impact how providers across settings utilize the GMA to detect aberrant GMs in infants less than 5-months of age and thus, help to decrease the age in which a formal diagnosis is established.

Methods:

Trial Design and Setting

Democratizing Access to Early Identification of Neurodevelopmental Disorders project is an ongoing epidemiological study being conducted through Nationwide Children's Hospital's (NCH) network of primary care and speciality clinics. NCH's Institutional Review Board (study # IRB12-00001) has approved this study. The interim analysis described in this protocol report was based on a cross-sectional subsample of infants currently enrolled.

Eligibility Criteria

Infants were included in this study if: (a) they were less than 7-months, and (b) a parent or legal guardian (*hereby referred to inclusively as parent*) could read English and was willing to provide written informed consent. Infants of all gender, race, and ethnic backgrounds were eligible, with participants only excluded if the infant was unable to tolerate a 2-minute minimum video recording.

Study Staff Training Procedures

All study staff involved in data collection completed a hospital-based onboarding process in addition to attending a study-specific orientation. The central goal of this orientation was to standardize methods related to recruitment and data collection. The orientation was led by researchers and authors MI/KA with each study staff member evaluated for competence related to adhering to study protocols and operating necessary equipment and computer software.

Recruitment

A convenience sampling technique was used. Trained study staff approached parents to recruit participants in the waiting rooms of three primary care and eight specialty clinics (e.g., early developmental follow-up clinic, cardiology, and therapy services).

All parents of potential participants were informed orally of the procedures and risks of the study, privacy and data storage considerations, and other information outlined in the informed consent. If a parent agreed to have their infant participate, informed consent was obtained electronically as required by the ethics committee and in accordance with the Declaration of Helsinki.

The consenting process and collection of data were completed in a private testing area pre-designated by facility personnel and study staff. Demographic features such as an infant's age, race, and gender, as well as health-related factors such as complications occurring in pregnancy, birth history, and medical complications in the post-natal period were collected

from parents via a survey. This self-report survey also included a question for parents to list any current diagnoses for their infant in addition to information related to referrals made to specialty providers (see Appendix A for complete survey).

Videos of infants' GMs were recorded for up to 6-minutes (using a Microsoft Azure Kinect© camera) according to the standardized administration process delineated by the General Movements Trust. Each recording produced a MKV file with x, y and z coordinates of an infant's movements which was then converted and stored as a MP4 file.

Withdrawal Criteria

Families were informed that they could withdraw participation if their infant became inconsolable or for any other reason during or after the visit without influence on the services they receive from NCH clinics or hospital.

Assessment Procedure

To ensure integrity when categorizing GMs, a process was established to document independent and consensus opinion among a three-member assessment team. This team of three pediatric physical therapists all achieved Basic GMA Certification through the General Movement Trust, with two of the assessors also trained in the Advanced Certification course. Before reviewing study videos, all assessors categorized and discussed 20 training videos of infants with known classifications of GMs.

All processes related to recruiting, enrolling, and collecting survey data were completed by trained study staff; thus, the assessment team was blinded to each participant's health-related history and non-visible demographic features. In other words, the involvement of assessors was limited to reviewing and categorizing captured videos. Each video was independently reviewed and categorized as normal or aberrant by two assessors before ensuring consensus. If there was disagreement in how GMs were categorized, a third assessor reviewed the video.

A convention was also implemented to certify inter-rater reliability over time (i.e., all three assessors reviewed every 25th video). This interim analysis indicated that there was strong inter-rater reliability (k = 0.93). Moreover, there was 100% agreement by at least two assessors for 100% of cases following a systematic process where initial disagreements could be discussed.

Data Management and Monitoring

Videos were uploaded and stored using the password protected NCH Azure Cloud Services tenant, which meets HIPAA privacy and security standards (https://azure.microsoft.com/en-us/overview/trusted-cloud/). Only approved study staff with the need to view these videos have access. Other than the infant video, no additional identifiable information was included in the video files. A secure, custom-designed REDCap instrument was created to store the informed consent document, parental survey responses that have been deidentified, as well as how GMs were categorized.

Interim Sample Size

For this interim analysis, all available data were reviewed. At the time of this report, 949 infants had been enrolled (~15.8% of the targeted sample). However, fully completed records were only available for 561 infants (9.4%).

Statistical Analysis

Descriptive statistical analyses were completed to highlight findings and distribution of key demographic and health-related factors as well as the prevalence of aberrant GMs identified within this cross-sectional sample of infants with and without NDR. Frequency data, median values, and ranges were calculated, as appropriate. All analyses were completed using IBM SPSS 28.0 (IBM Corp. Armonk, NY).

Role of Funding Sources

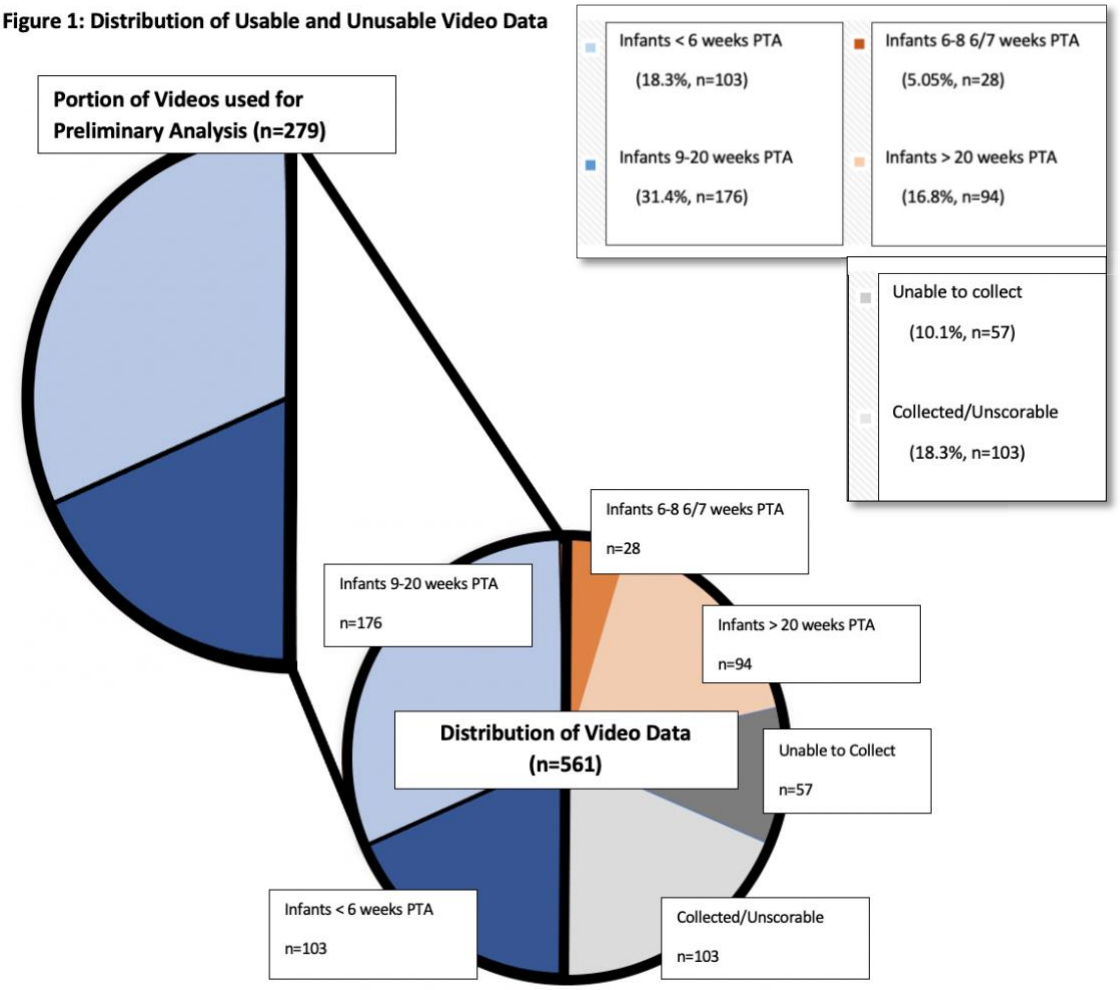
Funding was received from Microsoft Philanthropies and the American Physical Therapy Association Academy of Pediatrics. The funders had no role in the design, conduct, or reporting of this study.

Interim Results:

Of the 561 records reviewed, an additional 282 participants were excluded, resulting in a final sample of 279 infants (see Figure 1). The reasons that these infants were excluded reflected cases where infants were enrolled but GMs were not captured due to technical problems (n=57) or because an infant's GMs were influenced by uncontrollable factors (n=103).

Examples of these uncontrollable factors included infants that were crying, sleeping, wearing excessive clothing, or because a parent was touching or talking to the infant throughout the recording. Finally, because this larger, ongoing project aims to explore alternative methods to screen for neuromotor dysfunction in any infant less than 7-months of age, our cross-sectional sample included 122 (21.7%) infants recorded at ages that were not appropriate for their GMs to be categorized using the GMA; thus, these infants were also excluded from this interim analysis.

Figure 1: Distribution of Usable and Unusable Video Data



The distribution of key demographic and health-related factors of our interim, cross-sectional sample of infants with useable videos are included in Table 1. In addition to frequency data, median values and ranges were calculated for age at birth (median: 38 6/6 weeks PMA, range: 23-43 weeks PMA); birth weight (median: 3200 grams, range: 500-5000 grams); and duration of time spent in the NICU (median: 21 days, range: 0-217 days). There were slightly more males, (145, 52.0%) with a majority of infants being white or Black (128, 45.9% and 100, 35.8%, respectively). Seventy-five infants were classified without a single NDR (based on survey data collected from parents). Table 1 highlights the proportion of infants identified with specific NDR (e.g., preterm birth <37 weeks post-menstrual age [n=71, 25.4%], birth weights of <2500 grams [n=60, 21.8%], and/or any amount of time spent in the neonatal intensive care unit [n=93, 33.3%]).

Table 1: Frequency Distribution of Demographic Features of Current Sample

Age at Time of Video Recording (post-term age in weeks)	**N**	**%**
*Birth to 5 6/7	103	25.7
*9-20	176	43.9
6-8 6/7	28	7.0
>20	94	23.4
Total	**401**	**100.0**
*Participants in Ideal Ages for GMA (N=279)		
Gender	**N**	**%**
Female	133	47.7
Male	145	52.0
Total	**278**	**99.7**
Race	**N**	**%**
American Indian / Alaskan Native	1	0.4
Asian	9	2.9
Black	100	35.8
Native Hawaiian / Pacific Islander	1	0.4
White	128	45.9
Other	15	5.4
Biracial	24	8.6
Total	**277**	**99.4**

Table 1: Frequency Distribution of Demographic Features of Current Sample – Cont.

Age at Birth (post-menstrual age in weeks)	**N**	**%**
≥37 (259)	208	74.6
**32-36 6/7 (224)	36	12.9
**28-31 6/7 (196)	19	6.8
**<28	16	5.7
Total	**279**	**100.0**
Birth Weight (in grams)	**N**	**%**
≥2500	215	77.1
**1000-2499	45	16.1
**<1000	15	5.4
Total	**275**	**98.6**
Length of NICU Hospitalization (in days)	**N**	**%**
0	186	66.7 (0.0)
**1-6	12	4.3 (12.9)
**7-20	32	11.4 (34.4)
**≥21	49	17.6 (52.7)
Total	**279**	**100.0 (100.0)**
** = Newborn Detectable Risk		

Data were also analyzed to determine the distribution of GM categorization by age-specific type (i.e., writhing and fidgety GMs) and the clinic where an infant's GMs were captured (see Figures 2 and 3).

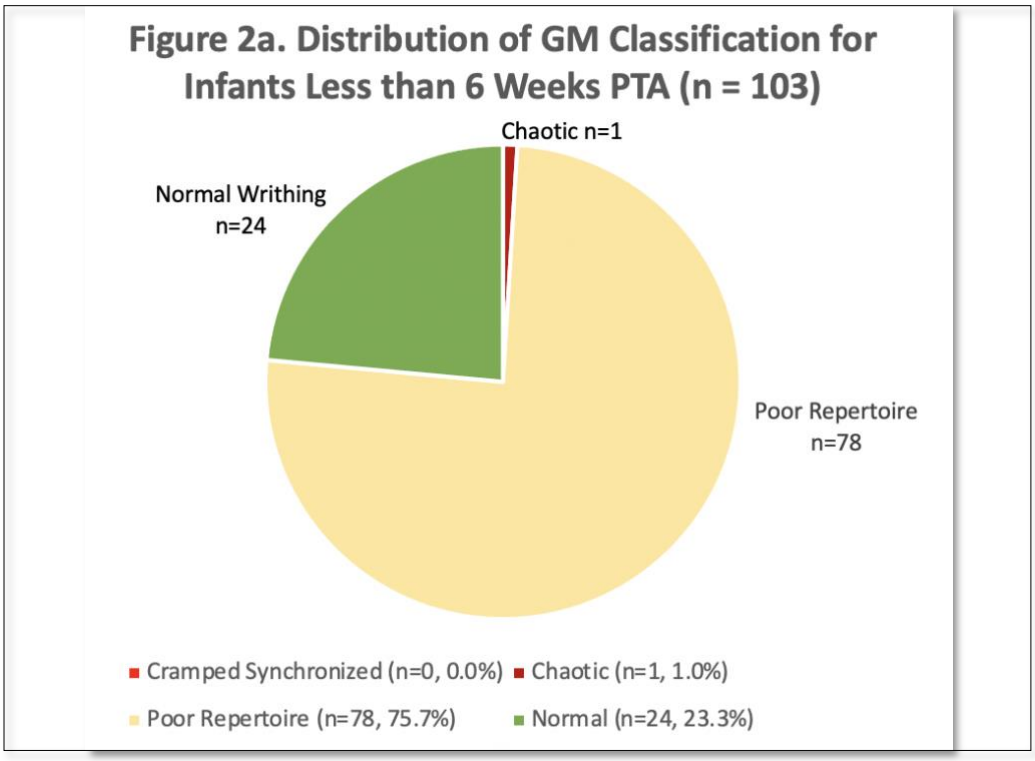


Figure 2a. Distribution of GM Classification for Infants Less than 6 Weeks PTA (n = 103)
Chaotic n=1
Normal Writhing n=24
Poor Repertoire n=78
Cramped Synchronized (n=0, 0.0%)
Chaotic (n=1, 1.0%)
Poor Repertoire (n=78, 75.7%)
Normal (n=24, 23.3%)

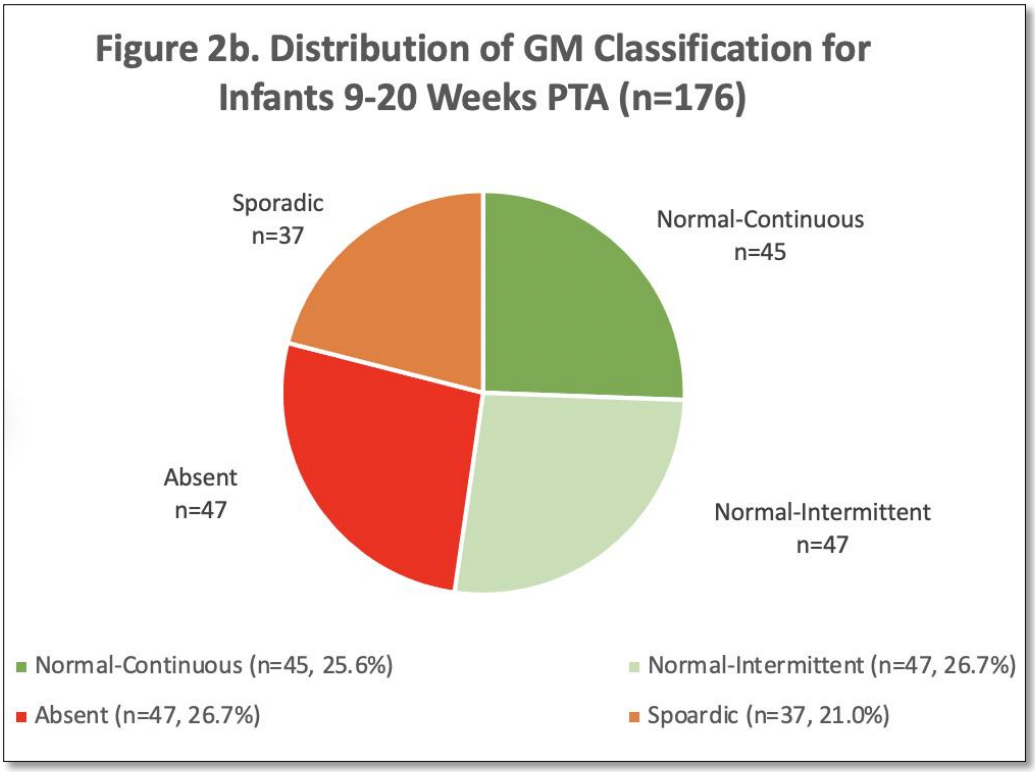


Figure 2b. Distribution of GM Classification for Infants 9-20 Weeks PTA (n=176)
Sporadic n=37
Normal-Continuous n=45
Absent n=47
Normal-Intermittent n=47
Normal-Continuous (n=45, 25.6%)
Normal-Intermittent (n=47, 26.7%)
Absent (n=47, 26.7%)
Spoardic (n=37, 21.0%)

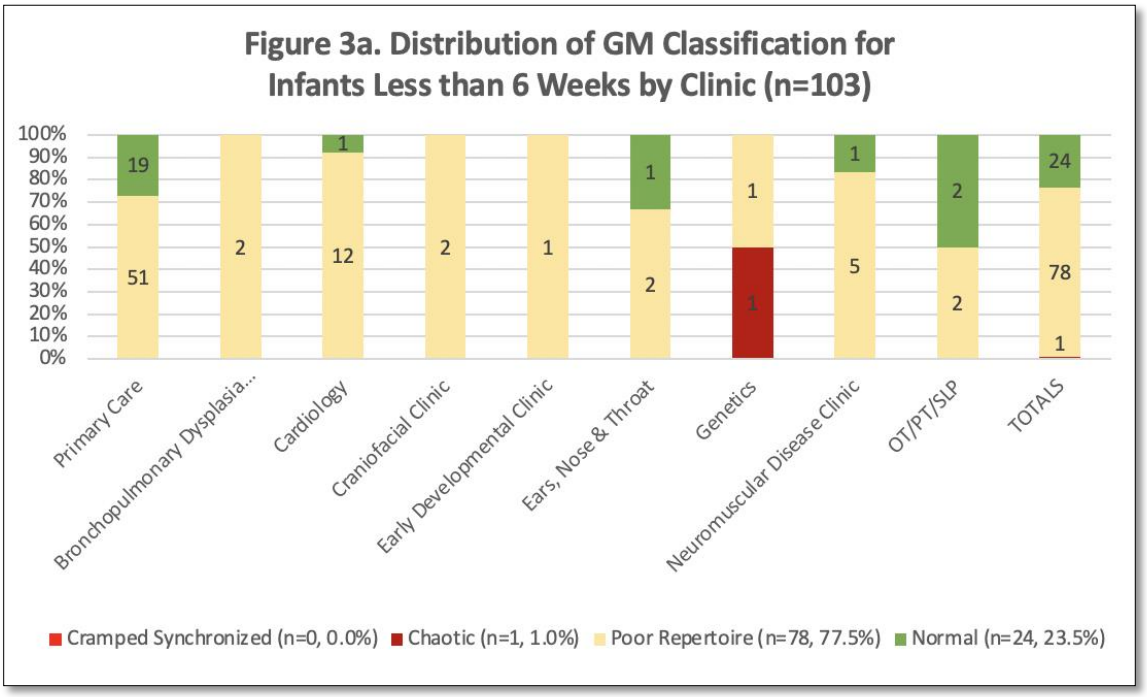


Figure 3a. Distribution of GM Classification for Infants Less than 6 Weeks by Clinic (n=103)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
19
51
2
1
12
2
1
1
2
1
1
5
2
2
24
78
1
Primary Care
Bronchopulmonary Dysplasia...
Cardiology
Craniofacial Clinic
Early Developmental Clinic
Ears, Nose & Throat
Genetics
Neuromuscular Disease Clinic
OT/PT/SLP
TOTALS
Cramped Synchronized (n=0, 0.0%)
Chaotic (n=1, 1.0%)
Poor Repertoire (n=78, 77.5%)
Normal (n=24, 23.5%)

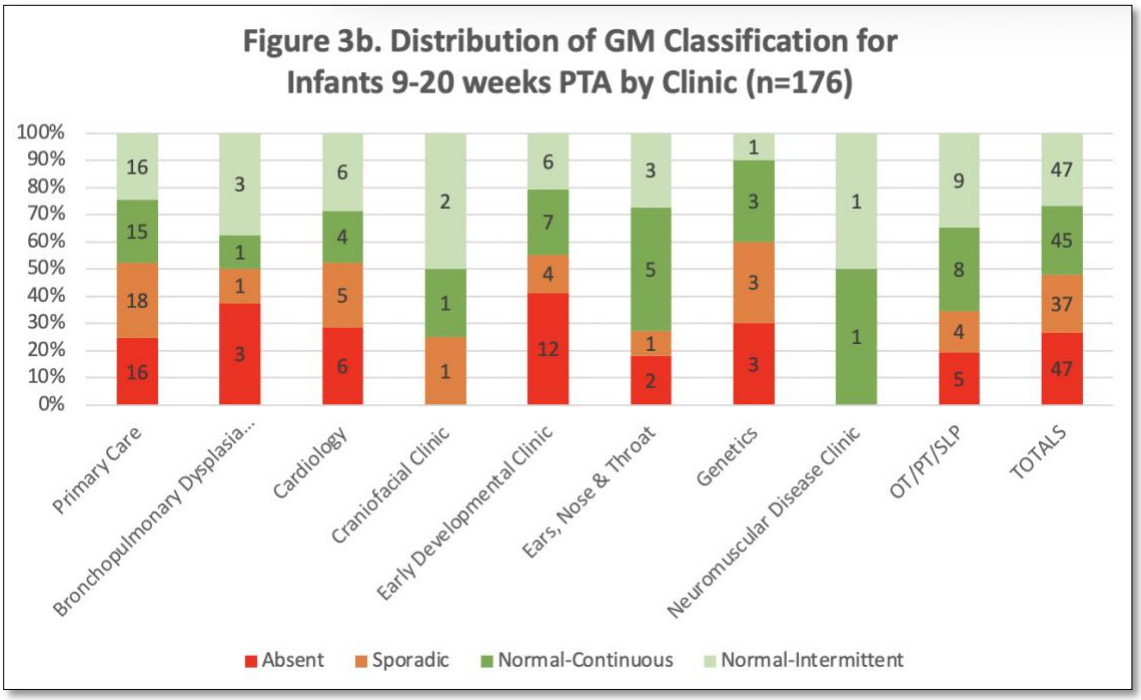


Figure 3b. Distribution of GM Classification for Infants 9-20 weeks PTA by Clinic (n=176)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
16
15
18
16
3
1
1
3
6
4
5
6
2
1
1
6
7
4
12
3
5
1
2
1
3
3
3
1
1
3
1
9
8
4
5
47
45
37
47
Primary Care
Bronchopulmonary Dysplasia...
Cardiology
Craniofacial Clinic
Early Developmental Clinic
Ears, Nose & Throat
Genetics
Neuromuscular Disease Clinic
OT/PT/SLP
TOTALS
Absent
Sporadic
Normal-Continuous
Normal-Intermittent

Overall, poor repertoire GMs (occurring in infants less than 6-weeks PTA) were equally distributed across all clinics. For infants between 9- and 20-weeks PTA, absent fidgety GMs were observed more often in clinics designed to manage the care of infants with bronchopulmonary dysplasia (BPD) and genetic conditions, as well as the early development clinic which primarily follows infants who are born preterm (i.e., presenting with NDR).

Missing Values

As there was a heavy reliance on parental report for capturing demographic and health-related data, there were some missing data. Retrospective chart reviews were completed to gather missing data before adjusting the total number of participants for the applicable variables (i.e., birth weight [n=397], race [n=398] and gender [n=400]).

Discussion

The findings from this interim analysis identified two important refinements to the larger project that is still actively recruiting participants. These refinements do not entail substantial alterations to the initial study design. The changes recommended, the benefits gained, and their impact on the ongoing study are described below.

Refinement #1: Minimizing unusable videos

After realizing that 28.5% (n=160/561) of infants were recorded while their GMs were influenced by uncontrollable factors (i.e., behavioral state or excessive external stimulation), all study staff now receive training on basic infant handling and calming

techniques to be used to prepare the baby prior to capturing GMs. Similarly, portable heaters are now used to keep the infant from getting chilled. Recording the infant's GMs prior to the infant receiving shots or other medical procedures has also resulted in more usable videos. Moreover, the investigation team devised a mechanism to flag infants who were crying or sleeping, with requests made to record that infant again at a subsequent visit.

Refinement #2: Reinforcing pathways for evaluating the diagnostic accuracy of the GMA once long-term neurodevelopmental outcomes are known

An established diagnosis of a neurodevelopmental disorder is the true clinical standard for knowing with confidence that an underlying pathology exists. However, the diagnostic process can take years; thus, we used a proxy, or the presence of aberrant GMs to indicate neuromotor dysfunction for this analysis. At the time of this report, the long-term outcome of interest (i.e., a diagnosed neurodevelopmental disorder) for enrolled subjects was not yet know. This limits our ability to make claims regarding the effectiveness of the GMA for identifying neurodevelopmental disorders in a more general population of infants with and without NDR. This multi-year project plans to track neurodevelopmental outcomes of participants until they are 18 years of age. Although some children will be lost to follow-up, plans are in place to document and link any report of such conditions back to the categorization of GMs. This interim analysis reinforced the need for pathways (e.g., mailing additional surveys for parents to report on their child's development) to ensure these data are collected. This will allow for future evaluation of the diagnostic accuracy of the GMA which can potentially decrease the age in which a formal diagnosis is established.

Secondary Aim: Interim Prevalence of Aberrant GMs

Finally, to the best of our knowledge, this is the first known report of the prevalence of aberrant GMs in a more inclusive population of infants. Within our interim sample, 45.2% of infants presented with aberrant GMs (i.e., absent fidgety [26.7%], poor repertoire [75.7%], or chaotic writhing [1.0%]). However, until final neurodevelopmental outcomes are known, the clinical significance of this prevalence is unclear. We can, however, postulate that using the GMA for infants less than 6-weeks PTA is ineffective, as we would assume the rate of poor repertoire GMs (occurring in 75.7% of our sample) would match the known prevalence of neurodevelopmental disorders which impacts one out of six (16.7%) of children in the United States.[12] Therefore, many of the infants we categorized with poor repertoire GMs will likely present with normal neurodevelopmental outcomes. This aligns with previous reports that have recognized that poor repertoire GMs are less predictive for identifying CP as compared to cramped synchronized GMs (which of interest, no infant within our cross-sectional sample was categorized with cramped synchronized GMs).[23] Therefore, future research could explore if the presence of poor repertoire GMs in combination with other health-related risks or features (e.g., a history of preterm birth) is more predictive of neurodevelopmental outcomes.

In conclusion, the foundational knowledge generated from this completed multi-year project will help inform developmental screening practices. Based on these interim results, this could include assessing GMs to universally screen for neuromotor dysfunction in infants with or without NDR between 9- and 20-weeks PTA. Ultimately, widespread

identification of infants at the earliest ages possible can foster access to time-sensitive, condition-specific interventions with the potential to help ameliorate long-term disability. With forthcoming data, we will better understand if using GMs as a functional biomarker to detect neuromotor dysfunction is an effective proxy for adverse neurodevelopmental outcomes. Until then, we must continue to advocate for detection efforts that triangulate data from multiple sources (e.g., the presence of aberrant GMs combined with a history of preterm birth and/or developmental concerns noted by a parent) to support identification of neurodevelopmental disorders in infants as young as possible.

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3 Trends associated with aberrant general movements assessed in infants with or without newborn detectable risks: a binomial regression analysis

3.1 Overview

This original research (target journal: *Pediatric Physical Therapy*) used descriptive statistics, correlational analysis, binomial logistic regression, and a Chi-Square Test of Independence to analyze how aberrant GMs were related to a variety of demographic and health-related features (see Table 1 for the complete list of variables). This paper addressed:

> Specific Aim 2: Identify significant relationships between aberrant GMs and certain demographic or health-related features.

Understanding the association between aberrant GMs (as an immediate, or short-term outcome for detecting neuromotor dysfunction) and other demographic or health-related features has the potential to improve a clinician's ability to accurately establish a formal diagnosis in infants as young as possible. This foundational work can then help inform if a combination or triangulation of different variables is more predictive for identifying neurodevelopmental disorders once long-term developmental outcomes are known. For example, our analysis found a significant correlation between aberrant GMs and the presence of preterm birth, or birth less than 37-weeks' gestation (Pearson $r = 0.18$, $p < 0.001$) with infants born preterm are twice as likely to express aberrant GMs as compared to those born at term (OR 2.32, 95% CI 1.05, 5.11, $p = 0.037$).

Moreover, the resultant model generated to predict aberrant GMs based on a history of preterm birth was large and significant (-2 Log likelihood = 531.85), classifying 59.2% of cases correctly. In addition, when comparing infants without a single NDR to those with at

least one NDR (e.g., preterm birth, birth weight less than 2500 grams, and/or history of admission to the neonatal intensive care unit), the goodness of fit between these variables and the presence of aberrant GMs was significant for infants between 9- and 20-weeks PTA ($\chi^2 = 5.32$, $p = 0.02$), but not significant for infants less than 6-weeks PTA ($\chi^2 = 0.72$, $p = 0.40$). This can be partially explained by the finding that 75.7% of infants less than 6-weeks PTA were categorized with aberrant, or poor repertoire GMs. Thus, the GMA may be more effective when used in slightly older infants (i.e., infants between 9- and 20-weeks PTA).

3.2 Abstract

Purpose: To evaluate if associations between aberrant general movements (GMs) and newborn detectable risks (NDR) can enhance early detection of neurodevelopmental disorders.

Methods: Correlational trends between eight NDR and GMs were appraised followed by logistic regression and Chi-Square analyses to determine the associations and significance for NDR predicting aberrant GMs.

Results: Aberrant GMs occurred three times as often in infants with NDR as compared to those without, with an overall prevalence of 45.2%. For infants 9-20 weeks, the ability for preterm birth (an NDR) to predict absent fidgety GMs was significant ($\chi^2 = 5.32$, $p = 0.021$). For infants less than 6-weeks NDR were not a significant predictor of aberrant, poor repertoire GMs ($\chi^2 = 0.72$, $p = 0.397$).

Conclusion: Linking a history of preterm birth with the presence of aberrant GMs assessed in infants greater than 9-weeks may foster earlier detection of neuromotor dysfunction and, thus, neurodevelopmental disorders.

What this adds to the evidence:

It is widely recognized that early detection of neurodevelopmental disorders (e.g., cerebral palsy) is critical for implementing time-sensitive, condition-specific interventions geared to optimize long-term function. While there have been numerous reports that have linked CP to a variety of causal indicators (e.g., preterm birth) the science behind predicting which infants will be affected is still imprecise, as there is no one laboratory biomarker or assessment that can definitively rule in or out such conditions. This study investigated how general movements could be used as a functional biomarker to enhance early detection efforts by understanding how these patterns of movement are associated with newborn detectable risks. Analyses revealed a significant association between preterm birth and aberrant general movements (i.e., absent fidgety) in infants between 9- and 20-weeks PTA, with the generated predictive model correctly classifying 59.2% of cases. This foundational work is an important first step to inform if a combination or triangulation of different variables is more predictive for identifying neurodevelopmental disorders once long-term developmental outcomes are known.

3.3 Manuscript

INTRODUCTION:

Globally, there are nearly 53 million children under the age of five who have been diagnosed with a neurodevelopmental disorder.[1] Attention-deficit disorder, autism

spectrum disorder, intellectual disabilities, and cerebral palsy (CP) are a few conditions that are included under this categorical umbrella.[2] Within the United States, approximately 764,000 children and adults have a CP diagnosis, making this the most common physically disabling condition occurring in childhood.[3,4] Short- and long-term outcomes for individuals diagnosed with CP can vary.[3–9] Similarly, each child with CP can experience different developmental achievements as associated impairments can affect motor, cognitive and sensory functions, all of which can delay or alter how a child moves, learns, communicates, socializes, and behaves.[5,6,8,10] Provision of targeted interventions during the first 1000 days of life when neuroplasticity is at its greatest can help counter potentially disabling effects;[1,6,9–16] although, access to these services may be restricted until a formal diagnosis is established.[2,12,14,17–19]

In high-income countries, the average age for CP diagnosis occurs between 12- and 24-months.[6,14,19] However, due to health inequalities in underserved areas both in the United States and around the world diagnosis may not be established until much later.[20] Current International Clinical Guidelines have pushed for earlier identification of CP and other neurodevelopmental disorders,[14] but this is challenged since there is no one laboratory biomarker or assessment that can definitively predict clinical outcomes during infancy.[6,14,19] Certain newborn detectable risks (NDR) have been consistently and significantly predictive of CP (e.g., birth before 37-weeks' gestation, birth weight less than 2500 grams, health-related complications in the intrapartum period [i.e., emergent cesarean delivery], and complications in the neonatal period [i.e., seizures and/or infection]).[6] For example, previous literature has reported that up to 10% of infants born before 28-weeks'

gestation eventually receive a CP diagnosis.[6] It has also been reported that aberrant general movements (GMs), more specifically cramped synchronized followed by absent fidgety GMs, can reliably predict CP in infants with NDR (with a sensitivity of 98%).[14,21] Therefore, understanding the association between probabilistic NDR and GMs (as a functional biomarker) could help detect which infants may end up having a neurodevelopmental disorder.

There has been a recent (although inconsistent) trend for assessing GMs in specialty clinics, where a team of specialty providers (e.g., neonatologist, neurologist, developmental pediatrician, nurse practitioners, and pediatric occupational or physical therapists) routinely monitor the health and developmental progress of infants with NDR.[14,17] This additional layer of monitoring accompanies preventative services provided through primary care. In contrast, the health and developmental progress of infants without NDR is typically monitored by primary care providers only, even though half of children diagnosed with CP present without NDR.[6,12,14] From a clinical perspective, this means that infants without NDR may not have an opportunity to have their GMs assessed.[17,18] Instead, ill-fitted milestone checklists (that can be quickly and easily used) may be what is used to evaluate an infant's development during health supervision visits with primary care providers. Historically, primary care providers will wait to see if two key milestones, unsupported sitting and unassisted walking are achieved at 9- and 18-months, respectively before declaring neuromotor dysfunction or delay. This aligns with guidance from the American Academy of Pediatrics, with recommendations for developmental screenings to be conducted beginning at 9-months.[5,7,23,24] Yet, waiting this long can unnecessarily

postpone the establishment of a diagnosis and delay the initiation of time-sensitive, condition-specific treatments. There is, however, a potential to minimize these delays by incorporating an assessment of GMs to screen for neuromotor dysfunction in all infants less than 5-months.[6,18,23,25,26]

The GMA requires gestalt perception to identify qualitatively distinct, age-specific patterns of movement.[21] Previous studies have demonstrated that there is a high degree of inter-rater agreement (93%) among trained assessors.[27] The first pattern, writhing GMs, can be observed in infants less than 6-weeks post-term age (PTA). These elliptical and complex movements flow from legs to arms to trunk to neck, in variable patterns that are hard to predict.[21,28] Aberrant writhing GMs can be characterized as being repetitive and stiff (i.e., cramped synchronized), lacking complexity and fluidity (i.e., poor repertoire), or jerky (i.e., chaotic).[21,28] Fidgety GMs, observed in infants between 9- to 20-weeks PTA, are expressed within joint spaces, occurring with moderate speed and acceleration.[21,28] Aberrant fidgety GMs are characterized by having exaggerated excursions (i.e., abnormal) or are absent.[21,28] The clinical effectiveness of the GMA to identify CP in infants with NDR is most accurate when patterns of cramped synchronized are followed by absent fidgety (sensitivity = 98%).[21,28]

However, before pushing for broader adoption of the GMA to screen all infants with or without NDR we must first understand if it will be clinically useful. The purpose of this study, therefore, was to investigate the prevalence of aberrant GMs in a more inclusive

population of infants with and without NDR and determine the association between GMs and other demographic or health-related factors.

METHODS:

Study Design

This cross-sectional analysis utilized a sample of 401 infants who were enrolled as a part of a larger, multi-year project approved by Nationwide Children's Hospital Institutional Review Board (study # IRB12-00001).

Participants

Participants were enrolled from three different primary care practices (n = 188) and eight different specialty clinics (n = 213). Any infant less than 7-months (corrected age if born before 37-weeks' gestation) was included, as long as a parent or legal guardian (*hereby referred to inclusively as parent)* was able to read English and consented to participation. Infants were excluded from analysis if they did not tolerate being recorded for at least two minutes.

Data Collection

A team of three pediatric physical therapists was assembled to categorize the GMs of each infant video. All three assessors completed the basic training course through the General Movements Trust and two assessors completed the advanced training course. In addition, the assessment team engaged in a series of structured discussions using 20 videos with known categorizations of GMs prior to reviewing study videos which were marked as

normal or aberrant, with at least two assessors independently categorizing each case. A third assessor was included where assessors one and two disagreed. Moreover, all three assessors reviewed every 25th video to check inter-rater reliability which was strong (k = 0.93).

Video data were collected using a standardized process established by the General Movements Trust. Parents were asked to undress their infants down to their diapers and position them on their backs on an anti-reflective mat directly underneath a mounted camera. Study staff also discouraged parents from talking to or touching their child during the recording. GMs were recorded for up to six minutes. Two types of video files were generated and stored: MP4 files for which the assessment team used to categorize GMs, and MKV files that can reproduce x, y, and z coordinates which will be used for a later analysis as part of the lager project (see Figure 1 for a diagram of the video capture set-up).

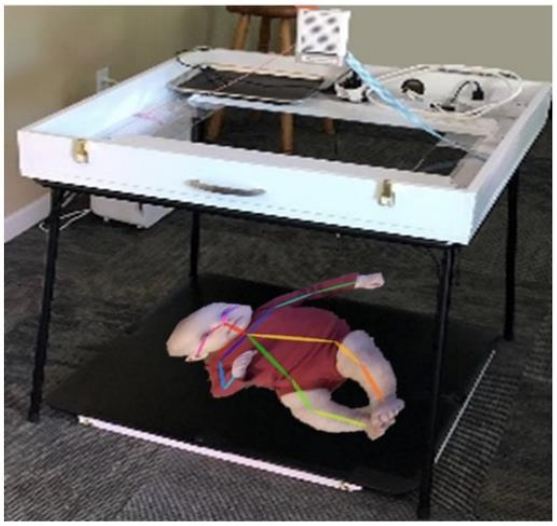

Figure 1. GMA Video Capture Set Up

Description: Infants are undressed as completely as possible before being positioned on their back directly underneath a mounted Microsoft Azure Kinect camera (1) on top of an anti-reflective mat (2) with recordings completed through a Microsoft Surface tablet (3). Parents are discouraged

from talking to or touching their child during the 6-minute recording to avoid influencing the expression of spontaneously generated GMs. Data is collected as a MKV file that can reproduce x, y, and z coordinates to more precisely map limb and trunk movements for future computerized analysis as well as a MP4 file that the assessment team utilizes to categorize GMs as normal or aberrant. All videos are securely transferred from the Microsoft Surface tablet to be stored in a password protected Azure Cloud Service Tenet through NCH which meets HIPPA privacy and security standards.

A parental report survey was designed to capture demographic and health-related features (see Appendix A for complete list of variables). The questions in this study-specific survey were iteratively developed by the research team after a review of previously published surveys, existing literature, and pediatric outcome related data registries (e.g., the Vermont Oxford Network eNICQ Patient Data Booklet). The investigators then discussed which factors presenting in pregnancy, birth, or the post-natal period were most likely to be associated with the presence of aberrant GMs and should be included in the survey. Questions were formatted as yes/no, multiple choice, or multiple select so that answers could be nominally categorized for analysis (see Appendix B for complete survey).

Five key demographic and health-related constructs were represented in the final survey: (1) infant race, (2) infant ethnicity, (3) infant gender, (4) pregnancy history, and (5) birth history. A sixth construct about how parents perceived their child to be developing, as well

as if someone other than the parent (e.g., a healthcare provider) had identified developmental concerns was also included but was not part of this analysis. Spaces allowing for free-text entry also allowed parents to provide additional comments if desired. In general, parents were able to complete this survey within 5-10 minutes. All information was subsequently entered and stored into a password-protected, study-specific REDCap instrument.

Statistical Analysis

Demographic data were evaluated using mean, median, mode, and ranges, as applicable. A preliminary bivariate correlational analysis was conducted to determine relationships between aberrant GMs and all eight demographic and health-related factors (see Appendix A for complete lists of variables). A binomial logistic regression analysis was then completed to evaluate if features that were significantly correlated could predict the presence of aberrant GMs. Finally, a Chi-Square Test of Independence was performed to determine if there was an association between aberrant GMs in the group of infants with NDR compared to the group of infants without NDR. All data analyses were completed using IBM SPSS 28.0 (IBM Corp. Armonk, NY).

Sample Size Calculation

An a priori analysis for binomial logistic regression was performed in G*Power 3.1 (Heinrich-Heine Universität, Düsseldorf, Germany). With an odds ratio of 1.96 and alpha level of 0.05, it was determined that a minimum sample size of 342 infants was needed.

Missing Values

There were minimal data missing (<10% of fields for any variable). To address this, adjustments were responsively made to the total number of participants for the applicable variable (i.e., birth weight [n=397], race [n=398] and gender [n=400]).

RESULTS:

Overall, 45.2% (n=126/279) of infants in the standardized age ranges for the GMA (i.e., less than 6-weeks or between 9- and 20-weeks PTA) were categorized with aberrant GM, with 73.1% (n=204/279) presenting with at least one NDR. When segmented by age, 75.7% (n=78/103) of infants less than 6-weeks PTA presented with poor repertoire, 0% with cramped synchronized, and 1.0% (n=1/103) with chaotic GMs. For infants between 9- and 20-weeks PTA, 26.3% (n=47/176) presented with absent fidgety GMs and there were no infants (0%) categorized with abnormal fidgety GMs. This distribution of GMs by age is presented in Table 1.

Table 1. Frequency and Distribution of Aberrant GMs for Infants Inside and Outside the Standardized Ages for Administration of the GMA

Categorization of GMs	Standardized Ages (N=279 / 401)		Non-Standardized Ages (N= 122 / 401)	
	N	**%**	**N**	**%**
Writhing less than 6-weeks	24	8.6 / 6.0	-	-
Fidgety 9- to 20-weeks	129	46.2 / 32.2	-	-
Writhing between 6- to 9-weeks	-	-	2	1.6 / 0.5
Fidgety between 6- to 9-weeks	-	-	6	4.9 / 1.5
Fidgety greater than 20-weeks	-	-	23	18.9 / 5.7
TOTAL NORMAL GMS	**153**	**54.8 / 38.2**	**31**	**25.4 / 7.7**

Table 1. Frequency and Distribution of Aberrant GMs for Infants Inside and Outside the Standardized Ages for Administration of the GMA – Cont.

Poor Repertoire less than 6-weeks	78	28.0 / 19.5	-	-
Chaotic less than 6-weeks	1	0.4 / 0.2	-	-
Fidgety 9- to 20-weeks	47	16.8 / 11.7	-	-
Poor Repertoire between 6- to 9-weeks	-	-	12	9.8 / 3.0
Absent Fidgety between 6- to 9-weeks	-	-	8	6.6 / 2.0
Absent Fidgety greater than 20-weeks	-	-	71	58.2 / 17.7
TOTAL ABERRANT GMS	**126**	**45.2 / 31.4**	**91**	**74.6 / 22.7**

The frequencies and distribution of demographic and health-related factors, as well as the significance of their association with aberrant GMs are represented in Tables 2 and 3. For our total sample (n=401), the average age of infant participants was 13 3/7 weeks PTA (range: 36 3/7 weeks post-menstrual age through 32 1/7 weeks PTA, SD 8 4/7 weeks). There were slightly more male participants (n=214, 53.5%), with the predominant races identified as white (n=192, 47.9%) and black (n=132, 32.9%). Findings from the correlational analysis (Table 2) showed significant associations between the presence of aberrant GMs and a history of preterm birth or those infants born before 37-weeks' gestation (Pearson's r = -0.18, p = <.001), birth weight less than 2500 grams (Pearson's r = 0.13, p = .008), history of NICU admission (Pearson's r = -0.13, p = .009), and medical events occurring after birth (Pearson's r = -0.14, p = .006). The remaining variables such as race, gender, and history of emergent cesarean delivery were determined to be non-significant and were therefore not included as independent variables in the binomial logistic regression analysis.

Table 2. Frequency & Correlations between Aberrant GMs, Demographic, and Health-Related Factors

			Pearson *r*	***p* (2-tailed)**
Sex (N = 400)			0.01	0.814
	Female (n=186)	46.5		
	Male (n=214)	53.5		
	TOTAL	**100.0**		
Race (N = 398)			-0.02	0.763
	American Indian/ Alaskan Native (n=1)	0.3		
	Asian (n=16)	4.0		
	Black (n=132)	33.2		
	Native Hawaiian or Pacific Islander (n=1)	0.3		
	White (n=192)	48.2		
	Other (n=21)	5.2		
	Biracial (n=35)	8.8		
	TOTAL	**100.0**		
Total Events Occurring During Pregnancy (N = 401)			0.01	0.887
	0 (n=243)	60.6		
	1 (n=136)	33.9		
	2 (n=19)	4.7		
	3 (n=3)	0.8		
	TOTAL	**100.0**		
History of Preterm Birth (N = 401)			0.10*	0.037
	37 weeks post-menstrual age (n=307)	76.6		
	< 37 weeks post-menstrual age (n=94)	**23.4**	**-0.18*** **	**<0.001**
	32-36 6/7 weeks post-menstrual age (n=50)	12.5		
	28-31 6/7 weeks post-menstrual age (n=21)	5.2		
	<28 weeks post-menstrual age (n=23)	5.7		
	TOTAL	**100.0**		
Method of Delivery (N = 401)			-0.08	0.105
	Unplanned Cesarean Section	22.7		
Birth Weight (N = 397)			0.13**	0.008
	2500 grams (n=305)	77.6		
	1000-2499 grams (n=68)	17.3		
	<1000 grams (n=20)	5.1		
	TOTAL	**100.0**		

Table 2. Frequency & Correlations between Aberrant GMs, Demographic, and Health-Related Factors – Cont.

Medical Events Occurring After Birth (N = 401)			-0.14**	0.006
	0 (n=215)	53.6		
	1 (n=130)	32.4		
	2 (n=34)	8.5		
	3 (n=13)	3.3		
	4 (n=9)	2.2		
	TOTAL	**100.0**		
Duration of Time Admitted to NICU (N = 401)			-0.09	0.065
	0 days (i.e., did not spend time in NICU) (n=276)	0.0 / 68.8		
	1 day (n=125)	**-- / 31.2**	**-0.13****	**0.009**
	1-6 days (n=18)	14.4 / 4.5		
	7-20 days (n=44)	35.2 / 11.0		
	21 days (n=63)	50.4 / 15.7		
	TOTAL	**100.0/100.0**		
	= newborn detectable risk	Note: * p< .05 ** p<.01		*** p<.001

Table 3. Distribution of Key Demographic and Health-Related Factors

Study Variable	**Mean**	**Median**	**SD**	**Mode**	**Range**
Age at birth (days/weeks post-menstrual age) (N=401)	261.3 / 37 2/7	272 / 38 6/7	+/- 26.7 / 3 5.7/7	273 / 39	161-301 / 23-43
Birth Weight (kg) (N=397)	3.0	3.2	+/- 0.9	3.3	0.5-5.0
Medical Events since birth (events) (N=401)	<1 (0.7)	0	+/- 0.9	0	0-4
Length of Time Spent in NICU (days) (N=401)	13.7	21	+/- 34.2	0	0-217

The binomial logistic regression analysis indicated that aberrant GMs occurred two times as often when an infant was born preterm (standardized beta = 0.84, $p = 0.037$, OR 2.32, 95% CI 1.05, 5.11). The overall fit of the model was large and significant (-2 Log likelihood = 531.85), classifying 59.2% of the cases correctly (see Table 4). In addition, when comparing infants without a single NDR to those with at least one NDR (e.g., preterm birth), Chi-Square analyses demonstrated that the relationship between these variables and the presence of aberrant GMs was significant for infants between 9- and 20-weeks PTA ($\chi^2 = 5.32$, $p = 0.02$), but not significant for infants less than 6-weeks PTA ($\chi^2 = 0.72$, $p = 0.40$)

Table 4. Binomial Regression Results for Predicting the Presence of Aberrant GMs (N = 401)

Study Variable	**B**	**Wald**	**df**	***p***	**Odds Ratio (95% CI)**
History of Preterm Birth	0.84	4.35	1	0.04	2.32 (1.05, 5.11)
Medical Events Since Birth	-0.19	2.27	1	0.13	0.83 (0.65, 1.06)
History of Admission to NICU	0.08	0.08	1	0.77	1.09 (0.62, 1.89)
Birth Weight	-0.10	0.32	1	0.57	0.90 (0.64, 1.28)
Constant	0.16			0.12	

DISCUSSION:

Aberrant GMs were found in almost half of our sample of infants with and without NDR, although less so in infants between 9- and 20-weeks PTA (i.e., absent fidgety GMs were categorized in only n=47/176, 26.7%). It is also important to note that GMs were used as

a short-term outcome, or proxy for identifying neuromotor dysfunction in our sample of infants, even though an eventual diagnosis of CP (or another neurodevelopmental disorder) is considered to be the true clinical standard or long-term outcome of interest. This was done intentionally, as establishing such a diagnosis can take years. However, based on this inference, we hypothesized that the prevalence of aberrant GMs would be similar to the prevalence of neurodevelopmental disorders (i.e., 16.7%), which was not the case. One possible reason for this discrepancy is that nearly three-fourths of our sample (n=204/279, 73.1%) were documented as having at least one NDR (e.g., preterm birth), a cohort of infants who we found to be nearly three times as likely to present with aberrant GMs as compared to infants without NDR. Our calculated prevalence of aberrant GMs (i.e., 45.2%) was also skewed by the proportion of infants less than 6-weeks PTA who were categorized with aberrant or poor repertoire GMs (i.e., n=78/103, 75.7%). And as previous research has already determined that poor repertoire GMs are less specific for predicting CP as compared to GMs that are classified as cramped synchronized or absent fidgety,[15,21] we can postulate that a large proportion of infants categorized with aberrant or poor repertoire GMs will have normal neurodevelopmental outcomes (i.e., will be falsely identified). Thus, the GMA may be more effective when used in slightly older infants (i.e., infants between 9- and 20-weeks PTA).

Regarding the predictive model generated from our binomial logistic regression, while there was a significant relationship between the presence of aberrant GMs and preterm birth (i.e., birth before than 37-weeks' gestation), only 59.2% of the cases were classified correctly. This indicates a need for continued exploration of how a combination or

triangulation of additional variables could further improve the accuracy for predicting neurodevelopmental disorders once long-term developmental outcomes are known. However, these findings do complement existing evidence and further supports current recommendation for administering the GMA in infants who are already known to have NDR (e.g., preterm birth) as a means to detect early signs of neuromotor dysfunction. In other words, using GMs as a functional biomarker may help further discriminate which preterm infants are most in need of time-sensitive, conditions-specific interventions, as not all infants who are born preterm will experience neuromotor dysfunction or be diagnosed with CP (or another neurodevelopmental disorder).

The collection and categorization of GMs in infants between 6- and 9-weeks PTA as well as those older than 20-weeks PTA (which are non-standardized ages for administering the GMA) was deliberate. This was done to allow for a more detailed computerized analysis of these types of movement patterns in an expanded age range of infant's (which will be completed as part of the previously mentioned larger project that is interconnected with this study). The desire to learn more about how infants move throughout the first 7-months of life is related to the fact that infants without NDR are routinely seen for health supervision visits at 2- and 6-months PTA (8- and 24-weeks, respectively). Regrettably, assessing GMs at these time-points to detect neuromotor dysfunction would seem to be futile as our data revealed that 74.6% of non-standardized aged infants presented with aberrant GMs which we can again postulate would result in a number of infants being falsely identified.

Moreover, we must not be naïve in thinking that a broader implementation of the GMA during routinely scheduled health supervision visits will be sufficient for reaching every young infant. In fact, almost 25% of the general population of children are not seen for preventative medical care during the course of one year, which can be influenced by the presence of other psychosocial factors (which have also been associated with an increased risk for being diagnosed with a neurodevelopmental disorder).[29] Therefore, it could be beneficial to find ways to conduct developmental screenings (for young infants as well as toddlers) in community-based locations to catch a cohort of children who may otherwise fall through the cracks. The success of such an endeavor will likely require collaboration between various pediatric healthcare professionals who have the skills and abilities to complete such an assessment and then make recommendations from interpreted findings.[7,12,17,24] For example, pediatric physical or occupational therapists could be commissioned to conduct a more comprehensive developmental evaluation for young infants at a time when GMs can be reliably assessed. Results from this sort of pre-screening approach can then be relayed to primary care providers. Alternatively, there are emerging undertakings that are harnessing technology to allow parents to take a video capturing their infant's GMs in their home environment at specific ages to then send to trained healthcare professional who can assess for aberrant GMs (e.g., the BabyMoves smartphone application).[19,23,28,30] This could save time and resources that would be then required to record an infant's GMs during an actual visit and, ergo, give diagnostician's more time for making informed clinical decisions to establish a diagnosis, refer infants to additional providers who can initiate time-sensitive treatments, and/or reassure parents that their infant's development is progressing as expected.

From a feasibility perspective, we must also consider that implementing the GMA to screen for neuromotor dysfunction in every infant less than 5-months would require substantially more resources to provide specialty training and purchase video equipment, not to mention finding mechanisms to protect time needed to administer the GMA and interpret findings. Moreover, it is questionable as to whether providers would comply, based on previous reports that less than one-third of children 9- to 35-months have had their development screened in accordance with recommendations put forth by the American Academy of Pediatrics.[5] And when looking at less-traditional methods for early detection (i.e., community-based screenings or using technology to capture an infant's GMs), the benefits of such an endeavor is dependent on establishing partnerships where providers across settings can effectively and efficiently communicate relevant development screening findings.[7,13,17,23]

A limitation of this study was that data were collected from a parental survey. While these data may accurately reflect what parents believe to be true, it is also possible that answers given were consciously or unconsciously biased, and thus, imprecise. How parents read and answered a question may also have been influenced by their health literacy, their ability to accurately assess their circumstances, or understand what the question was asking.

Suggested areas for further exploration include assessing the diagnostic accuracy for using the GMA in an expanded age range of infants (i.e., any infant less than 7-months old) once long-term neurodevelopmental outcomes become known. This could then help inform

recommendations as to whether the GMA could be used as part of health-supervision visits routinely scheduled at 2- and 6-months, or instead, drive changes at an organizational or systems level to adjust the timing of preventative care visits or plan for community-based screenings that align with ages when GMs can be more accurately assessed. There may also be value in evaluating the congruence between the classification of GMs captured during health supervision visits to those captured by a parent in a more familiar setting using a repeated measure design. With advances in technology and many families having access to smart phones that could readily record an infant's movements, this type of study could help discern if the presence of poor repertoire or other aberrant GMs could be an artifact of the environment which incidentally influences an infant's behavioral state, and thus, expression of GMs. Finally, despite the extreme prevalence, it would still be beneficial to investigate if a combination or triangulation of poor repertoire GMs, documented NDR (e.g., birth before 37-weeks' gestation), and/or psychosocial related factors would be more predicting neurodevelopmental disorders. However, until this is done, we recommend waiting to administer the GMA until an infant is between 9- and 20-weeks PTA as the presence of aberrant GMs during this time period was shown to have a greater clinical meaning and therefore, would be a more effective use of resources.

CONCLUSION:

This study has demonstrated a potential benefit for using aberrant GMs in infants with or without NDR between 9- and 20-weeks PTA as a functional biomarker to detect neuromotor dysfunction and promote earlier identification of neurodevelopmental disorders. This contrasts to the clinical utility for using the GMA in infants less than 6-

weeks PTA, with our data suggesting that there may be a high-rate of false positive findings as 75.7% of infants within our sample were categorized with aberrant, or poor repertoire GMs. Still, we cannot claim that there is a single laboratory or functional biomarker that can definitively rule in or out such conditions. Therefore, we must systematically consider an amalgamation of health-related features (i.e., history of preterm birth or birth before 37-weeks' gestation) and functional signs (i.e., aberrant GMs in infants between 9- and 20-weeks PTA) to enhance efforts for detecting neuromotor dysfunction as a way to identify neurodevelopmental disorders in infants as young as possible. Establishing a formal diagnosis early can then foster the provision of time-sensitive, condition-specific interventions which can help lessen the overall disease burden by optimizing long-term functional outcomes for children and their families.

Appendix A: Demographic and Health-Related Features Collected

Type of Variable D=dependent I=independent	**Variable Name**	**Variable Label**	**Level of Measurement** N=nominal I-R=interval-ratio
D	**global_judgement_ for_ analysis**	**Does the infant express normal GMs?**	**N** (0 = aberrant GMs, 2 = normal GMs)
I	**pma_at_birth_calc**	**How many days was the infant born before his/her expected due date?**	**I-R** (Post-menstrual age at birth - 280 days)
I	**length of NICU stay**	**How many days did the infant spend in the NICU?**	**I-R** (In days)
I	**Sex**	**Is the infant male?**	**N** (0 = female, 1 = male)
I	**race_from_epic**	**What is the infant's race?**	**N** (0 = American Indian, 1 = Asian, 2 = black, 3 = Native Hawaiian, 4 = white, 5 = other, 6 = biracial)
I	**during_pregnancy_ __1-8**	**How many medical events were documented during pregnancy?**	**I-R** (Total number of documented medical events occurring during pregnancy)
I	**mode_of_delivery_ __3 (unplanned c-section)**	**Was an unplanned c-section required during delivery?**	**N** (0 = no, 1 = yes)
I	**birth_weight**	**Infant birth weight**	**I-R**
I	**medical_events_ since_ birth___1-7**	**How many medical events were documented during the post-natal period?**	**I-R** (Total number of documented post-natal medical events)

Appendix B: Parent Survey to Collect Infant Demographic and Health-Related Features

Study ID:_____ Visit Date: _____

Person completing form: Mother Father Grandparent Legal Guardian Other:_____

Infant Race (select all that apply):

American Indian/Alaska Native

Asian

Black/African American

Native Hawaiian or Pacific Islander

White/Caucasian

Other: _____

Prefer not to answer

Infant Ethnicity:

Hispanic or Latino

Not Hispanic or Latino

Prefer not to answer

Infant Gender:

Female

Male

Prefer not to answer

Pregnancy History:

Did any of the following occur during this pregnancy (please select any/all that apply):

Assisted reproduction Gestational diabetes Maternal pre-eclampsia Infection Substance use

Maternal surgery during pregnancy History of tick-borne disease/Lyme disease Other: _____

Birth History:

Mode of delivery (select any/all that apply):

Vaginal Scheduled C-section Unplanned C-section Vaginal birth after C-section (VBAC)

Use of forceps Vacuum-assisted delivery Induced

Infant length at birth: _____inches

Number of weeks born early: _____ OR *Number of days/weeks born late:* _____ OR Not Applicable

Number of infants delivered (with this pregnancy, e.g. 2 for twins): _____

Medical events happening since birth (select any/all that apply)

Jaundice Infection Seizures Surgery Feeding Assistance

Neonatal Abstinence Syndrome Other: _____

Did your child spend time in the NICU? Yes No If yes, how long was their NICU stay: _____

Current Medical History:

Does your child have any current diagnoses: Yes No, If yes, please specify: _____

Do you have concerns about your child's development: Yes No, If yes, please specify: _____

_____

Has someone told you your child's development is delayed? Yes No

If yes, who:

Another caregiver or family member

Primary care doctor or nurse practitioner

Specialist pediatrician

Dietician/nutritionist

Doula/ Midwife

Neonatologist

Early Intervention specialist (Help Me Grow provider)

Occupational therapist

Physical therapist

Speech language pathologist

Social Worker/Case Manager

Other: _____

Unknown/Prefer not to respond

Has your child been referred to or seen another provider due to concerns about your child's development? Yes No

If yes, who:

Pediatrician/primary care provider at regular visits

Pediatrician/primary care provider at more frequent visits

Specialist Pediatrician

Dietician/nutritionist

Early Intervention specialist (Help Me Grow)

Neurologist

Occupational therapist

Physiatrist

Physical therapist

Psychologist

Speech language pathologist

Social worker/case manager

Other: _____

Unknown/prefer not to respond

If you were told there were concerns about your child's development, did you also have concerns?

I didn't/don't agree my child has a developmental problem

No, I was completely surprised

I suspected it, but decided it wasn't something to worry about

I was pretty sure there was a problem

I knew something was wrong before my doctor told me

Are there any additional comments you would like to provide on this survey: _____

_____

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4 Should we trust our gut? An analysis of perceived developmental concerns and the presence of aberrant general movements in infants less than five months of age

4.1 Overview

This original research (target journal: *Developmental Medicine and Child Neurology*) analyzed the relationship between the presence of aberrant GMs and perceived concerns by a parent or non-parent caregiver (e.g., another family member, childcare provider, or healthcare professional). This paper addressed:

> Specific Aim 3: Identify the degree of congruence between the presence of aberrant GMs and report of developmental concerns by the infant's parent or a non-parent caregiver.

One study reported that 86% of parents of children with CP knew something was wrong before a formal diagnosis was established (Baird et al., 2000). This diagnostic purgatory can be detrimental to the physical and mental health for both infants and their families. Therefore, understanding the association between the presence of aberrant GMs and perceived concerns about an infant's development reported by a parent or non-parent caregiver (e.g., another family member, childcare provider, or healthcare professional) can add value to decision-making processes related to early detection and treatment of neurodevelopmental disorders.

Our analysis revealed a significant association between the presence of absent fidgety GMs and developmental concerns perceived by a non-parental caregiver (e.g., another family member, childcare provider, or healthcare professional) for infants between 9- and 20-weeks PTA ($\chi^2 = 7.98$, $p < 0.01$). For infants less than 6-weeks PTA, the non-significant

findings between aberrant GMs and developmental concerns perceived by a parent or non-parental caregiver can be explained by the high rate of aberrant GMs, as 75.7% of this subsample of infants were categorized with poor repertoire GMs. This analysis supports a continued need to triangulate a variety of data (e.g., preterm birth, perceived developmental concerns, and the presence of aberrant GMs in infants between 9- and 20-weeks PTA) to optimize efforts for earlier detection of neuromotor dysfunction. This will help clinicians use objective findings to reassure parents, and therefore minimize stress, anxiety, and depression that may be experienced if the process for establishing a diagnosis was unnecessarily delayed or poorly communicated.

4.2 Abstract

Aim: To identify the degree of congruence between the presence of aberrant general movements (GMs) and report of developmental concerns by a parent or a non-parent caregiver (e.g., a healthcare provider or someone other than the parent).

Method: A Chi-Square Test of Independence was used to analyze a cross-sectional sample of infants (N=279) enrolled as part of a larger, multi-year project. All infants were either less than 6-weeks or between 9-20-weeks. Each infant's GMs were recorded, categorized, and correlated to developmental concerns as perceived by parents or non-parent caregivers via a study-specific survey distributed to parents.

Results: Developmental concerns were reported for 36 infants (12.9%). For infants between 9- and 20-weeks, the relationship between non-parental concerns and the presence of aberrant (absent fidgety) GMs was significant (χ^2= 7.98, $p < 0.01$) and congruent (agreement in 69.5% of cases). This relationship was not significant for infants less than 6-weeks (χ^2= 0.64, $p = 0.43$)

Interpretation: This combination of variables (i.e., non-parental concerns and absent fidgety GMs) has the potential to decrease the age for identifying neurodevelopmental disorders, and therefore minimize parental stress, anxiety, and depression that may be experienced if the process for establishing a diagnosis was unnecessarily delayed.

What this Paper Adds

- Non-parental caregiver-perceived developmental concerns correlate with aberrant general movements (absent fidgety)
- Discrepancies exist between perceived concerns and rates of poor repertoire general movements
- Administering the GMA following report of concerns could enhance early detection efforts
- Triangulating data from multiple sources best supports early detection of neuromotor dysfunction

4.3 Manuscript

Eighty-six percent of parents reported knowing something was wrong with their child before a formal diagnosis of cerebral palsy (CP) had been confirmed.[1] This is concerning because when the identification process is delayed or poorly communicated, parents can enter a diagnostic purgatory that has been associated with increased rates of stress, anxiety, and depression.[1–3] Failing to establish a formal diagnosis can also obstruct access to time-sensitive, condition-specific interventions.[2–7] Implementation of such interventions during the first 1,000 days of life is important as this is a time when the brain and nervous system are most malleable and adaptable to change which can maximize long-term developmental outcomes.[3,8–12] In general, treatment is provided to optimize an individual's motor and

cognitive competence while fostering educational achievements, participation within the home, school/work, and community, while limiting the development of secondary complications (e.g., musculoskeletal deformities or deconditioning due to immobility).[8,9,13,14] When effective, early identification and treatment of CP can reduce healthcare utilization across an individual's lifespan and decrease the economic burden resulting from illness-related costs.[14,15] Strategies used to ameliorate disability are important, especially since 16.7% of children in the United States are diagnosed with CP or another neurodevelopmental disorder.[16]

By itself, CP impacts the neuromotor function in 1 out of 345 children in the United States.[17] The pathophysiological changes associated with CP can include difficulties in how a child moves, talks, and/or thinks.[17,18] Yet these functional limitations may not manifest until early childhood, thus, identifying CP in infants can be challenging particularly since no single laboratory biomarker or assessment can definitively rule in or out this condition.[3,7,11] Instead, CP evolves from an interplay of risk factors, many of which can be appreciated in the newborn period.[11] These newborn detectable risks (NDR) include a history of preterm birth, admission to the neonatal intensive care unit, neonatal asphyxia, maternal substance abuse during pregnancy, genetic variations, and/or congenital birth defects.[3,11] Fortunately, these infants are often referred to specialty providers (e.g., neonatologists, neurologists, pediatric occupational and/or physical therapists) who possess the training and skills to more comprehensively assess for early signs of CP.[3,4,19] However, infants without NDR may not have an appreciable reason to be seen by a specialty provider and these early signs can go undetected.[3,4,6,7,19] This is clinically

significant because infants without NDR account for 50% of children who are diagnosed with CP.[3,6,11]

In an attempt to help address this problem, the American Academy of Pediatrics recommends that primary care providers (who have greater opportunities to interface with every infant) should incorporate developmental surveillance (e.g., asking a parent if they have concerns) as part of every health supervision visit in addition to completing developmental screenings at 9-, 18- and 30-months of age, or when warranted based on perceived concerns or identification of delayed achievement of key motor milestone.[13,20–23] Even so, the first signs of dysfunction may not be recognized until 9- and 18-months when providers are respectively evaluating if a child has achieved independent sitting and walking.[6,13,20,22,24] This wait and see mentality can be ineffective and delay the establishment of a formal CP diagnosis, which on average, does not occur until 12-24-months of age in high-income countries.[3,6,7,11,12,22,23,25]

Recent literature has affirmed that early signs of neuromotor dysfunction, such as the presence of aberrant general movements (GMs) which can be observed during the first 5-months of life, can be used to accurately identify CP in infants with NDR who present with cramped synchronized followed by absent fidgety movement patterns (sensitivity = 98%).[3,26] Accordingly, International Clinical Guidelines disseminated by Novak and colleagues recommend using Prechtl's General Movement Assessment (GMA) for this population of at-risk infants.[3,4,7] Endogenous in nature, GMs can reflect the integrity of the nervous system and could theoretically be used as a functional biomarker to detect

neuromotor dysfunction as a proxy for adverse neurodevelopmental outcomes.[27] These distinct patterns of movement can be observed during two age-specific periods.[26] Writhing GMs are expressed from birth until 6-weeks post-term age (PTA) whereas fidgety GMs appear between 9-20-weeks PTA. Normal writhing GMs can be compared to that of a calm ocean wave, where movements appear to flow throughout the entire body with elegant changes in direction, speed, and space.[26,27] Contrastingly, aberrant writhing GMs lack variability and complexity with movements characterized as being stiff, jerky, or predictable.[26,27] Normal fidgety GMs seem to ratchet within more finite joint spaces with a moderate speed, with aberrancies reflected by movements that are exaggerated or absent.[26,27] And while gestalt perception is required to correctly identify if GMs are normal or aberrant, previous studies have indicated that with training, the degree of inter-observer reliability is high ($k = 0.86$).[28]

It can be inferred that efforts for early detection can be enhanced when there is congruence between findings from the GMA and perceived developmental concerns by a parent or someone else other than a parent, such as another family member, childcare provider, or healthcare professional (*hereby inclusively referred to as non-parent caregiver)*. Or, in a similar light, when a parent or non-parent caregiver expresses concerns with how an infant is developing, that the GMA could then be used to check for aberrant GMs that could corroborate or disprove this worry. Learning more about how these two distinguishable constructs (i.e., perceived concerns and the presence of aberrant GMs) are related can further the understanding about if there would be benefit for modifying current developmental surveillance practices and screen for neuromotor dysfunction using the

GMA in all infants less than 5-months. Therefore, the purpose of this study was to determine the congruence between the proportion of infants presenting with aberrant GMs to the proportion of developmental concerns reported by parents or a non-parent caregiver.

Methods:

This cross-sectional analysis included 279 participants who were enrolled as a part of a larger, multi-year project. Infants were included based on 1) their age (i.e., less than 6-weeks or between 9-20-weeks PTA, as these are the standardized ages for administering the GMA) and 2) if the English-speaking parent or legal guardian (*hereby inclusively referred to as parent*) was willing to provide informed consent. Infants were excluded if they were unable to tolerate having their GMs recorded for a minimum of 2 minutes. This study was approved by Nationwide Children's Hospital (NCH) Institutional Review Board (study # IRB12-00001).

Assessment Procedures:

Study staff recruited, enrolled, and collected data at three different primary care offices and eight different specialty clinics (designed to monitor infants with NDR) within Nationwide Children's Hospital. Once consented, parents were asked to complete a brief survey before the infant's GMs were recorded.

The GMs of each infant were collected for up to 6-minutes using a Microsoft Azure Kinect© camera and Surface tablet. The process for recording these movements followed protocols established by the General Movements Trust. For example, infants were

undressed to their diapers and positioned on their back while external stimulation was minimized (e.g., parents were asked not to talk to the infant during recording and pacifier use was discouraged). All videos were uploaded and stored on a password-protected Azure Cloud Services tenant, meeting HIPAA privacy and security standards (https://azure.microsoft.com/en-us/overview/trusted-cloud/).

A blinded assessment team comprised of three pediatric physical therapists was responsible for categorizing GMs. All three assessors received basic training through the General Movements Trust with advanced training completed by two of the three assessors. Reliability was established through a structured review of 20 videos with known classifications of GMs.

The videos collected from study participants were independently reviewed and categorized as normal or aberrant by at least two assessors, with the third assessor included in cases of disagreement. In addition, all three assessors reviewed every 25th video (n=45, 16.1%) to check and ensure ongoing inter-rater reliability. For the 279 infant videos included in this analysis, inter-rater reliability between assessors was excellent (average $k = 0.93$; $k = 0.92$ for infants less than 6-weeks and $k = 0.94$ for infants 9-20-weeks PTA).

A study-specific survey was iteratively developed by the team of investigators (see Appendix A). Questions were created after reviewing relevant literature, surveys, and registries geared to track developmental outcomes in children (e.g., the Vermont Oxford Network eNICQ Patient Data Booklet). The purpose of this survey was to capture

demographic and health-related features of the participant (e.g., infant's age at birth, birth weight, mode of delivery, pregnancy or post-natal medical events, and duration of time spent in the neonatal intensive care unit). Additional questions were included to ascertain if the parent perceived concerns about how their infant was developing. The parent was also asked if a non-parent caregiver had identified a developmental concern. All yes/no, multiple-choice and multiple select options were then nominally categorized for analysis. All information collected was entered and stored into a password-protected REDCap instrument designed specifically for this study.

Frequency data were compiled to highlight the distribution of key demographic features. A Chi-Square Test of Independence was then performed by age-specific type of GM (i.e., writhing GMs for infants less than 6-weeks PTA and fidgety GMs for infants between 9-20-weeks PTA). This was done to determine if there was a relationship between how GMs were categorized (as normal or aberrant) and perceived developmental concerns by the parent or non-parent caregiver (as no concerns or yes concerns). All analyses were completed using IBM SPSS 28.0 (IBM Corp. Armonk, NY).

An a priori power analysis for a Chi-Square Test of Independence was performed by means of G*Power 3.1 (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany). This yielded a minimum sample of 88 participants using a medium effect size of 0.3, power level of 0.80, alpha level of 0.05 and 1 degree of freedom.

Results:

Table 1 contains key demographic data, the distribution of GMs by category and age, and rates of perceived concerns by a parent or non-parent caregiver. In total, 82.4% (n=230) of parents completed the survey question about if they had concerns about their infant's development while 83.2% of parents (n=232) reported about concerns noted by a non-parent caregiver. Overall, aberrant GMs were categorized in 45.2% of infants (n=126/279). When segmented by age, these aberrancies were present in 76.7% of infants less than 6-weeks PTA (n=79/103) and in 26.7% (n=47/176) of infants between 9-20-weeks PTA, the later proportion excluded infants presenting with sporadic fidgety GMs.

Table 1. Frequency Distribution of Data Collected

Gender	**N**	**%**
Female	133	47.7
Male	145	52.0
TOTAL	278	99.7
Race		
American Indian / Alaskan Native	1	0.4
Asian	9	2.9
Black	100	35.8
Native Hawaiian / Pacific Islander	1	0.4
White	128	45.9
Other	15	5.4
Biracial	24	8.6
TOTAL	**277**	**99.4**
Categorization of General Movements		* = aberrant
Writhing (infants less than 6-weeks PTA)	103	36.9
Normal	24	23.3
*Poor Repertoire	79	76.7
Fidgety (infants from 9- to 20-weeks PTA)	176	63.1
Normal	92	52.3
*Absent	47	26.7
Sporadic Fidgety (may be normal or aberrant)	37	21.0
TOTAL	**279**	**100.0**

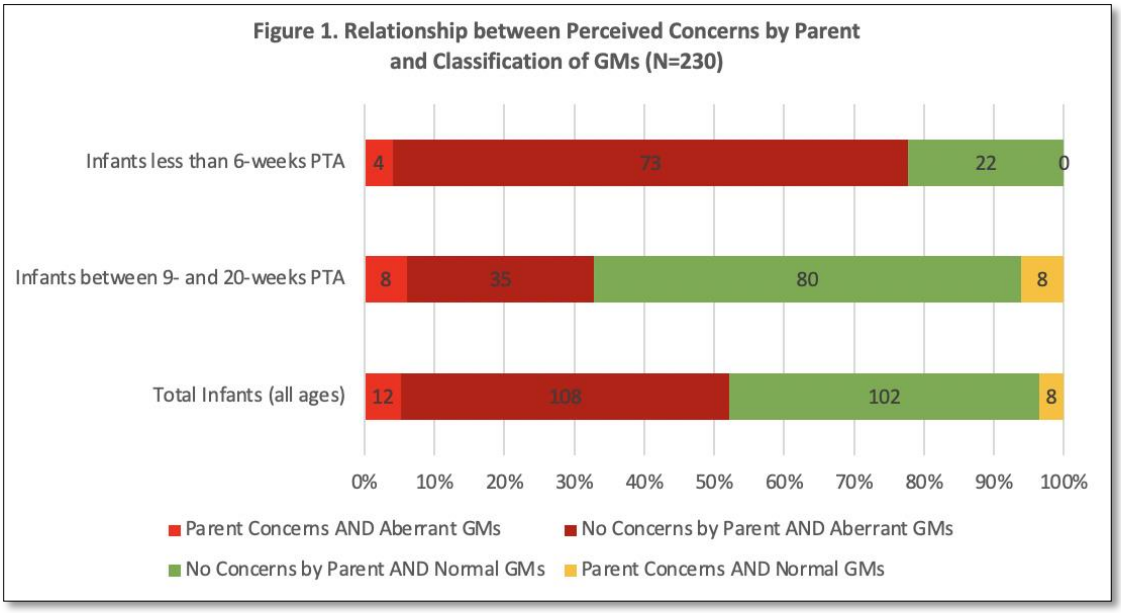
Table 1. Frequency Distribution of Data Collected – Cont.

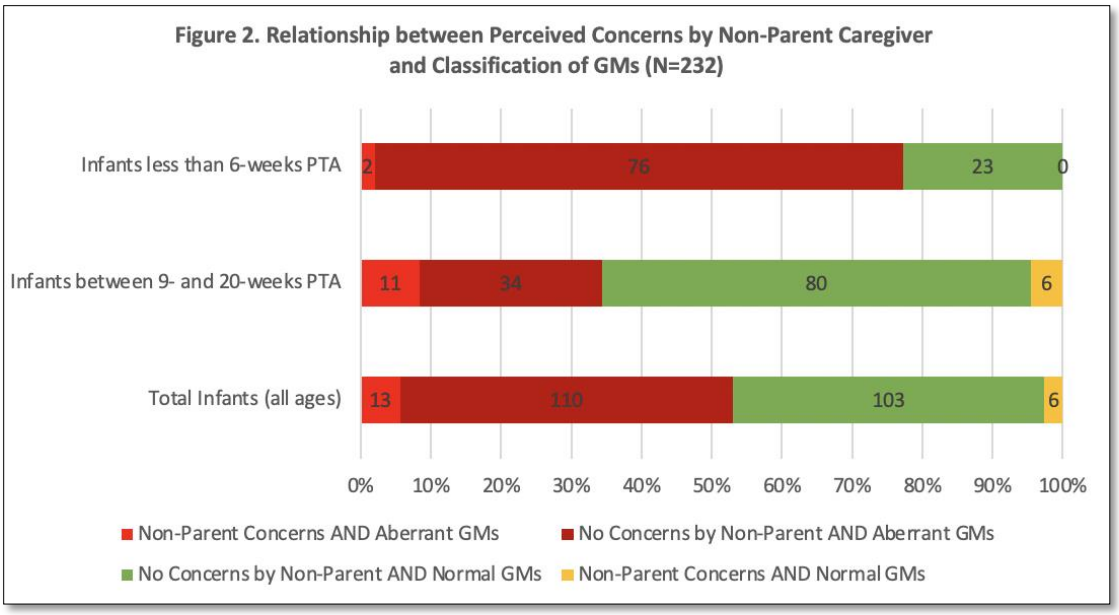
Does the parent perceive their infant's development is delayed?		
Yes	20	8.7
No	210	91.3
TOTAL	**230**	**100.0**
Did someone else other than the parent say that the infant's development is delayed?		
Yes	19	8.2
No	213	91.8
TOTAL	**232**	**100.0**
Clinic where infant was enrolled		
Primary Care	135	48.4
Bronchopulmonary Dysplasia Clinic	10	3.6
Cardiology	34	12.2
Craniofacial	6	2.2
Early Developmental Clinic	30	10.7
Ears, Nose & Throat	14	5.0
Genetics	12	4.3
Neuromuscular Disease Clinic	8	2.9
OT/PT/SLP	30	10.7
TOTAL	**279**	**100.0**

Analyzing a subsample of infants without NDR (n=75) revealed that aberrant GMs were categorized in 35.9% of infants (n=37/103) less than 6-weeks PTA and 5.7% of infants (n=10/176) between 9-20-weeks PTA. Finally, there was relatively equal distribution of infants enrolled from primary care offices (i.e., 48.4%, n=135) as compared to all other specialty care clinics.

Figures 1 and 2 depict the relationship between aberrant GMs and the perceptions of developmental concerns by the infant's parent or non-parent caregiver. In total, there were 20 parents who perceived concerns about their infant's development (20.0%, n=4/20 for infants less than 6-weeks PTA and 80.0%, n=16/20 for infants between 9-20-weeks PTA). In addition, parents documented that a non-parent caregiver had reported concerns in 19

cases (10.5%, n=2/19 for infants less than 6-weeks PTA and 89.5%, n=17/19 for infants between 9-20-weeks PTA). Having concerns noted by the parent and a non-parent caregiver occurred in 7 cases, which 100% of these infants presented with at least one NDR and 57.1% (n=4/7) were categorized as having aberrant GMs. Moreover, in a subsample of infants without NDR (n=75) developmental concerns noted by a non-parent caregiver was limited to 1 infant (which coincided with categorization of absent fidgety GMs at 17 5/7 weeks PTA). In addition, there was another infant without NDR noted to have developmental concerns as perceived by a parent (which coincided with normal fidgety GMs at 12 4/5 weeks PTA but was confounded by a known diagnosis of torticollis).





Pearson's Chi-square values revealed a significant relationship between concerns noted by a non-parent caregiver and absent fidgety GMs (χ^2=7.98, $p < 0.01$) for infants between 9-20-weeks but was not significant for infants less than 6-weeks (χ^2= 0.64, $p = 0.43$). More specifically, perceived concerns noted by a non-parent caregiver matched categorization of aberrant GMs (i.e., absent fidgety) in 11/45 cases, while an absence of concerns matched with normal fidgety GMs in 80/86 cases; thus, there was congruence between perceived concerns and GM categorization in 69.5% of cases. Subsequent analyses that did not control for an infant's age revealed non-significant associations between categorization of GMs and parental-perceived concerns (χ^2 = 0.60, p = 0.44) as well as a non-parent caregiver perceived concerns (χ^2 = 2.08, p = 0.15) (see Table 2).

Table 2. Association between Aberrant Movements and Developmental Concerns as Perceived by Parent and/or Non-Parent Caregiver

	Value	df	Asymp. Sig (2-sided)
	Developmental Concerns Perceived by Parent (All infants N=230)		
Pearson Chi-Square	0.60	1	0.44
	Developmental Concerns as Perceived by Non-Parent Caregiver (All infants, N=232)		
Pearson Chi-Square	2.08	1	0.15
	Developmental Concerns as Perceived by Parent or Non-Parent Caregiver (All infants, N=238)		
Pearson Chi-Square	2.88	1	0.09
	Developmental Concerns as Perceived by Non-Parent Caregiver (Infants less than 6-weeks PTA, N=101)		
Pearson Chi-Square	0.64	1	0.43
	Developmental Concerns as Perceived by Non-Parent Caregiver (Infants 9- to 20-weeks PTA, N=131)		
Pearson Chi-Square	7.98	1	<0.01

Discussion:

There were 36 unique infants that were identified as having developmental concerns as reported by a parent or non-parent caregiver, the majority of whom were between 9-20 weeks PTA. Using existing prevalence data, we estimated that 46 infants within our sample of 279 infants could be diagnosed with a neurodevelopmental disorder (i.e., 16.7% of 279 ≈ 46). We then used this estimate to calculate the "concern rate" or proportion of infants documented with developmental concerns (i.e., 36/46 = 78.3%). This is similar to previously reported retrospective data where 86% of parents of children with CP who "knew something was wrong" before a formal CP diagnosis was established.[1] When pairing aberrant GMs with perceived concerns by parents (n=12) or non-parent caregivers (n=13), 100% of these infants were documented to have at least one NDR. More positively, our analysis revealed that there was strong agreement (92.7%, n=102/110) between normal GMs and an absence of parent or non-parent caregiver concerns. Again, it is important to

note the perception of developmental concerns was linked to the presence of aberrant GMs as a proxy for adverse neurodevelopmental outcomes, not an established CP diagnosis, although neurodevelopmental outcomes will be tracked as part of the larger project over the next 18 years.

Regardless of the overall rate or eventual long-term outcome, every single parent with a concern about their infant's development may experience undue stress, anxiety, and depression. It can also be inferred that the worry is most warranted when there is a combination of indicators including aberrant GMs, perceived developmental concerns, and/or NDR. Therefore, healthcare professionals must be intentional and timely when addressing such concerns using consistent, honest, and transparent messaging about what is known or unknown about the infant's neuromotor function. This may include creating a collaborative plan that incorporates additional diagnostic testing or developmental screening that will allow for a more comprehensive evaluation of an infant's health and age-specific developmental competence. This is clinically important as providers could then assign a high-risk for CP diagnosis based on the presence of aberrant GMs among other risks or perceived concerns that would allow for implementation of time-sensitive interventions. Or, on the other hand, providers could feel more confident when reassuring parents that developmental progress is as expected when GMs are normal.

One unexpected finding from this investigation was that 75.7% of the sample of infants less than 6-weeks PTA were categorized with aberrant, or poor repertoire GMs. Instead, we had expected this incidence to match the known prevalence of neurodevelopmental

disorders of 16.7%.[16] It can therefore be inferred that a number of the infants categorized with poor repertoire GMs will in fact have normal neurodevelopmental outcomes (i.e., there is a high-degree of false-positives when using the GMA for infants less than 6-weeks). This aligns with previous research that has indicated that poor repertoire GMs are considered to be less specific for predicting neuromotor dysfunction as compared to cramped synchronized GMs (which were not appreciated within our sample). Thus, assessing GMs as a functional biomarker, or proxy for adverse neurodevelopmental outcomes should be saved for infants between 9-20-weeks PTA (which also appears to be a time when more concerns are noted by a parent or non-parent caregiver) as this may be a better use of time and resources. In addition, how sporadic fidgety GMs should be categorized needs to be addressed, as an infant's age can subjectively influence whether this pattern is considered normal or aberrant, which was why these infants were excluded from this analysis.

One limitation of this study was the small number of participants who were documented as having developmental concerns as perceived by a parent or non-parent caregiver, although the level of significance for Pearson Chi-Square and Fisher's Exact Test were non-distinguishable. Another limitation of this study is that data were collected through a parental survey. Thus, how a question was interpreted may have influenced the given answer. While our reasoning for administering this survey prospectively was to limit the effect of recall bias, it is plausible that parents of young infants subconsciously avoided or answered a question differently when phrasing inadvertently evoked negative emotions. Reflexively, revisions were made in how questions were worded to minimize

stigmatization. Formatting revisions were also completed to optimize the visual appearance of the survey which included changes to how some of the questions were ordered, to address incidents where parents answered questions that were not relevant to their infant. The updated version of this parental survey will be used for future data collection in the larger, multi-year project that is still enrolling participants. In the future, adding qualitative interviews would allow for more descriptive explanations of a parent's perceptions and could help provide additional context for why certain answers were selected and allow for a more accurate account of an infant's perceived health status.

In conclusion, using GMs as a functional biomarker to screen for neuromotor dysfunction in infants less than 5-months has the potential to stimulate earlier identification of CP. However, to feasibly implement such an endeavor would require substantially more time and resources. But the benefit is priceless, particularly when parental concerns reported during the first 5-months of a child's life can be objectively addressed in a timely manner without having to wait 18-months to see if a child will achieve independent walking. Healthcare organizations should therefore consider innovative approaches to more consistently refer infants suspected of having neuromotor dysfunction to providers who have the skills and abilities to assess for aberrant GMs with relevant findings communicated to the diagnostician. Alternatively, providers who commonly interface with infants less that 5-months should seek out additional training in how to administer and interpret the GMA. Ultimately, the developmental progress of young infants should be assessed by triangulating relevant findings from an assortment of sources including the presence of NDR, perceived concerns about a child's development, and assessment of

GMs. By doing so, these infants can receive additional diagnostic testing including but not limited to a more comprehensive evaluation of their age-specific developmental competence and minimize undue worry, stress, and anxiety experienced by parents when the process for establishing a CP diagnosis is unnecessarily delayed.

Art by: Demetra Christina Wendland

Appendix A: Parent Survey to Collect Infant Demographic and Health-Related Features

Study ID:_____ Visit Date: _____

Person completing form: Mother Father Grandparent Legal Guardian Other:_____

Infant Race (select all that apply):

American Indian/Alaska Native

Asian

Black/African American

Native Hawaiian or Pacific Islander

White/Caucasian

Other: _____

Prefer not to answer

Infant Ethnicity:

Hispanic or Latino

Not Hispanic or Latino

Prefer not to answer

Infant Gender:

Female

Male

Prefer not to answer

Pregnancy History:

Did any of the following occur during this pregnancy (please select any/all that apply):

Assisted reproduction Gestational diabetes Maternal pre-eclampsia Infection Substance use

Maternal surgery during pregnancy History of tick-borne disease/Lyme disease Other: _____

Birth History:

Mode of delivery (select any/all that apply):

Vaginal Scheduled C-section Unplanned C-section Vaginal birth after C-section (VBAC)

Use of forceps Vacuum-assisted delivery Induced

Infant length at birth: _____inches

Number of weeks born early: _____ OR *Number of days/weeks born late:* _____ OR Not Applicable

Number of infants delivered (with this pregnancy, e.g. 2 for twins): _____

Medical events happening since birth (select any/all that apply)

Jaundice Infection Seizures Surgery Feeding Assistance

Neonatal Abstinence Syndrome Other: _____

Did your child spend time in the NICU? Yes No If yes, how long was their NICU stay: _____

Current Medical History:

Does your child have any current diagnoses: Yes No, If yes, please specify: _____

Do you have concerns about your child's development: Yes No, If yes, please specify: _____

_____

Has someone told you your child's development is delayed? Yes No

If yes, who:

Another caregiver or family member

Primary care doctor or nurse practitioner

Specialist pediatrician

Dietician/nutritionist

Doula/ Midwife

Neonatologist

Early Intervention specialist (Help Me Grow provider)

Occupational therapist

Physical therapist

Speech language pathologist

Social Worker/Case Manager

Other: _____

Unknown/Prefer not to respond

Has your child been referred to or seen another provider due to concerns about your child's development? Yes No

If yes, who:

Pediatrician/primary care provider at regular visits

Pediatrician/primary care provider at more frequent visits

Specialist Pediatrician

Dietician/nutritionist

Early Intervention specialist (Help Me Grow)

Neurologist

Occupational therapist

Physiatrist

Physical therapist

Psychologist

Speech language pathologist

Social worker/case manager

Other: _____

Unknown/prefer not to respond

If you were told there were concerns about your child's development, did you also have concerns?

I didn't/don't agree my child has a developmental problem

No, I was completely surprised

I suspected it, but decided it wasn't something to worry about

I was pretty sure there was a problem

I knew something was wrong before my doctor told me

Are there any additional comments you would like to provide on this survey: _____

_____

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5 Summary and conclusions

5.1 Summary of Study Finding

5.1.1 Specific Aim 1: Identify the prevalence of aberrant GMs for infants with and without NDR

Within a sample of 279 infants, 45.2% of infants presented with aberrant GMs (i.e., absent fidgety, poor repertoire, or chaotic writhing). When separated by age, 75.7% of infants less than 6-weeks PTA were categorized as expressing poor repertoire GMs with 26.7% of infants between 9- and 20-weeks PTA categorized as expressing absent fidgety GMs.

5.1.2 Specific Aim 2: Identify significant relationships between aberrant GMs and certain demographic or health-related features.

Four NDR were determined to be correlated to the presence of aberrant GMs among 401 participants: birth before 37-weeks' gestation (Pearson r = -0.18, $p < 0.001$, OR 2.32, 95% CI 1.05, 5.11), birth weight less than 2500 grams (Pearson r = 0.13, $p < 0.01$, OR 0.83, 95% CI 0.64, 1.28), medical events happening after birth (Pearson r = -0.14, $p = 0.006$, OR 1.09), and time spent in the NICU (Pearson r = -0.130, $p = 0.009$, OR 0.90). A Chi-Square Test of Independence found that the prevalence of aberrant GMs was significantly associated with the presence of NDR (e.g., preterm birth) for infants between 9- and 20-weeks PTA ($\chi^2 = 5.32$, $p = 0.02$) but not for infants less than 6-weeks PTA ($\chi^2 = 0.72$, $p = 0.40$). Preterm birth was also found to be significant for predicting aberrant GMs through a binomial logistic regression analysis (-2 Log likelihood = 531.854) although the generated model only predicted 59.2% of cases correctly.

5.1.3 Specific Aim 3: Identify the degree of congruence between the presence of aberrant GMs and report of developmental concerns by the infant's parent or non-parent caregiver (e.g., another family member, childcare provider, or healthcare professional)

A total of 279 infants were included in this cross-sectional analysis, with 36 infants documented with developmental concerns as noted by a parent or non-parent caregiver

(e.g., another family member, childcare provider, or healthcare professional). Using existing prevalence data, we estimated that 46 infants within our sample of 279 infants could be diagnosed with a neurodevelopmental disorder (i.e., 16.7% of 279 ≈ 46). We then used this estimate to calculate the "concern rate" or proportion of infants documented with developmental concerns (i.e., 36/46 = 78.3%), which is similar to previously reported retrospective data where 86% of parents of children with CP who "knew something was wrong" before a formal diagnosis was established (Baird et al., 2000). It is important to note the perception of developmental concerns was linked to the presence of aberrant GMs as a proxy for adverse neurodevelopmental outcomes and not a formal diagnosis as has yet to be confirmed; thus, some of these perceived concerns (or lack of perceived concerns) may not match long-term neurodevelopmental outcomes.

A Chi-Square Test of Independence was used to determine if there was a significant relationship between the perception of developmental concerns by a parent or non-parent caregiver (e.g., another family member, childcare provider, or healthcare professional) and aberrant GMs. For infants of all ages (i.e., those less than 6-weeks and those between 9-20 weeks PTA), there was a non-significant relationship between the presence of aberrant GMs and parental perceived concerns ($\chi^2 = 0.60$, $p = 0.44$, n=230) and between aberrant GMs and the presence of non-parent caregiver perceived concerns ($\chi^2 = 2.08$, $p = 0.15$, n=232). However, when controlling for age, aberrant, or absent fidgety GMs categorized in infants between 9- and 20-weeks PTA were found to be significantly correlated to perceived developmental concerns noted by a non-parent caregiver ($\chi^2 = 7.29$, $p < 0.01$, n=131). Thus, there was agreement between perceived concerns by a non-parent caregiver

and categorization of GMs in slightly older infants. For example, 11 out of 45 cases were documented with both absent fidgety GMs and reported concerns, while an additional 80 out of 86 cases were documented with both normal fidgety and an absence of concerns. This congruence was present in a total of 69.5% of cases (91/131) for infants between 9- and 20-weeks PTA.

5.2 Limitations of the Studies:

There were a few limitations that were relevant to all studies/dissertational work which will be described more generally before discussing study-specific limitations.

Parental Report Survey

The most prominent limitation impacting all studies was the reliance on a parental survey to collect demography data as well as information about health-related features (i.e., complications occurring in pregnancy, birth history, and medical events occurring in the post-natal period). Missing data was anticipated with additional processes implemented to complete a retrospective chart review before adjusting the individual sample size for affected variables. In addition, there were also questions included in this survey about whether the infant had been referred to a specialty provider, if there were any current diagnoses that could impact the infant's development, and if a parent or a non-parent caregiver (e.g., another family member, childcare provider, or healthcare professional) had perceived concerns with how the infant was developing. These questions were more subjective, which resulted in some incongruencies in how a parent answered (e.g., parents reported that they did not have any concerns about their child development in question 2 on page 2, but then documented that "I was pretty sure there was a problem" in question 5 on page 2) that will be addressed in future studies.

In addition, this iteratively developed, study-specific survey has not been validated, although it is evidence-informed as questions were created after a comprehensive review of previously published survey (e.g., Guttmann et al., 2018), existing literature (e.g., Mclntyre et al., 2011) and pediatric outcome-related data registries (e.g., the Vermont Oxford Network eNICQ Patient Data Booklet). Our team of investigators discussed what we believed to be the most important constructs or NDR that were most relevant to the presence of aberrant general movements (see Table 1 for the complete list of variables). Study-specific questions were then made to collect information on these variables.

Forthcoming Long-Term Neurodevelopmental Outcomes

GMs were used as a short-term outcome, or proxy for identifying neuromotor dysfunction in our sample of infants, even though an eventual diagnosis of CP (or another neurodevelopmental disorder) is considered to be the true clinical standard or long-term outcome of interest. This was done because establishing such a diagnosis can take years. Use of GMs as our short-term outcome of interest was evidence-informed, as the GMA is the most sensitive and specific tool for identifying CP in infants less than 5-months of age. Yet, we must be cautious in how our results are interpreted as the reported psychometric soundness of the GMA (i.e., sensitivity of 98% and specificity of 96%) is specific to identifying CP in infants with NDR as opposed to a more inclusive population of infants with or without NDR who comprised our sample (Einspieler & Prechtl, 2005; Novak et al., 2017). Therefore, additional work will need to be completed to fully realize the clinical effectiveness of using the GMA to detect neuromotor dysfunction in young infants with or without NDR (which is dependent on knowing long-term neurodevelopmental outcomes).

We can postulate, however, that aberrant GMs (specifically poor repertoire GMs occurring in 75.7% of infants less than 6-weeks PTA) are ineffective in predicting adverse neurodevelopmental outcomes which has been reported to impact only ~16.7% of children in the United States (Zablotsky et al., 2019). Nonetheless, there is still merit in reporting the overall prevalence of aberrant GMs in a more inclusive population of infants and the relationship between aberrant GMs and other demographic and health-related features as well as perceived developmental concerns as this foundational work can then help inform if a combination or triangulation of variables reflecting a variety of constructs is more predictive for identifying neurodevelopmental disorders once long-term developmental outcomes are known.

Reflecting on the Rate of Aberrant GMs

One unexpected finding from this investigation was that 75.7% of the sample of infants less than 6-weeks PTA were categorized with aberrant, or poor repertoire GMs, as we had expected this incidence to match the known prevalence of neurodevelopmental disorders impacting 16.7% of infants in the United States (Zablotsky et al., 2019). To the best of our knowledge this is the first report of the prevalence of aberrant GMs in a more inclusive population of infants, therefore, there is nothing to corroborate if this rate of aberrant GMs is consistent with groups of infants from other geographical regions or perhaps over-inflated. And because previous research has already determined that poor repertoire GMs are less specific for predicting CP as compared to GMs that are classified as cramped synchronized or absent fidgety (Einspieler & Prechtl, 2005; Novak et al., 2017), knowing

that an infant has been categorized with aberrant or poor repertoire GMs is not clinically useful.

Within our specially trained assessment team, our inter-rater reliability was strong (average $k = 0.93$; $k = 0.92$ for infants less than 6-weeks and $k = 0.94$ for infants 9-20-weeks PTA) which was greater than the inter-rater reliability ($k = 0.86$) reported in previous literature (Valentin et al., 2005). Therefore, it is likely that our assessment procedures were true to the established methodology and that the prevalence of aberrant GMs (particularly poor repertoire GMs noted in 75.7% of infants less than 6-weeks PTA) is accurately reflective of this more inclusive population of infants. However, we do plan to add additional conventions to check intra-rater reliability as part of the larger, ongoing project. Our reason for doing so is that it can add a complementary safeguard to ensure assessors remain calibrated in their gestalt perception to correctly discern normal from aberrant GMs (against themselves as well as each other).

5.2.1 Chapter 2

Specific to this study, one limitation related to the data collection process was the difficulties experienced for capturing a usable video. After realizing that 28.5% (n=160/561) of infants were recorded while their GMs were influenced by uncontrollable factors (e.g., behavioral state), we decided to provide additional training to all study staff on basic infant handling and calming techniques that could be used to prepare the infant before starting the video recording. We also adjusted the timing of when GMs were recorded (when possible), trying to ensure all data was collected prior to state-altering activities (i.e., receiving a vaccination).

5.2.2 Chapter 3

As previously mentioned, an overarching limitation influencing all studies, a parental survey was used to collect demography data as well as information about health-related features for which some answers may have been imprecise (see section 5.2 for additional details about this limitation including in the section on parental report survey).

In addition, the fact that the majority of infants within our sample presented with at least one NDR, could have skewed our data and subsequent analysis. This is further supported by the fact that this study found that aberrant GMs occurred two times as often in infants with NDR (see section 5.2 for additional details about this limitation included in the section on reflection on the rate of aberrant GMs).

5.2.3 Chapter 4

One limitation specific to this study was the small number of participants who were documented as having developmental concerns as perceived by a parent or non-parent caregiver (e.g., another family member, childcare provider, or healthcare professional), although the probabilistic estimate for Pearson Chi-Square Tests of Independence and Fisher's Exact Tests were non-distinguishable.

5.3 Future Research

Several areas for which additional research is needed were exposed from this dissertational work.

First, even though the findings from these studies corroborate that the GMA is most reliable when used in infants less than 6-weeks or between 9- and 20-weeks PTA, additional research could assess the diagnostic accuracy for using the GMA in an expanded age range of infants (i.e., any infant less than 7-months old) once long-term neurodevelopmental outcomes become known.

Second, there may be value in assessing the congruence between the classification of GMs captured during health supervision visits to those captured by a parent in a more familiar setting using a repeated measure design. With advances in technology and many families having access to smart phones that could readily record an infant's movements, this type of study could help discern if the presence of poor repertoire or other aberrant GMs could be an artifact of the environment which incidentally influences an infant's behavioral state, and thus, expression of GMs.

Third, despite the unexpectedly high prevalence, it would still be beneficial to further investigate if poor repertoire GMs, documented NDR, and/or psychosocial related factors could be used in combination to enhance the accuracy in predicting neurodevelopmental disorders. However, until this is done, we recommend waiting to administer the GMA until an infant is between 9- and 20-weeks PTA as the presence of aberrant GMs during this time period was shown to have a greater clinical meaning, and therefore, would be a more effective use of resources.

Fourth, by tracking the age of infants when they are diagnosed with neurodevelopmental disorders (secondary to enhanced early detection efforts) researchers can begin to document at what age, time-sensitive, condition-specific interventions have the greatest impact.

Fifth, and finally, implementation efforts designed to broadly incorporate the GMA to screen for neuromotor dysfunction in all infants could be evaluated across multiple sites. This could then help inform recommendations as to whether the GMA could be used as part of health-supervision visits routinely scheduled at 2- and 6-months, or instead, drive changes at an organizational or systems level to adjust the timing of preventative care visits or plan for community-based screenings that align with ages when GMs can be more accurately assessed.

5.4 Implications for Clinical Practice

The foundational knowledge generated from this project should be used to help inform developmental screening practices. This could include assessing GMs to universally screen for neuromotor dysfunction in all infants between 9- and 20-weeks PTA who present with certain NDR including a history of preterm birth or perceived developmental concerns by a non-parent caregiver (e.g., another family member, childcare provider, or healthcare professional). This can help ensure early detection and treatment of neurodevelopmental disorders, including CP, and ameliorate long-term disability for a more inclusive population of infants.

5.5 Conclusions

Key findings from this dissertational work include:

- Finding a prevalence of aberrant GMs in 26.7% of infants between 9- and 20-weeks PTA and 76.7% of infants less than 6-weeks PTA
- Corroborating that preterm birth and aberrant GMs are significantly correlated in infants between 9- and 20-weeks PTA (Pearson $r = 0.183$, $p < 0.001$)
- Revealing a significant congruence between developmental concerns reported by a non-parental caregiver (e.g., another family member, childcare provider, or healthcare professional) and the presence of absent fidgety movements in infants between 9- and 20-weeks PTA ($\chi^2 = 7.98$, $p < 0.01$)
- Combining aberrant GMs as a functional biomarker along with other health-related features (e.g., preterm birth) and perceived developmental concerns has the potential to effectively detect neuromotor dysfunction in a more inclusive population of infants between 9- and 20-weeks PTA and foster earlier identification of neurodevelopmental disorders.

Ultimately, healthcare professionals interfacing with young infants must systematically consider a variety of health-related features (e.g., history of preterm birth), developmental concerns perceived by a parent or non-parent caregiver, and functional signs (i.e., the presence of aberrant GMs in infants 9- to 20-weeks PTA) to improve the accuracy and decrease the time it takes to detect neuromotor dysfunction in infants with and without NDR. Through additional research, we can continue to improve processes for early identification and treatment of neurodevelopmental disorders and help to ensure that long-term outcomes for both the infant and their family can be optimized.

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6 Appendices

6.1 Appendix A.1: Institutional Review Board Documents

6.1.1 Youngstown State University IRB Approved December 2, 2020

Subject: 057-21(ltr)
Date: Wednesday, December 2, 2020 at 4:41:25 PM Eastern Standard Time
From: Karen H Larwin
To: Ken Learman, Madalynn Wendland
CC: ckcoy@ysu.edu

Dear Investigators,

Your protocol entitled ACTIVE mini movement tracking system to identify movement problems in infants' birth to 6 months of age has been reviewed and is deemed to meet the criteria of an exempt protocol. You will be using preexisting data that is being collected as part of a previously approved study at Nationwide Children's Hospital for an investigation on the mini movement tracking system. No new participants will be recruited by you; no new data is being collected by you. You will be using data provided to you from a non-invasive data collection completed with 6000 infants.

The research project meets the expectations of 45 CFR 46.104(d)(4) and is therefore approved. You may begin the investigation immediately. Please note that it is the responsibility of the principal investigator to report immediately to the YSU IRB any deviations from the protocol and/or any adverse events that occur. Please reference your protocol number 057-21 in all correspondence about the research associated with this protocol.

Best wishes for the successful completion of your research.
Karen

Karen H. Larwin, Ph.D.
Distinguished Professor & YSU IRB Chair
Beeghly College of Liberal Arts, Social Sciences, & Education
Youngstown State University
One University Plaza
Youngstown, Ohio 44555-0001

"If you can't explain it simply, you don't understand it well enough." -Einstein

Leadership is not about titles, positions or flowcharts. It is about one life influencing another." — John C. Maxwell

6.1.2 Nationwide Children's Hospital IRB Approved June 8, 2020

APPROVAL

June 8, 2021

Linda Lowes
Center for Gene Therapy

Dear Linda Lowes:
On 6/8/2021, the IRB reviewed the following submission:

Type of Review:	Modification / Update
Title:	Parent Study: ACTIVE-mini movement tracking system to identify movement abnormalities in infants: birth to 6 months of age. Modification Name: ACTIVE mini AI for Healthcare
Investigator:	Linda Lowes
IRB ID:	MOD00008874
IND, IDE, or HDE:	None
Risk Level:	No greater than minimal risk
Documents Approved:	• 17May2021_The 5,000 Baby Project_Study Flyer_Final.pdf, Category: Recruitment Materials; • NCH INFORMED CONSENT_ACTIVE-mini AI for Health v.1.7 18 May 2021_clean.pdf, Category: Consent Form; • Protocol_ACTIVE-mini_early detection V1.7_18May2021_clean.docx, Category: IRB Protocol;
Waivers Granted:	None

Under the 2018 Common Rule, no continuing review is required. However, any modifications, SAEs, etc. to the study need to be submitted to the IRB for review and approval.

In conducting this protocol, you are required to follow the requirements listed in the INVESTIGATOR MANUAL (HRP-103).

Sincerely,

Karen A. White, Ph.D., Chair
Institutional Review Board

cc:

This is an official email communication from Research Information Solutions and Innovation (RISI).
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6.1.3 Study Protocol

ACTIVE-mini: infant early detection

PROTOCOL TITLE:

ACTIVE-mini movement tracking system to identify movement abnormalities in infants' birth to 6 months of age

PRINCIPAL INVESTIGATOR:

Name: Linda P Lowes
Department/Center: Center for Gene Therapy
Telephone Number: (614)722-2849
Email Address: Linda.Lowes@nationwidechildrens.org

VERSION NUMBER/DATE:

Version 1.1/ 14Apr2020

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
Version 1.1	14Apr2020	Updated protocol and consent to include additional information gained through discussions with all team members	Yes

1.0 Study Summary

Study Title	ACTIVE-mini movement tracking system to identify movement abnormalities in infants' birth to 6 months of age
Study Design	Prospective
Primary Objective	Compare the agreement between the classification of movements as healthy or abnormal between the ACTIVE-mini motor function score (MFS) and the General Movement Assessment on infants between 10 – 20 weeks of age as that is the regarded as the most accurate time frame for GMA predictions.
Secondary Objective(s)	Evaluate the relationship of the General Movement Optimality Score (GMOS) and the ACTIVE-mini MFS infants from birth to 6 months of age.
Research Intervention(s)/ Investigational Agent(s)	N/A
IND/IDE #	N/A
Study Population	Infants between the ages of birth and 6 months
Sample Size	Up to 6000
Study Duration for individual participants	15-20 minutes

Study Specific Abbreviations/ Definitions	
GMA	General Movement Assessment
GMOS	General Movement's Optimality Score
ICC	Interclass correlation coefficient
IND	Investigational new drug
MFS	Motor Function Score
MRI	Magnetic Resonance Imaging
SEM	Standard error of measure
SMA	Spinal muscular atrophy

2.0 Objectives

Objective:

2.1 Purpose: The overall goal of our work is to develop a portable, low-cost, non-invasive way to accurately identify infants with atypical movement patterns that does not require intensive training to operate and can be used in both industrial and developing countries. Early identification of infants would enable "at-risk" infants to receive additional evaluations by the appropriate specialist.

We believe this will have a lasting and meaningful impact on the health of infants globally as movement abnormalities can be identified at a very early age leading to a targeted referral of "at risk" infants to specialists. We know that the sensitivity and specificity of our system must be evaluated closely so we don't cause undue stress or delay diagnosis by misclassifying an infant. For this study, no information will be given to the families as we are updating our classification algorithm and do not yet have an accurate and valid algorithm.

Specific Aims:

Aim 1) Compare the agreement between the classification of movements as healthy or abnormal between the ACTIVE-mini MFS and the General Movement Assessment on infants between the ages of 10 to 20 weeks of age as that is the regarded as the most accurate time frame.

Aim 2) Evaluate the relationship of the General Movement Optimization Score (GMOS) and the ACTIVE-mini motor function (MFS) score on up to 5000 infants between the ages of 0 ≤ 6 months with and without known risk factors for developmental delay.

2.2 Hypothesis: ACTIVE-mini will detect and monitor abnormal movement patterns in infants with a sensitivity and specificity matching or exceeding the General Movements Assessment.

3.0 Background and Rationale

Development of ACTIVE-mini:

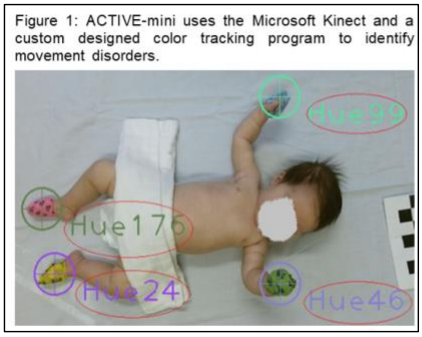


Figure 1: ACTIVE-mini uses the Microsoft Kinect and a custom designed color tracking program to identify movement disorders.

ACTIVE-mini was developed in preparation for a phase 1 clinical trial of gene therapy in spinal muscular atrophy (SMA) type 1. The Microsoft Kinect camera captures positional data of the infant's arms and legs while the infant lays on his/her back for 2 minutes (Figure 1). To date our team has captured 660 recordings of infant movement in our pilot cohort of 62 infants with genetically-confirmed spinal muscular atrophy and 75 typically-developing infants. The ACTIVE-mini proof-of-concept data collection system utilized color tracking to mark the positional coordinates of an infant's arms and legs in three-dimensional space (Figure 1). Using these data, an algorithm was used to estimate the propensity that an infant is exhibiting health movements. In short, feature engineering using 5 movement features: distance, direction, change in direction, velocity and acceleration. A machine learning analysis of the 100 most frequent produces a motor function score (MFS). Results from our initial dataset indicated ACTIVE-mini discriminates well between infants with symptomatic SMA and typical controls (mean MFS typical infants = 91 ± 12; children with SMA mean MFS = 2 ± 3). Of note, typical children can have periods of 'laziness' or temporarily reduced movement, however infants with

SMA never achieve an MFS similar to controls (i.e. >90 points) despite periods of high activity. Similarly, visualizations of movement patterns of infants with SMA within the first months of life are characteristically different than those of age-matched controls (Figure 2). The young infant with SMA demonstrates quite limited movement utilizing an arc-like pattern. This arc-like movement pattern occurs because the child was unable to move their limbs up against gravity. Conversely, the age-matched typical control moves all extremities in a much more complex pattern with higher variation and randomness to their movements.

MFS scores were moderately correlated to the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (INTEND) scores (r=0.56, *P*<0.001) with some of the variability in scores being related to the ceiling effect commonly reported in the INTEND as it does not capture higher level skills.

Ohio approved newborn screening for SMA in 2018, with its programmatic implementation beginning in early 2019. In the first 6 months of 2019, our SMA clinic received 7 newborn screening referrals which put us in a unique position to further evaluate young infants with SMA that would have likely been considered 'pre-symptomatic.' A total of 5 patients with genetically-confirmed SMA with 2 – 4 copies of SMN2 completed ACTIVE-mini recordings, as well as traditional functional assessments including the INTEND. Table 1 shows that ACTIVE identified movement problems in all 5 infants whereas the INTEND only detected movement problems in 1 of the 5 infants. This is not surprising as the INTEND was designed to assess chronic disease progression in infants with historical, untreated SMA type I. The INTEND was never designed, tested or validated to detect motor delays at birth and therefore should not be expected to provide this information.

Conversely, the ACTIVE-mini MFS score was sensitive to movement differences in the first few months of life AND quantified declines in movement complexity in 2 patients within 1 week. Figure 3 demonstrates the difference in MFS by SMN2 copy number. Of note, even the child with 4 copies of SMN2 does not achieve an MFS within the expected average range

Figure 2: ACTIVE-mini tracings of infant hand and feet movement demonstrate the difference in movement complexity in an infant with SMA and an age-matched peer.

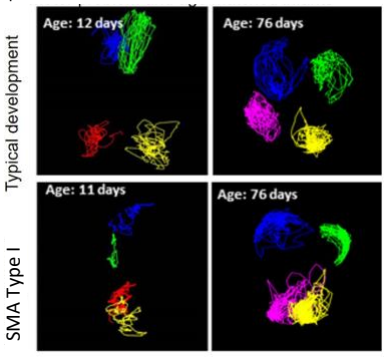


Figure 3: Infants with SMA, identified via newborn screening, scored very low ACTIVE-mini MFS compared to typical age-matched peers. MFS scores were higher in infants with higher protein levels, indicative of more mild disease. However, none of the infants with SMA

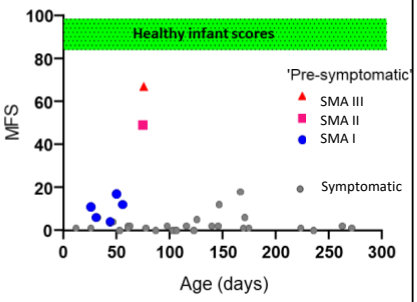


Table 1: MFS & INTEND scores for infants considered clinically pre-symptomatic

Subject	Copy #	Age (days)	MFS	INTEND
1	2	50	17	45
		56	12	47
2	2	26	11	50
3	2	31	6	55
		44	4	54
4	3	75	49	62
5	4	76	67	63

for typical controls although all other clinical testing categorized him as pre-symptomatic.

These preliminary data gave us confidence that ACTIVE-mini MFS scores, while less relevant in an SMA population with early identification available via expanding availability of newborn screening, to expand our target population to determine the sensitivity and specificity with which ACTIVE-mini in detecting other neurodevelopmental conditions with more subtle differences in movement complexity than traditional SMA type I.

When a parent brings an infant into a pediatrician's office with concerns about the baby's development it is difficult to accurately determine, in the short course of the visit, if the baby has real movement problems or if the parent simply needs reassured. We know "typical development" varies quite dramatically with infant temperament, environmental factors and parenting styles and that most infants will follow the typical motor developmental timeline as they grow. This sets up a difficult situation. Alarming parents needlessly can be traumatic and waste time and resources better spent elsewhere; conversely, referral to early intervention as quickly as possible could be beneficial to infants with developmental delays.

Developmental and behavioral conditions are the top 5 chronic disabilities in the world. These conditions affect 12-16% of children in the United States alone and reported prevalence is on the rise. One in 323 children will be diagnosed with cerebral palsy and 1 in 59 with autism. Despite their prevalence, the diagnosis of these disorders can be delayed for over a year. This delay in diagnosis matters, because early intervention has been shown to improve outcomes in children with reported cost savings of $30-100K per child, or $48.3 billion per year in the U.S. alone. However, UNICEF reports that only 20-30% of infants considered 'at risk' for motor delay are identified in time to benefit from services.

Disruption in one area of development influences development throughout the body, thus detection of movement abnormalities may identify infants with significant motor delays, but also help identify other disorders. To quantify these early differences in movement, we developed the ACTIVE-mini system. ACTIVE-mini leverages the skeletal tracking technology from the Microsoft Kinect camera to track spontaneous infant movement and assigns a Motor Function Score (MFS) to quantify movement complexity. The overall goal is to enhance providers' ability to detect movement differences earlier, within the first months of life.

Our plan is to:

Aim 1: **Refine the ACTIVE-mini MFS algorithm to accurately classify infant movement as 'typical' or 'at risk' using the General Movement Assessment classification scores**

General Movement Assessment (GMA) reports the presence of "fidgety movements" at 10-20 weeks of age post-term as the best indicator of healthy movements. In trained and certified practitioners, accuracy of the GMA has been reported upward of 95% during the fidgety movement period; however, the major limitation of the GMA is that it is dependent on the skill level of the evaluator, and there are very few individuals who specialize in performing these assessments due to the cost of training and skill required. Our team has expertise in GMA classification of infants, so we will use this tool to code our videos of infants between the ages of 10-20 weeks of age to feed into the ACTIVE-mini MFS algorithm development.

Aim 2: **Establish the convergent validity of ACTIVE-mini MFS to General Movement Optimality Score**

Another tool, the General Movements Optimality Score (GMOS) quantifies movement characteristics on an ordinal scale (up to 28 points) is not considered to be as predictive of motor delays as the absence of fidgety movement but is a tool that can be used to quantify movement across infancy. We will compare ACTIVE-mini MFS and GMOS of all infant videos to determine the utility of ACTIVE-mini from birth to 6

months of age.

Our hypothesis is ACTIVE-mini will accurately and objectively classify infants into 'at risk' or 'typical' groups based on complexity of movement alone at an early age. The advantage of ACTIVE-mini over traditional tools described above, is ACTIVE-mini is a low-cost, low-training, portable tool that can be easily implemented in tertiary care centers to rural, underserved, outreach clinics around the globe.

Collaboration with AI for Health:

While differentiating movements of infants with SMA and typical controls was a feasible proof-of-concept, refining our algorithm would take a lengthy amount of time to explore in the absence of a data scientist(s) with expertise in development of this type of classification algorithm. In February 2020, we were invited to collaborate with the newly formed AI for Health team, as part of the Microsoft Philanthropies group (https://www.microsoft.com/en-us/ai/ai-for-health). This division has a purely philanthropic aim to advance the AI field and technologies to improve access to quality healthcare services and products. AI for Health is a separate entity from the for-profit Microsoft technology company, and as such is not interested in profiting from collaborations or retaining intellectual property. They provide grants which consist of in-kind donations of their time, expertise, and/or services depending on the needs of a given project. After our meeting in February, our team was granted an in-kind donation of $1,030,000 worth of products and services, including $30,000 worth of Surface tablets and Azure Kinect cameras, and an estimated $500,000 in Azure Cloud credits, and $500,000 in AI for Health data scientist time and expertise. To capitalize on this collaboration, our team has been tasked with collecting videos of infant movement, both 'at risk', with known diagnoses, and typically-developing for processing and algorithm refinement.

4.0 Study Endpoints

4.1 Primary:

- *Refine ACTIVE-mini MFS algorithm to accurately classify infant movement using the GMA score in a cross-sectional sample of up to 6,000 infants*

4.2 Secondary:

- *Establish convergent validity of ACTIVE-mini MFS to GMOS in infants from birth – 6 months of age*
- *Determine long-term accuracy of ACTIVE-mini MFS in a longitudinal sample of infants up to 5 years post enrollment*

5.0 Study Intervention/Investigational Agent

N/A

6.0 Study Design and Endpoints

The proposed study will enroll up to 6,000 infants across the motor developmental spectrum including: typically developing, infants considered at risk for developmental delay due to prenatal and/or birth history, and infants with known motor delay or diagnoses. Subject selection will not exclude anyone on the basis of gender, race, or ethnic background.

Study staff will be available for data collection a various approved sites within the Nationwide Children's Hospital network of sites including, the neonatal intensive care unit, Early Developmental Follow Up clinic, Genetics clinic, Ear Nose and Throat (ENT) clinics, Clinical Therapies outpatient clinics, Neurology clinics,

Complex Care clinic, Myelomeningocele clinic, Neuromuscular Physical Therapy, and others with approval of clinic leadership and team.

ACTIVE-mini is a portable system that can be set up in a designated room, if available within the clinic space, or sanitized and moved around across sites or within a clinic as deemed necessary for each clinic's needs and workflow.

Testing:

Once consented, study staff will collect information about the infant's age, prenatal and birth history and list of any current diagnoses to determine risk level for having a developmental disability. This could be obtained from parent interview or a review of the child's medical record (dependent on clinic workflow).

The infant will then be positioned on their back under the ACTIVE-mini camera system and the baby's spontaneous movement will be recorded for up to 5 minutes, as tolerated. If the infant does not tolerate the video or becomes fussy, the recording can be stopped. If after a rest break, snack, or parent soothing it is determined the infant could re-attempt a recording, a follow up trial may be attempted. Additionally, if the child is inconsolable or the parent changes his/her mind about participating the visit will end.

Data collection is focused on video capture at the visit. No 'risk' determination will be provided to families during the visit as the algorithm refinement is ongoing. Families will be thanked for their participation and contribution to our study.

Longitudinal follow up:

We plan to consent families for the option to follow enrolled infants longitudinally to determine the long-term accuracy and predictive ability of the ACTIVE-mini MFS. We will consent families to allow our team to contact the family by email, phone, mail, or chart review to collect any information about the child's motor development that has occurred since enrollment including any diagnoses received, therapy services, or early intervention services. Consenting parents may 'opt in' or 'opt out' of this longitudinal testing option at enrollment and may decline future participation at any time even after consent is provided.

7.0 Data and Specimen Banking*

The motor function score and GMOS will be saved indefinitely to allow us to compare our initial prediction to any diagnosis made in the first 5 years. It will be kept in a password protected computer and in a locked cabinet.

8.0 Sharing of Results with Subjects*

Visits will solely include parent interview and capture of the 5-minute video recording. There will be no 'results' to share with families during the visit as these videos will be post-processed and fed into the AI algorithm and compared to GMA assessment to refine the accuracy of the algorithm.

9.0 Study Timelines and Enrollment Feasibility

We plan to enroll infants meeting enrollment criteria at their regularly scheduled clinic visits. Actual study visits are expected to take 20 minutes or less and will be completed around clinic workflows and family availability.

We are targeting full enrollment within 18 months from first visit, once COVID-19 access restrictions are lifted. Initial feasibility indicates our timeline is reasonable within the Nationwide Children's Hospital system as 26,000+ unique infants were seen in a 12-month period for a total of 60,000+ visits. The table

below includes a number of total unique patients and visits within 1-year for those infants at the highest volume primary care clinics within NCH network. We have agreement from Dr. Alex Kemper, Division Chief of Primary Care Pediatrics for access to primary care network of clinics and will assess site feasibility and work flow to ensure optimal efficiency of data collection without disruption to patient care.

Unique Patients	# Visits	Location
1351	4373	Sharon Woods
1329	4392	Northland
1219	4579	Westside
1182	3956	Whitehall
1058	3029	Downtown
1012	3178	Eastland
936	2548	Primary Care - Red
794	2574	Hilltop
629	2014	Linden
627	1763	Near East
603	2074	Olentangy

Additionally, the clinics in the chart below have the highest volume of infants ≤6 months of age, and those highlighted in green have provided initial interest and support in collaborating. Dr. Leif Neilan and Lawrence Baylis have indicated a room can be provided on T4 for testing and study staff can approach families in the waiting room with interest to participate before or after their appointments in Early Developmental Follow Up or Genetics Clinics. Dr. Neilan and Jennifer Hofherr have indicated access to infants on various NICU units with the ability to tolerate video recordings was reasonable and visits could be coordinated between the NICU therapy staff and Neuromuscular PT group. Main campus sites have a larger number of infants attending visits than offsites, but additional offsite targets can be added if enrollment lags.

Unique Patients	# Visits	Location
1938	2503	ENT & Audiology
1342 *596*	*1682* *821*	*ENT Clinics* *Audiology Clinics*
1632	2278	Urology Clinics
953	1062	Early Development Follow-Up
803	1196	Cardiology Clinic Main Campus
727	996	GI Clinic Main Campus
663	1138	Eye Clinic Main Campus
656	874	Neurosurgery Main Campus
596	735	Surgery Clinic Main Campus
529 225+178 +126	1521 623+527+371	PT Main + Dublin + Westerville
367	433	Care Navigation
292	411	Plastic Surgery Clinic

280	451	Dermatology Clinic
274	299	Genetics Clinic Main Campus
244	526	Craniofacial Clinic Main Campus
210	249	Neurology Clinic Main Campus
* Current targets & confirmed institutional support		

Finally, once the infant videos are captured and complete post-processing, ACTIVE-mini algorithm refinement is expected to be completed 24 months from first visit.

10.0 Inclusion and Exclusion Criteria*

10.1 Inclusion Criteria:

- Infants from birth to ≤6 months of age (corrected age, if born prematurely)
- Caregiver is ability to read and provide written informed consent

10.2 Exclusion Criteria:

- Caregiver is unable or unwilling to consent
- Infants that are unable to tolerate video recording for a minimum of 2-minutes

11.0 Vulnerable Populations*

If the research involves individuals who are vulnerable to coercion or undue influence, describe additional safeguards included to protect their rights and welfare.

- The checklist for enrolling children is included is submission

12.0 Local Number of Subjects

We are targeting enrollment of up to 6,000 infants.

13.0 Recruitment Methods

Infants will be recruited through the Nationwide Children's Hospital network of clinics. Approval from each clinic site's administration team will be obtained prior to study staff approaching families in those clinics. The general onsite recruitment method is listed below.

- Onsite recruitment efforts will involve study staff approaching families in the clinic waiting area or during an approved time at the visit (individual clinic workflow dependent) to determine their interest in study participation.
- A brief summary of the study purpose, time commitment, and procedures for participation will be presented:

  Hello – I am XXXXXXXX, working with Dr. Linda Lowes, a physical therapist at Nationwide Children's Hospital. Our team is collecting 5-minute videos of infants with and without motor delays. Our goal is to develop an algorithm to identify children with movement differences. Today, we are looking for families interested in participating in our study. To participate, we would ask a few questions about your infant's birth history and then record a 5-minute video. Are you potentially interested in participating or learning more about our study?
- If they agree, the study staff will take them to the private testing area, set up the testing equipment in the clinic room (individual clinic workflow dependent), or plan to have the family

visit the prespecified testing area after their regular visit to provide additional study information and complete the consenting process.

☐ Recruitment material is attached to this submission.

☐ Subjects and families will not be paid for participation.

14.0 Withdrawal of Subjects*

If the infant becomes inconsolable during the recording the parent may decide to withdraw the child from the study. Additionally, if the family wishes to withdraw participation at any time during the visit for any reason, they may do so without influence on the care they receive from NCH clinics or hospital.

Similarly, if families 'opt in' to allow our study staff to update their child's future medical history and be recontacted by our study team, they may withdraw this consent at any time using any convenient method.

15.0 Risks to Subjects*

There is minimal risk to the subjects in participating in this study.

The infant may become upset during the video recording. Additionally, because videos will be uploaded to Azure Cloud Services, they will be accessible to study staff at Nationwide Children's Hospital and approved external parties at ThePlanWorks and Microsoft Philanthropies.

16.0 Potential Benefits to Subjects*

There is no direct benefit of participation to the study subjects.

17.0 Data Management* and Confidentiality

All data will be collected on Surface tablets with secure unique login required for access. Patient demographic data and medical history will be collected and stored in RedCap. Infant videos will be captured on the computer using the specific equipment required for this collection: Surface tablet, Azure Kinect camera, tripod/mounting device.

In collaboration with the NCH RISI team, videos will be uploaded to an NCH server and securely transferred to the NCH Azure Cloud Services tenant, meeting HIPAA privacy and security standards (https://azure.microsoft.com/en-us/overview/trusted-cloud/). Only approved staff with the need to view these videos will have access. Other than the infant video, no additional identifiable information will be included in the video files. An enrollment log with patient demographics and de-identified study ID will be housed in RedCap. Collaborators at AI for Health will not have access to RedCap or any identifiable information other than infant videos.

All study data will be stored on password protected computer, and in the event a paper form is created or required, will be stored in a locked cabinet. Data will be stored indefinitely on NCH servers or via approved fire-proofing methods. Infant videos will be extracted from Azure Cloud Services storage upon completion of the study.

18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects*

N/A

19.0 Provisions to Protect the Privacy Interests of Subjects

19.1 **Consenting process:** The study purpose, procedures, benefits and risks, privacy and data storage considerations, and other information outlined in the informed consent document will be reviewed with the parent. The parent will have the opportunity to review the consent and ask any questions. Once questions have been sufficiently answered, and the parent is in agreement to participate, they will sign the informed consent document via the RedCap portal. The consent document will be sent to the family via the family's preferred method (i.e. email or mail). If the family declines to consent, no further study procedures will be completed.

19.2 **Describe what steps you will take to make the subjects feel at ease with the research situation in terms of the questions being asked and the procedures being performed. "At ease" does not refer to physical discomfort, but the sense of intrusiveness a subject might experience in response to questions, examinations, and procedures.**

Recruitment procedures within each clinic will likely differ due to the unique patient populations and will be approved by clinic administration prior to implementation. In some clinics (i.e. NICU), families will be approached by known clinicians and ability to tolerate participation/video recording will be cleared prior to our team approaching these patients.

Most clinics (i.e. Early Developmental Follow Up clinic, outpatient Clinical Therapies, Primary Care clinics) have approved our team to set up a private testing area within their clinic space or near their waiting area. Additionally, they have provided approval for our study staff to approach families with an initial summary of our study to determine their interest in participating. All study staff will use the approved recruitment script when approaching families in clinic waiting areas:

Hello – I am XXXXXXXX, working with Dr. Linda Lowes, a physical therapist at Nationwide Children's Hospital. Our team is collecting 5-minute videos of infants with and without motor delays. Our goal is to develop an algorithm to identify children with movement differences. Today, we are looking for families interested in participating in our study. To participate, we would ask a few questions about your infant's birth history and then record a 5-minute video. Are you potentially interested in participating or learning more about our study?

If families are interested in learning more, the formal informed consent process will begin. Study staff will make it clear to families that our sole purpose is to collect a large number of infant videos to better measure and understand how babies move. Study staff will make it clear that the family can decline to answer any questions or discontinue participation at any time without having an impact on the care their child receives. Additionally, the study team will only

20.0 Compensation for Research-Related Injury

There are no study funds available to over any injuries occurring during study visits. As study procedures simply involve a video of the infant's spontaneous movement, we do not anticipate any injuries occurring during our study. If an injury were to occur, study staff would encourage the family to seek appropriate medical attention.

21.0 Economic Burden to Subjects

There is no cost to participate in this study. Families will be approached at their regularly

scheduled clinic visits. It is possible that participation in our study could lengthen their appointment time up to 30 minutes, however families are not required to participate if they don't have the additional availability.

22.0 Consent Process

22.1 Indicate whether you will you be obtaining consent, and if so describe:

- **Where will the consent process take place:** the consent process will take place in a private, quiet location unique to each clinic. Space has been allocated in each location for this process and data collection to take place. Once consent is completed, infant demographic and medical history will be obtained, as well as the infant video. No subsequent visits are required unless the family consents to be recontacted.
- We will be following SOP: Informed Consent Process for Research (HRP-090)

23.0 Non-English Speaking Subjects – if known, skip if not known

- Non-English speaking subjects may be enrolled if an interpreter is present for their visit. If an interpreter is not present, we will not attempt to consent the parent.

Subjects who are not yet adults (infants, children, teenagers)

- Infants under the age of 6 months will be enrolled and therefore can not provide assent.

There is minimal risk to being in this study so parental permission will be obtained from one parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child. Parental consent will be required to enroll in the study.

24.0 Process to Document Consent in Writing

Our study staff will follow the institutional policies for consenting "SOP: Informed Consent Process for Research (HRP-090)." In short, study staff will review and explain the study purpose, procedures, benefits and risks, privacy and data storage considerations, and other information outlined in the informed consent document with the parent. The parent will have the opportunity to review the consent and ask any questions. Once questions have been sufficiently answered, and the parent is in agreement to participate, they will sign the informed consent document via the RedCap portal. The consent document will be sent to the family via the family's preferred method (i.e. email or mail). If the family declines to consent, no further study procedures will be completed.

25.0 Setting

Describe the sites or locations where your research team will conduct the research

- We plan to enroll subjects at sites within the Nationwide Children's Hospital network. We currently have clinic leadership approval for study staff to enroll in the NICU, Early Developmental Follow Up clinic, Genetics Clinic, Complex Care Clinic, Outpatient Clinical Therapies, Neurology, and Primary Care Clinics.

26.0 Resources Available

As mentioned above, the AI for Health team has granted our institution with $1,030,000 worth of in-kind donations including $30,000 worth of Surface tablets and Azure Kinect cameras. An

estimated $500,000 worth of Azure Cloud Services credits for data storage and upload needs. The NCH RIS team estimates these funds should be sufficient for all data storage, upload, and extraction fees required across the term of our project (estimated 3 years from start date). An additional, $500,000 worth of AI for Health data scientist time has been granted which will be allocated for the team to turk the current skeletal tracking algorithm to better track the expected proportion of an infant skeleton, and data scientists to refine our ACTIVE-mini MFS classification algorithm.

Additionally, we plan to train students, study coordinators, and our NMD PT staff to collect study data across sites. We have existing relationships with pre-PT/OT student club and the Scholar's program at The Ohio State University with several students contacting us with interest in obtaining school credit for participation in our project. Students will receive standard hospital/research training as outlined in our Student Management Plan and student activities will be monitored by the PI and NMD PT program manager. Students will collect data at sites with established workflows and low-risk infant populations. Trained study coordinators will be deployed at sites with more involved communication/work flow needs, and physical therapy staff will perform all data collection in high-risk areas (i.e. NICU).

27.0 Multi-Site Research*

N/A: all data will be completed by our study team within the NCH network of sites.

28.0 Protected Health Information Recording

1.0 Indicate which subject identifiers will be recorded for this research.

- ☒ Name
- ☒ Complete Address
- ☒ Telephone or Fax Number
- ☐ Social Security Number (do not check if only used for ClinCard)
- ☒ Dates (treatment dates, birth date, date of death)
- ☒ Email address , IP address or url
- ☒ Medical Record Number or other account number
- ☐ Health Plan Beneficiary Identification Number
- ☒ Full face photographic images and/or any comparable images (x-rays)
- ☐ Account Numbers
- ☐ Certificate/License Numbers
- ☐ Vehicle Identifiers and Serial Numbers (e.g. VINs, License Plate Numbers)
- ☐ Device Identifiers and Serial Numbers
- ☐ Biometric identifiers, including finger and voice prints
- ☐ Other number, characteristic or code that could be used to identify an individual
- ☐ None (Complete De-identification Certification Form)

2.0 Check the appropriate category and attach the required form* on the Local Site Documents, #3. Other Documents, page of the application. (Choose one.)

☒ Patient Authorization will be obtained. (Include the appropriate HIPAA language (see Section 14 of consent template) in the consent form OR attach the HRP-900, HIPAA AUTHORIZATION form.)

☐ Protocol meets the criteria for waiver of authorization. (Attach the HRP-901, WAIVER OF HIPAA AUTHORIZATION REQUEST form.)

☐ Protocol is using de-identified information. (Attach the HRP-902, DE-IDENTIFICATION CERTIFICATION form.) (Checked "None" in 1.0 above)

☐ Protocol involves research on decedents. (Attach the HRP-903, RESEARCH ON DECEDENTS REQUEST form.)

☐ Protocol is using a limited data set and data use agreement. (Contact the Office of Technology Commercialization to initiate a Limited Data Use Agreement.

***Find the HIPAA forms in the IRB Website Library, Templates.**

Attach the appropriate HIPAA form on the "Local Site Documents, #3. Other Documents", page of the application.

3.0 How long will identifying information on each participant be maintained?

The videos will be stored indefinitely as this is an artificial intelligence learning project and the videos may need to be re-analyzed if errors are noted or new technology enables more efficient processing or algorithm refinement.

4.0 Describe any plans to code identifiable information collected about each participant.

Each subject will be given a unique, deidentified study ID that will be used to separate the videos from the infants PHI.

5.0 Check each box that describes steps that will be taken to safeguard the confidentiality of information collected for this research:

X Research records will be stored in a locked cabinet in a secure location

X Research records will be stored in a password-protected computer file

X The list linking the assigned code number to the individual subject will be maintained separately from the other research data

X Only certified research personnel will be given access to identifiable subject information

6.0 Describe the provisions included in the protocol to protect the privacy interests of subjects, where "privacy interests" refer to the interest of individuals in being left alone, limiting access to them, and limiting access to their information. (This is not the same provision to maintain the confidentiality of data.)

Only pertinent medical history relevant to the infant's development will be collected as part of this study. Additionally, parents have the ability to 'opt in' or 'opt out' of longitudinal data collection as part of the informed consent process. This longitudinal data collection will be used to validate our algorithm, but is not required for participation in the initial video collection.

29.0 Confidential Health Information

1.0 Please mark all categories that reflect the nature of health information to be accessed and used as part of this research.

☒ Demographics (age, gender, educational level)

☒ Diagnosis

☒ Laboratory reports

☒ Radiology reports

☒ Discharge summaries

☒ Procedures/Treatments received

☒ Dates related to course of treatment (admission, surgery, discharge)

☐ Billing information

☐ Names of drugs and/or devices used as part of treatment

☒ Location of treatment

☐ Name of treatment provider

☐ Surgical reports

☐ Other information related to course of treatment

☐ None

2.0 Please discuss why it is necessary to access and review the health information noted in your response above.

To properly code our infant videos in the 'typically developing' or 'at risk' categories for post-processing analysis, we need to ensure we have sufficient information about the infant's birth history, MRI findings, or diagnoses received by the time of enrollment. Only information needed to make this determination will be accessed.

3.0 Is the health information to be accessed and reviewed the minimal necessary to achieve the goals of this research?

☒ Yes ☐ No

4.0 Will it be necessary to record information of a sensitive nature?

☐ Yes ☒ No

5.0 Do you plan to obtain a federally-issued Certificate of Confidentiality as a means of protecting the confidentiality of the information collected?

☐ Yes ☒ No

6.2 Appendix B: Parental Survey used to Collect Infant Demographic and Health-Related Features

Study ID:_____ Visit Date: _____

Person completing form: Mother Father Grandparent Legal Guardian Other:_____

Infant Race (select all that apply):

American Indian/Alaska Native

Asian

Black/African American

Native Hawaiian or Pacific Islander

White/Caucasian

Other: _____

Prefer not to answer

Infant Ethnicity:

Hispanic or Latino

Not Hispanic or Latino

Prefer not to answer

Infant Gender:

Female

Male

Prefer not to answer

Pregnancy History:

Did any of the following occur during this pregnancy (please select any/all that apply):

Assisted reproduction Gestational diabetes Maternal pre-eclampsia Infection Substance use

Maternal surgery during pregnancy History of tick-borne disease/Lyme disease Other: _____

Birth History:

Mode of delivery (select any/all that apply):

Vaginal Scheduled C-section Unplanned C-section Vaginal birth after C-section (VBAC)

Use of forceps Vacuum-assisted delivery Induced

Infant length at birth: _____inches

Number of weeks born early: _____ OR *Number of days/weeks born late:* _____ OR Not Applicable

Number of infants delivered (with this pregnancy, e.g. 2 for twins): _____

Medical events happening since birth (select any/all that apply)

Jaundice Infection Seizures Surgery Feeding Assistance

Neonatal Abstinence Syndrome Other: _____

Did your child spend time in the NICU? Yes No If yes, how long was their NICU stay: _____

Current Medical History:

Does your child have any current diagnoses: Yes No, If yes, please specify: _____

Do you have concerns about your child's development: Yes No, If yes, please specify: _____

_____

Has someone told you your child's development is delayed? Yes No

If yes, who:

Another caregiver or family member

Primary care doctor or nurse practitioner

Specialist pediatrician

Dietician/nutritionist

Doula/ Midwife

Neonatologist

Early Intervention specialist (Help Me Grow provider)

Occupational therapist

Physical therapist

Speech language pathologist

Social Worker/Case Manager

Other: _____

Unknown/Prefer not to respond

Has your child been referred to or seen another provider due to concerns about your child's development? Yes No

If yes, who:

Pediatrician/primary care provider at regular visits

Pediatrician/primary care provider at more frequent visits

Specialist Pediatrician

Dietician/nutritionist

Early Intervention specialist (Help Me Grow)

Neurologist

Occupational therapist

Physiatrist

Physical therapist

Psychologist

Speech language pathologist

Social worker/case manager

Other: _____

Unknown/prefer not to respond

If you were told there were concerns about your child's development, did you also have concerns?

I didn't/don't agree my child has a developmental problem

No, I was completely surprised

I suspected it, but decided it wasn't something to worry about

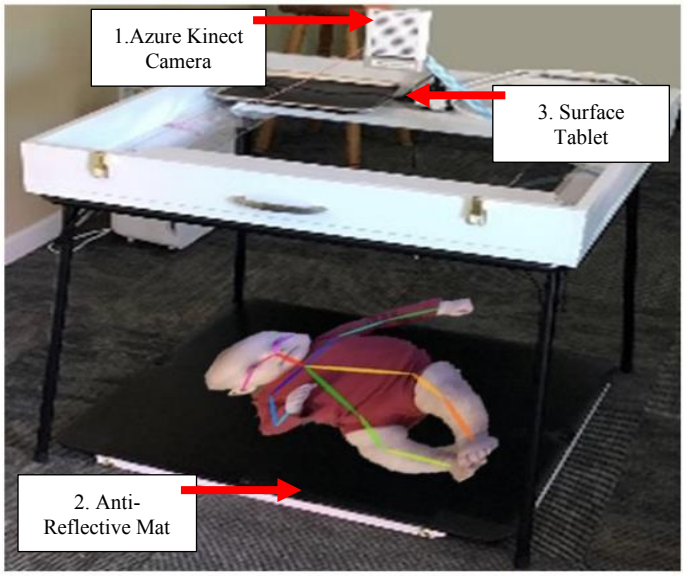
I was pretty sure there was a problem

I knew something was wrong before my doctor told me

Are there any additional comments you would like to provide on this survey: _____

_____

6.3 Appendix C: Video Set Up for Capturing General Movements



Description: Infants are undressed as completely as possible before being positioned on their back directly underneath a mounted Microsoft Azure Kinect camera (1) on top of an anti-reflective mat (2) with recordings completed through a Microsoft Surface tablet (3). Parents are discouraged from talking to or touching their child during the 6-minute recording to avoid influencing the expression of spontaneously generated GMs. Data is collected as a MKV file that can reproduce x, y, and z coordinates to more precisely map limb and trunk movements for future computerized analysis as well as a MP4 file that the assessment team utilizes to categorize GMs as normal or aberrant. All videos are securely transferred from the Microsoft Surface tablet to be stored in a password protected Azure Cloud Service Tenet through NCH which meets HIPPA privacy and security standards.