**Symposium Title**: Clinical and Research considerations for Autism Screening, Assessment, and Diagnosis in conditions with Early Onset and Severe Motor Impairments

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**Overview**: While motor impairments were not central to historical conceptualizations of autism, accumulating literature indicates various difficulties with motor coordination (e.g., odd gait, clumsiness, other abnormal motor signs) in autistic individuals across a lifespan. Conditions with early onset and severe motor impairments are often highly associated with autism spectrum disorder (ASD). These conditions include cerebral palsy (CP) and many neurogenetic conditions considered to be caused by high confidence ASD risk genes. However, the presence of significant motor impairments can both influence social communication abilities (e.g., ability to gesture, look, reach) and impede the ability to use the most well-established screening and diagnostic measures for ASD. There is a need to better understand (1) how motor impairments were first considered when creating and operationalizing ASD diagnostic criteria, (2) how the presence of motor impairments can affect manifestation and measurement of ASD symptoms, and (3) the clinical judgements made around ASD diagnoses in conditions with early onset and severe motor impairments. In this symposium we share insights on these clinical and research relevant topics from three different diverse studies of motor impairments in ASD, genetic neurodevelopmental conditions (chromatin modifying conditions), and CP. We start with a description of the motor requirements in current ASD diagnostic instruments and the motor skills in the validation samples for these instruments as well as large scale data on motor profiles of children referred for ASD evaluation. We will discuss the use of ASD diagnostic tools for children with genetic neurodevelopmental syndromes and our findings on a study of autism symptoms and motor profiles in these children compared to those with non-genetic ASD. Lastly, we will present the results of an international survey on professionals’ perceptions on the challenges and appropriateness of assessing for ASD in individuals with CP and other early onset motor conditions. Investigation into motor impairments in ASD and ASD related conditions, particularly how they impact the use of standardized diagnostic tools and shape ASD symptomatology is critical in informing clinical care and research practices in these conditions. Ultimately, these data can inform diagnosis, management, and the development of personalized therapeutic strategies for children with ASD and primary motor impairments.

**Paper 1 of 3**

**Paper Title**: Motor profiles in children with autism spectrum disorders

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**Introduction**: People with intellectual disability of all levels, and especially those with severe and profound intellectual disability, often have motor impairments that are just as clinically significant, if not more so, than cognitive impairments. Criterion E of the Autism Diagnostic criteria in the Diagnostic and Statistical Manual of Mental Disorders requires ruling out the diagnosis when disturbances are not better explained by intellectual disability or global developmental delay. However, their explanation by motor impairment was not written as an explicit rule out, although implied, as motor impairments can significantly interfere with valid assessments of social communication. Importantly, commonly used measures of social communication impairment, such as the Autism Diagnostic Observation Schedule (ADOS: Lord et al., 2012), were never developed or validated for children with very significant motor impairments, in large part because primary motor deficits were not considered in early conceptualizations of autism. In fact, because motor is an area of relative strength for many children with autism, commonly used tests were developed with an assumption of motor skills being intact at least at the same level as cognitive and language abilities. As a result, delays in motor skills required to effectively participate in activities or interact with play materials may lead to reduced specificity of commonly used assessment tools in children with primary motor impairments, who make up an increasingly large segment of autism referral populations.

**Method:** Following a review and description of previous validation samples for the Autism Diagnostic Interview-Revised (ADI-R; Lord Ruter and LeCouteur, 1994) and Autism Diagnostic Observation Schedule (ADOS) as related to motor ability, we will present new findings about motor profiles in a large sample of 2-to-8-year-old children with autism (n=2754) and other non-ASD diagnoses (n=1687) obtained from multiple existing clinical-research databanks. These children were aggregated as part of a larger project focused on individualizing and improving assessment approaches for diagnosis of ASD (project number 1R01MH128288-01A1). All participants included in the databanks had been clinically referred for autism-related concerns and/or were recruited for participation in autism-focused research projects. All sites adhered to best practice diagnostic assessment guidelines (Bishop & Lord, 2023), which included administration of standardized caregiver report (including the Vineland Adaptive Behavior Scales (Sparrow, Balla, and Cicchetti, 1984), direct observation (e.g., ADOS), and developmentally appropriate cognitive/developmental measures.

**Results:** Examination of adaptive behavior and cognitive profiles indicated that across all domains of adaptive behavior (Communication, Socialization, Daily Living, and Motor), Motor scores were highest in the ASD group, indicating the least degree of impairment. This profile was observed in the total sample of children with ASD, as well as a subsample of children with ASD and IQ below 80. In addition, among children with IQ below 80, Motor scores were the only scores that did not differ significantly between the ASD (*M*= 71.86, *SD*=13.6) and non-ASD groups (*M*=71.08, *SD*=15.86), *t*(1815)=-0.83, *p*=0.41, with mean motor scores higher than nonverbal IQ (*M*=55.7, *SD*=15.91) in the ASD group. To understand how clinically significant motor impairments might affect measurement of specific social communication deficits on autism diagnostic instruments, further analyses will investigate measurement invariance on the ADOS as a function of Vineland Motor Scores.

**Discussion:** While mean Vineland motor scores were below average in this sample of young children diagnosed with ASD, analyses of profiles showed that adaptive motor skills were, on average, significantly higher than other other adaptive skill domains and nonverbal IQ. This is consistent with several previous studies showing that certain aspects of motor development appear to be relatively protected in ASD, especially compared to other domains like language (Wickstrom et al., 2021). Even in a subset of children with cognitive impairment, motor scores were *not* identified as a relative deficit in young children with ASD, but rather exceeded scores across all other domains. These findings, derived from a very large number clinical research assessments conducted during the past 20ish years, echo several studies on autism highlighting motor as an area of relative strength (e.g., Yang, Paynter, & Gilmore, 2016). This highlights the need to consider apparent “delays” in motor skills within the context of broader developmental profiles, and reminds us to exercise caution when applying instruments that were developed based on historical conceptualizations of autism, to populations that may have very different profiles (e.g., individuals with primary motor impairments and/or genetic conditions).

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**Paper 2 of 3**

**Paper Title**: Examining motor and autism phenotypes through direct and objective assessment in genetic neurodevelopmental disorders

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**Introduction**: Advances in genetic testing have rapidly expanded the identification of genetic conditions highly penetrant for autism spectrum disorder (ASD) and intellectual disability (ID), often coined syndromic ASD1 or genetic neurodevelopmental disorders (genetic NDDs). Identification of these syndromes presents an opportunity to develop targeted treatments informed by molecular mechanisms 2, but a comprehensive understanding of the clinical phenotypes of these genetic NDDs is needed to inform treatment targets. Motor impairments have emerged as a key feature in genetic NDDs and are often present earlier and with greater severity compared to individuals with ASD without a known genetic cause (nonsyndromic ASD, nsASD)3–6. Furthermore, despite the high prevalence of ASD in these conditions, it is likely that motor impairments impact autism symptoms such as non-verbal social communication. Yet, few studies have prospectively evaluated individuals with genetic NDDs using comprehensive motor and autism assessments to understand the manifestation of these symptoms and how they may differ compared to individuals with nsASD. Here we present data on motor and autism profiles in children with chromatin modifying disorders (CMDs), which are some of the most rapidly expanding genetic conditions confidently associated with ASD and ID. We use a multi-modal approach to best ascertain the range of motor impairments in these conditions and examine the differences in motor and autism profiles between children with CMDs and nonsyndromic ASD (nsASD).

**Methods**: Data were collected as a part of an ongoing study funded by the Simon’s Foundation (977910). Comprehensive phenotyping of motor function and autism symptoms was done in children ages 17-74 months with chromatin modifying conditions [CMD] (n = 43, Mean Age: 45 months, SD: 17 months) and nsASD (n = 15, Mean Age: 36 months, SD: 11 months). Neurological examination was conducted by a pediatric neurologist on all children to assess atypical motor signs. Given the extent of the examination, here we focus on tone as it is a prevalent manifestation in genetic NDDs. Full day movements were assessed using wearable sensors on the wrists and ankles. Sensor data were cleaned and processed to generate quantitative variables that are hypothesized to proxy movement differences related to hypotonia (average acceleration (m/s2) and movement rate [# of movements generated/hour awake]). Vineland Adaptive Behavioral Scale (VABS) was used to assess motor function and socialization. Autism symptoms and diagnosis were evaluated using the Autism Diagnostic Observation Schedule (ADOS-2), Autism Diagnostic Interview-Revised (ADI-R), and clinical observations.

**Results**: On direct neurological examination, children with CMDs showed greater degrees of hypotonia compared to children with nsASD. From the wearable sensor data, children with CMDs had lower average acceleration (Mean 2m/s2, SD, 0.6) and movement rates (Mean: 1040, SD: 382) compared to children with nsASD (average acceleration, Mean: 3 m/s2, SD 0.5, and movement rate, Mean: 132, SD 418). On the Vineland, children with CMDs had significantly lower motor skills (Mean: 55, SD: 20) compared to nsASD (Mean: 80, SD: 16) [p = 0.001). Children with CMDs also showed lower socialization scores (Mean: 65, SD: 12) compared to nsASD (Mean: 73, SD: 13) [p=0.05]. All children with CMDs met criteria for ASD. ADOS item level examination indicated that children with CMDs showed a relative strength in integration of gaze and initiation of joint attention compared to nsASD.

**Discussion:** Using quantitative and standardized assessments, we captured granular aspects of motor function and autism symptoms in children CMDs and nsASD. These data indicate that children with CMDs show greater degrees of motor impairments on direct examination and on objective and quantitative variables compared to children with nsASD. Lower measures of average acceleration and movement rate could be indicators of different degrees of hypotonia. These objective measures could better inform subjective measurement of tone by clinicians and are likely more sensitive in picking up changes in tone over time and with interventions. Although all children with CMDs showed clinical elevations on ASD measures, our data indicate that their motor skills are more impaired than their social skills compared to nsASD. We also found that children with CMDs show a relative strength in social motivation on specific item level analysis on the ADOS. Moving forward, we will examine the association of various quantitative motor metrics and ASD symptom severity across ADOS modules used in children with CMDs and nsASD. Ultimately, these data improve our understanding of the nature of motor impairments in genetic NDDs and how they may uniquely shape autism symptoms. These data can inform clinical surveillance and diagnoses in these conditions. Furthermore, motor measures that are more sensitive can better inform treatment targets and therapeutic monitoring in potential clinical trials for these conditions.

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**Paper 3 of 3**

**Paper Title:** Autism Spectrum Disorder assessment in people with Cerebral Palsy: perspectives of professionals from an international survey

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**Introduction:** Cerebral Palsy (CP) is the most common physical disability in childhood1. While screening methods have suggested rates of Autism Spectrum Disorder (ASD) among individuals living with CP is as high as 35%,2 several studies indicate that ASD’s apparent prevalence depends on the diagnostic procedures employed.2–5 Recent research and the National Institute for Health and Care Excellence emphasize the need to understand the prevalence of ASD in individuals with CP.6 However, the assessment of ASD in this population is limited partly because instruments commonly used to support ASD diagnoses are invalid and/or unsuitable without adaptations.2,3,5,7 Further, it remains unclear how challenging it is for clinicians to make diagnostic decisions regarding ASD in this population and why. To lay a foundation for the development of formal guidelines supporting diagnostic decisions in such cases, we aimed to understand professionals’ perceptions of the challenges and appropriateness of assessing for ASD in individuals with CP or other early onset motor conditions.

**Method:** An international online survey was conducted as part of a larger project aiming to improve ASD assessment for people with CP. Participants were eligible if they had experience evaluating, treating or providing other healthcare, teaching, or social services to both people living with CP (or other early onset motor conditions) and ASD. Respondents were identified via relevant 1) professional networks of the project researchers; 2) professional and/or family organizations; and 3) authors of systematically identified studies reporting ASD assessment among people living with CP or other early onset motor conditions. Professionals rated how much they agree/disagree with the following statements: Q1, “Beyond the use of standardized instruments, the diagnosis process for ASD is clinically challenging when certain motor impairments are present”; Q2, “Behavioural examples and/or wording in diagnostic manuals such as DSM and ICD are representative of how people with early onset motor conditions manifest ASD”; and Q3, “In all cases, the assessment for ASD and its diagnosis is feasible and appropriate, even when motor impairments are severe”. A two-tailed Mann-Whitney U test assessed differences in responses to the above questions between respondents who reported primarily providing services to peoples displaying more severe (GMFCS IV and V) versus less severe motor impairment.

**Results:** 123 eligible respondents provided their opinion (n female=99; mean age=45y, SD=13y) of whom 108 work in clinic, 53 in research, 39 in education and 7 in other settings. Respondents worked in five WHO regions (Africa=1, Americas=31, Europe=76, South East Asia=2, Western Pacific=12) with a limited spread across country income levels (low=1, lower middle=2, upper middle=15, high=104). Across all respondents, 95% agreed that the diagnosis process for ASD is challenging when certain motor impairments are present, with 43% “strongly” agreeing. More than half (62%) responded that the behavioral examples and/or wording in diagnostic manuals is not representative of how people with early onset motor conditions manifest ASD and that the assessment and diagnosis of ASD can be inappropriate when motor impairments are severe. There were no significant differences between responses for those reporting working primarily with GMFCS levels IV and V (n=63) versus those primarily working with less severe motor conditions (n=46; Q1, p=0.06; Q2, p=0.06; Q3 p=0.43).

**Discussion:** These survey responses highlight the need to better guide clinicians in conducting ASD assessment when motor impairments are present. Doing so will help reduce the barriers that people with motor disorders face in accessing healthcare services8. Of note, even professionals who work primarily with people with mild CP seem to perceive this clinical decision as challenging. Strikingly, the general agreement that behavioral examples and/or wording in diagnostic manuals is inappropriate for this population suggests ASD instruments and diagnostic guidelines should consider either clearly stating motor-capability prerequisites or provide explicit guidance about if/how they can be applied to people with varying levels of motor ability.

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