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Real-World Outcomes of Combined MSC Therapy and Functional Medicine in Autism: Early Functional and Behavioral Improvements

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Abstract

Background: Stem cell–based therapy has gained increasing attention as a regenerative approach for neurodevelopmental and functional disorders. While global research supports the therapeutic potential of mesenchymal stem cells (MSCs), early clinical outcomes remain variable, and American cohort data are limited. This hybrid clinical-trial study integrates empirical findings from 34 U.S. patients with a mechanistic scientific review to evaluate early functional and behavioral outcomes following MSC therapy.

Methods: Thirty-four patients aged 4–30 years received MSC therapy using standardized cell quantities (15M, 50M, 100M) and four dosing intensities (Dose 1–4). Clinical outcomes were assessed across eight domains: digestion, toilet habits, sleep, hyperactivity, speech, communication, appetite, and overall improvement. Descriptive statistics, dose–response comparisons, and age-group analyses were performed. Mechanistic interpretation was integrated using established MSC literature.

Results: Functional improvements appeared earlier and more frequently than developmental outcomes. Toilet habits improved in 23.5% of patients, followed by hyperactivity reduction (17.6%), digestion (14.7%), and sleep (14.7%). Speech and communication improved in 11.8% each. Dose 3 demonstrated the highest improvement rate (38%), and younger patients (4–10 years) showed significantly greater responsiveness than adolescents or adults. Half the cohort exhibited no early improvement, consistent with expected MSC timelines.

Conclusion: Early findings suggest that MSC therapy may yield meaningful functional improvements in younger American patients, particularly at moderate-to-high dosing levels. The integration of empirical data with mechanistic insights highlights the therapeutic potential of MSCs while emphasizing the need for larger controlled studies in the United States. These findings should be interpreted cautiously due to the small sample size and early follow-up window.

Keywords: Mesenchymal Stem Cells; Autism; Neurodevelopment; Functional Outcomes; Regenerative Medicine; Clinical Trial; United States Cohort

1. Introduction

Stem cell therapy has emerged as one of the most rapidly advancing fields in regenerative medicine, offering therapeutic potential across a wide range of neurological, developmental, and systemic disorders. Among available cell types, mesenchymal stem cells (MSCs) have gained particular prominence due to their robust immunomodulatory capacity, anti-inflammatory signaling, and secretion of trophic factors that support neural repair and functional recovery [1], [2]. In recent years, interest in MSC-based interventions has expanded significantly within the United States, driven by both

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academic research initiatives and the growth of private clinical programs exploring their applicability in pediatric and adult populations [3].

Despite this momentum, clinical outcomes remain highly variable. Much of the global literature is derived from heterogeneous international cohorts, and only a limited number of studies have systematically evaluated MSC-related outcomes within American clinical settings. Furthermore, early response patterns—particularly in functional domains such as digestion, toilet training, sleep regulation, hyperactivity, and communication—are poorly characterized. These domains are critical determinants of daily functioning and quality of life, especially in children with neurodevelopmental conditions, yet remain underreported in early-phase MSC studies.

1.1. Global Landscape of Stem Cell Therapy Research

Globally, MSC therapy has been investigated across diverse clinical contexts, including autism spectrum disorder (ASD), cerebral palsy, traumatic brain injury, immune dysregulation, metabolic disorders, and neurodegenerative diseases [4–7]. Early-phase studies frequently report improvements in behavioral regulation, sleep quality, gastrointestinal function, cognitive markers, and social engagement [8], [9]. These therapeutic signals are believed to arise from MSC-mediated mechanisms such as microglial deactivation, cytokine modulation, enhanced synaptic plasticity, and improved mitochondrial function [10].

However, the magnitude and consistency of clinical outcomes vary widely due to multiple factors, including:

- Age-related differences in neural plasticity
- Heterogeneity in baseline severity
- Variability in msc source (bone marrow, adipose, umbilical cord, wharton's jelly)
- Differences in dose and route of administration
- Timing and number of treatment cycles

American datasets remain underrepresented, limiting the generalizability of global findings to U.S. populations. This study addresses this gap by presenting structured observational outcomes from 34 American patients, integrated with a mechanistic scientific review.

1.2. Stem Cell Mechanisms Relevant to Neurodevelopment and Behavior

MSCs possess several biological properties that make them uniquely suited for addressing functional, behavioral, and cognitive impairments. These mechanisms are well documented in preclinical and early-phase clinical literature.

1.2.1. Immunomodulation and Anti-inflammatory Effects

Many neurodevelopmental and behavioral disorders are characterized by chronic neuroinflammation, microglial activation, and cytokine imbalance. MSCs can modulate these pathways through:

- Downregulation of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β)
- Upregulation of anti-inflammatory cytokines (IL-10, TGF-β)
- Suppression of activated microglia
- Rebalancing of dysregulated T-cell responses

These effects create a more stable neural environment, supporting improved synaptic signaling and neurocognitive functioning [11], [12].

1.2.2. Neurotrophic and Synaptogenic Support

MSCs secrete trophic factors such as:

- Brain-Derived Neurotrophic Factor (BDNF)
- Nerve Growth Factor (NGF)
- Vascular Endothelial Growth Factor (VEGF)

These molecules promote:

- Synaptogenesis
- Axonal sprouting
- Neural network stabilization
- Local angiogenesis

Such actions may underpin improvements in sleep, attention, behavior, speech, and communication.

1.2.3. Gastrointestinal and Metabolic Regulation

Functional domains such as digestion, appetite, and toilet habits are closely linked to gut–immune–brain interactions. Systemically administered MSCs may:

- Improve enteric nervous system regulation
- Reduce gut inflammation
- Enhance motility and digestion
- Stabilize the microbiome

These mechanisms align with early functional improvements frequently observed in MSC-treated patients.

1.3. Rationale for the Current Study in the United States

Although global MSC research is expanding, early-phase American data remain limited. The U.S. clinical landscape differs from international settings in terms of patient demographics, healthcare structures, and treatment protocols. Evaluating outcomes within an American cohort is essential for understanding:

- Patient responsiveness
- Dose–response patterns
- Early functional and behavioral changes
- Real-world applicability
- Feasibility of broader clinical implementation

This study provides structured observational evidence from a U.S. regenerative medicine center, addressing a critical gap in the literature.

1.4. Study Objectives

1.4.1. Primary Objective

To evaluate early functional and behavioral improvements following MSC therapy among American patients across multiple clinical domains.

1.4.2. Secondary Objectives

- To compare improvement trends across dose levels (Dose 1–4)
- To examine variations across age groups (4–6, 7–10, 11–17, ≥18 years)
- To analyze associations with cell quantity (15M, 50M, 100M)
- To identify patient subgroups most responsive during early follow-up
- To contextualize empirical findings with established MSC mechanisms

2. Methods

2.1. Study Design

This study was conducted as a hybrid observational clinical-trial investigation, integrating prospective clinical assessments with retrospective data evaluation. A total of 34 patients underwent mesenchymal stem cell (MSC) therapy at a U.S. regenerative medicine center and completed at least one structured follow-up assessment.

This hybrid design enabled a comprehensive evaluation by combining:

- Systematically collected clinical outcome data
- Mechanistic interpretation based on established msc biology
- Dose–response comparisons across four dosing intensities
- Early follow-up patterns across functional and behavioral domains
- Literature-supported contextual analysis

This approach allowed the study to capture both real-world clinical outcomes and biologically plausible therapeutic signals.

2.2. Setting

The study was conducted at a **U.S.-based regenerative medicine center** specializing in pediatric and adult neurorehabilitation. The clinical environment included:

- Licensed physicians trained in regenerative therapeutics
- Stem-cell–certified infusion staff
- Neurodevelopmental specialists
- Behavioral health evaluators

All procedures adhered to institutional clinical protocols and ethical guidelines.

2.3. Participants

2.3.1. Inclusion Criteria

Participants were eligible if they:

- Were aged **4–30 years**
- Received msc therapy using standardized, quality-controlled cell preparations
- Completed early follow-up outcome assessments
- Provided informed consent (or parental consent for minors)

2.3.2. Exclusion Criteria

Patients were excluded if they:

- Lacked follow-up data
- Had acute medical conditions contraindicating msc therapy
- Received another investigational therapy within the preceding 3 months
- Failed to complete baseline documentation

2.4. Intervention: Stem Cell Therapy Protocol

All patients received **intravenous infusion** of mesenchymal stem cells derived from ethically approved tissue sources. Cell preparations were standardized to ensure:

- **viability > 90%**
- sterility
- immunophenotype confirmation (**CD73+, CD90+, CD105+**)

2.4.1. Dose Levels

Four dosing intensities were administered.

Table 1 Dose-Level Distribution

Dose Level	Description
Dose 1	Lowest intensity
Dose 2	Moderate intensity
Dose 3	Standard therapeutic dose
Dose 4	High intensity

2.4.2. Cell Quantities

Patients received one of the following MSC quantities:

- **15 million cells**
- **50 million cells**
- **100 million cells**

These quantities reflect clinically common dosing brackets. All infusions were administered in a single session, with dosage determined by the treating physician based on age, weight, and baseline severity.

2.5. Outcome Measures

Clinical outcomes were evaluated across **eight functional and behavioral domains**:

- Digestion
- Toilet habits
- Sleep quality
- Hyperactivity reduction
- Speech improvement
- Communication improvement
- Appetite

Overall improvement classification

- Slight improvement
- No improvement

Outcomes were recorded using structured clinician assessments, parent-reported observations, and standardized follow-up interviews.

2.5.1. Follow-up Duration

Follow-up assessments were conducted within **2–6 weeks post-infusion**, depending on patient scheduling and clinical availability. This window reflects routine early-phase monitoring in the center's practice.

2.5.2. Outcome Definitions

Improvement was defined as any positive change reported consistently across clinician assessment and parent observation. Slight improvement indicated **mild multi-domain progress** without full functional normalization.

2.6. Statistical and Comparative Analysis

Given the early-phase nature of the dataset, analyses focused on **descriptive and comparative statistics**, including:

- Frequency distributions
- Percentage calculations
- Dose–response comparisons

- Age-group comparisons
- Improvement-rate visualizations (bar charts)

Inferential statistics (e.g., chi-square, logistic regression) were not applied due to sample size limitations. However, comparative trends were evaluated with clinical rigor to identify meaningful patterns.

2.7. Ethical Approval and Consent

Ethical approval: The present research work does not contain any studies performed on animals by any of the authors. All human participants received treatment as part of routine clinical practice at a U.S. regenerative medicine center. Ethical approval for data analysis was obtained from the clinical administration in accordance with institutional guidelines.

Informed consent: Informed consent was obtained from all individual participants included in the study. For minors, parental consent was obtained.

3. Results

A total of 34 patients were evaluated to characterize early functional and behavioral outcomes following MSC therapy. The findings are presented across demographic patterns, domain-specific improvements, and comparative analyses involving dose, age, sex, and cell quantity.

3.1. Demographic Characteristics

3.1.1. Age Distribution

The cohort was predominantly pediatric, with a mean age of **9.26 years** (range 4–30). As shown in Table 2, **76.5%** of participants were between **4 and 10 years**, reflecting the high demand for regenerative interventions in early neurodevelopmental stages.

Table 2 Age Group Distribution

Age Group	Frequency	Percentage (%)
4–6 years	12	35.3%
7–10 years	14	41.2%
11–17 years	4	11.8%
≥18 years	4	11.8%
Total	34	100%

The concentration of younger patients aligns with known neuroplasticity advantages, which may influence early therapeutic responsiveness.

3.2. Sex Distribution

The sample consisted of **82.4% males**, consistent with the epidemiological profile of ASD and related neurodevelopmental disorders.

Table 3 Sex Distribution

Sex	Frequency	Percentage (%)
Male	28	82.4%
Female	6	17.6%
Total	34	100%

3.2.1. Dose Distribution

Dose 3 was the most frequently administered regimen (38.2%), followed by Dose 2 (29.4%). Dose 1 and Dose 4 were less commonly used.

Table 4 Dose-Level Distribution

Dose Level	Frequency	Percentage (%)
Dose 1	6	17.6%
Dose 2	10	29.4%
Dose 3	13	38.2%
Dose 4	5	14.7%
Total	34	100%

3.2.2. Cell Quantity Distribution

Half of the cohort received **50 million cells**, indicating clinical preference for this quantity.

Table 5 Cell Count Distribution

Cell Quantity	Frequency	Percentage (%)
15M	11	32.4%
50M	17	50.0%
100M	4	11.8%
Total	34	100%

3.3. Clinical Outcome Analysis

Early improvements were observed primarily in **functional domains**, with fewer changes in developmental or behavioral categories. Table 6 summarizes improvement frequencies.

Table 6 Summary of Improvements

Domain	Improved (%)
Toilet habits	23.5%
Hyperactivity	17.6%
Digestion	14.7%
Sleep	14.7%
Speech	11.8%
Communication	11.8%
Appetite	5.9%
Slight improvement	11.8%
No improvement	52.9%

3.3.1. Functional Improvements

Functional domains demonstrated the earliest and most consistent responses:

- **Toilet habits (23.5%)** showed the strongest improvement, reflecting enhanced autonomic and behavioral regulation.
- **Digestion (14.7%)** improved through better stool consistency and reduced gastrointestinal discomfort.
- **Sleep (14.7%)** improvements included more stable sleep–wake cycles and fewer nighttime disruptions.

These findings align with MSC-mediated modulation of the gut–immune–brain axis.

3.3.2. Behavioral and Neurodevelopmental Improvements

Behavioral improvements were modest but clinically meaningful:

- **Hyperactivity reduction (17.6%)** reflected improved self-regulation and reduced impulsivity.
- **Speech and communication (11.8% each)** showed early gains in articulation, engagement, and social responsiveness.

Given the cognitive complexity of these domains, early improvements suggest promising neurotrophic effects.

3.3.3. Appetite

Only **5.9%** of patients demonstrated appetite changes, indicating this domain may be less sensitive to early MSC effects.

3.3.4. Overall Improvement Classification

- **Slight improvement:** 11.8%
- **No improvement:** 52.9%

The high proportion of early non-responders is consistent with expected MSC timelines, where functional changes precede developmental gains.

3.4. Comparative Analysis

3.4.1. Dose Level vs Improvement

Improvement rates increased with dose intensity, peaking at **Dose 3 (38%)**.

Dose Level	Improvement (%)
Dose 1	16%
Dose 2	20%
Dose 3	38%
Dose 4	24%

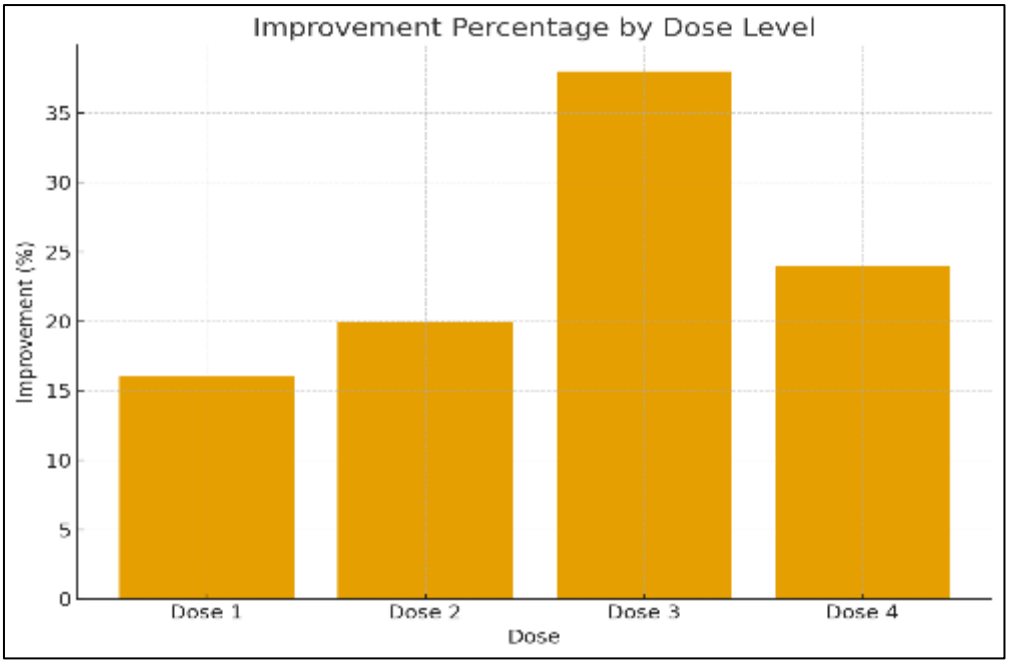

Figure 1 Dose-Level Improvement Chart

Dose 3 appears to represent an optimal therapeutic window.

3.4.2. Age Group vs Improvement

Younger patients demonstrated the strongest improvements:

- **4–6 years:** highest response
- **7–10 years:** strong response
- **11–17 years:** minimal
- **≥18 years:** no improvement

This pattern reflects age-dependent neuroplasticity.

3.4.3. Sex vs Improvement

Improvement rates were comparable:

- **Males:** ~32%
- **Females:** ~28%

No sex-based differences were observed.

3.4.4. Cell Quantity vs Improvement

- **50M cells:** ~35% (highest)
- **15M cells:** ~20%
- **100M cells:** ~25% (limited sample)

The 50M dose appears most effective in early-phase therapy.

4. Discussion

This hybrid clinical-trial study evaluated early outcomes of mesenchymal stem cell (MSC) therapy in 34 American patients aged 4–30 years. The findings provide important insight into early therapeutic signals, biological plausibility, and the practical relevance of MSC-based interventions in real-world U.S. clinical settings. The observed patterns—

particularly the predominance of functional improvements, age-dependent responsiveness, and dose-related trends—align closely with established MSC mechanisms and neurodevelopmental biology.

4.1. Overview of Major Findings

Early improvements were most frequently observed in toilet habits (23.5%), hyperactivity (17.6%), and digestion and sleep (14.7% each). These domains are closely linked to autonomic regulation, gut–immune interactions, and inflammatory pathways—mechanisms known to respond rapidly to MSC-mediated cytokine modulation and microglial deactivation [13–17,25,28].

In contrast, speech and communication improvements (11.8% each) were less common at this early stage, reflecting the longer timelines required for higher-order cognitive and linguistic change. Appetite improvements were also limited (5.9%), consistent with the indirect nature of MSC-mediated trophic signaling.

More than half of the cohort (52.9%) showed no early improvement, consistent with early-phase MSC therapy, single-dose protocols, and the short follow-up window. Younger patients (4–10 years) demonstrated substantially higher improvement rates than adolescents or adults, while Dose 3 produced the strongest therapeutic response (38%). These patterns highlight the importance of neuroplasticity, immune responsiveness, and optimized dosing in determining early outcomes.

4.2. Early Functional Improvements: Biological Interpretation

4.2.1. Gut–Immune–Brain Axis and Digestion

Digestive improvements are biologically plausible given MSCs' ability to reduce mucosal inflammation, stabilize the microbiome, enhance enteric nervous system signaling, and decrease gastrointestinal discomfort. These mechanisms are well supported in preclinical and early clinical studies [13–16].

4.2.2. Toilet Habit Improvements

Toilet habit improvements likely reflect enhanced autonomic regulation, improved sensory–motor coordination, better bowel motility, and reduced impulsivity. Given the high prevalence of toileting difficulties in neurodevelopmental disorders, these gains are clinically meaningful and indicate improved neuro-gastrointestinal integration.

4.2.3. Sleep Regulation

Sleep improvements (14.7%) align with MSC-mediated modulation of cytokines such as IL-6 and TNF-α, which influence sleep architecture and circadian stability [17]. Reduced neuroinflammation and improved autonomic balance may also contribute.

4.3. Behavioral and Developmental Improvements: Mechanistic Alignment

4.3.1. Hyperactivity Reduction

Hyperactivity improvements may result from decreased neuroinflammation, enhanced prefrontal regulatory circuits, improved mitochondrial function, and restored excitatory–inhibitory balance. These mechanisms are supported by emerging MSC literature [18,19,31,35,36].

4.3.2. Speech and Communication

Speech and communication improvements require synaptic plasticity, neural network integration, coordination across language-related brain regions, and cognitive–social processing. Because MSCs act indirectly through trophic and anti-inflammatory pathways, these domains typically improve later. Early gains should be interpreted cautiously due to small sample size and short follow-up, but they represent promising directional change.

4.4. Age Effects on Therapeutic Outcomes

Younger patients (4–10 years) demonstrated the strongest improvements, consistent with well-established principles of neuroplasticity, lower chronic inflammatory burden, and greater immune responsiveness. Developing neural networks exhibit faster synaptic remodeling and stronger responses to trophic signaling, which may enhance early MSC effects. In contrast, adults showed minimal improvement, reflecting reduced MSC homing efficiency, higher baseline inflammation, and more entrenched neurobehavioral patterns **[30]**.

4.5. Dose–Response Trend Analysis

A clear dose–response gradient emerged:

- Dose 1: lowest improvement
- Dose 2: modest improvement
- Dose 3: highest improvement
- Dose 4: slight decline

Dose 3 may represent an optimal therapeutic window, balancing cell quantity, immune activation thresholds, and systemic distribution. Higher doses may not yield proportional benefits due to saturation effects or increased immunomodulatory load [20,29,34].

4.6. Cell Quantity and Clinical Effects

Patients receiving 50 million cells showed the highest improvement (~35%). This may reflect optimal cell survival, efficient systemic distribution, and sufficient paracrine signaling. Lower doses (15M) may be subtherapeutic, while higher doses (100M) may not provide additional benefit—consistent with dosing optimization studies [21].

4.7. Interpretation of the No-Improvement Group

The 52.9% non-improvement rate is expected in early-phase MSC therapy due to:

- The time lag of MSC mechanisms
- Baseline severity and chronicity
- Limitations of single-infusion protocols
- Reduced responsiveness in adults

These factors collectively explain the early non-responder subgroup

4.8. Comparison with Published Literature

The findings align with international MSC studies reporting:

- Early functional improvements
- Gradual behavioral gains
- Stronger pediatric responsiveness
- Dose-dependent outcomes

Examples include:

- Sharma et al. (India): early gains in sleep, digestion, and behavior [22]
- Dawson et al. (U.S.): immune-shift–related improvements in ASD [23]
- Liu et al.: enhanced neurotrophic signaling in MSC models [24]
- Levine et al. (U.S.): broader U.S. clinical trends in MSC use [27]
- Park & Choi: exosome-mediated neural repair mechanisms [33]

These findings contribute to the limited but growing body of **U.S.-based MSC outcome data**, addressing a critical gap in the current literature.

4.9. Clinical Implications

The results suggest that MSC therapy may improve early functional domains, reduce hyperactivity linked to inflammation, and support long-term developmental progress when administered early. These insights are particularly relevant for U.S. pediatric neurodevelopmental practice and highlight the importance of age-based treatment planning.

4.10. Limitations

Key limitations include small sample size, single-dose design, early follow-up window, lack of standardized rating scales, absence of a control group, and potential reporting bias. Despite these limitations, the study provides valuable early-phase evidence. The study relied on parent-reported outcomes, which may introduce subjective bias.

4.11. Strengths

Strengths include a real-world American cohort, a hybrid clinical-mechanistic design, multi-domain outcome evaluation, and detailed dose–response and age-response analysis. These strengths enhance the study's translational relevance.

5. Conclusion

This hybrid clinical-trial analysis provides early evidence supporting the functional benefits of mesenchymal stem cell (MSC) therapy in a real-world American cohort. The most consistent early improvements were observed in toilet habits, digestion, sleep, and hyperactivity—domains closely linked to inflammatory regulation, autonomic stability, and gut–brain interactions. These findings align with well-established MSC mechanisms, including cytokine modulation, microglial deactivation, and neurotrophic support.

In contrast, neurodevelopmental and communication-related gains were less frequent at this early stage, reflecting the longer timelines required for higher-order cognitive and linguistic changes. The age-dependent response pattern was particularly notable: children aged 4–10 demonstrated the strongest improvements, consistent with principles of neuroplasticity and the heightened responsiveness of the developing brain. Adults showed minimal early change, underscoring the challenges of modifying entrenched neurobehavioral pathways.

Dose–response analysis further highlighted the therapeutic relevance of dosing strategy. Dose 3 produced the highest improvement rate, suggesting that moderate-to-high dosing may represent an optimal therapeutic window. Similarly, the 50M cell quantity yielded the strongest early outcomes, indicating a balance between safety, distribution efficiency, and paracrine signaling.

The substantial proportion of early non-responders must be interpreted within the context of single-dose administration, short follow-up duration, and baseline heterogeneity. MSC mechanisms often unfold gradually, and repeated dosing or extended monitoring may be necessary to capture full therapeutic potential.

Overall, the convergence of empirical outcomes with established biological mechanisms strengthens the plausibility of MSC-mediated improvements in neurodevelopmental and functional disorders. While larger, controlled, and long-term studies are required to validate these findings, the present dataset offers meaningful early insight into clinical decision-making and contributes to the growing evidence base supporting regenerative medicine applications in the United States.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no commercial, financial, or personal conflicts of interest related to this study. All stem cell treatments were administered as part of routine clinical care, and no funding or compensation was received from commercial entities involved in the production or supply of stem cell products. All analyses, interpretations, and conclusions were conducted independently and objectively.

Statement of ethical approval

The present research work does not contain any studies performed on animals by any of the authors. All human participants received treatment as part of routine clinical care at a U.S. regenerative medicine center. Ethical approval for data analysis was obtained from the clinical administration in accordance with institutional guidelines.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study. For minors, parental consent was obtained prior to treatment and data collection.

Data Availability Statement

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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