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RESEARCH REPORT

# Long-Term Cognitive and Functional Outcomes in Children with Mucopolysaccharidosis (MPS)-IH (Hurler Syndrome) Treated with Hematopoietic Cell Transplantation

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**Abstract** The long-term cognitive and functional outcomes of children with mucopolysaccharidosis type I (MPS-IH) post-hematopoietic cell transplant (HCT) are not well documented, and the role of genetic and treatment factors in these outcomes has yet to be defined. In this multi-site, international study, we (1) characterize the cognitive and functional status of 47 individuals (ages 2–25, mean of 10.6 years) with MPS-IH who are 1–24 years post HCT (mean = 9 years) and (2) examine contributions of genotype, transplant characteristics, and sociodemographic factors to cognitive ability, adaptive behavior, and quality of life. The overall cognitive ability of our sample was mildly impaired, more than two standard deviations below general population norms. Parent reported adaptive behaviors (i.e., communication, daily living, and motor skills) were similarly impaired with a relative strength in socialization. Quality of life, as reported by parents, fell more than two standard deviations below population norms for physical functioning; however, psychosocial quality of life (emotional well-being) approximated population norms. In linear regression analysis, adjusted for demographic and treatment factors, mutation severity was associated with lower cognitive ability ($p = 0.005$) and adaptive functioning ($p = 0.004$), but not parent ratings of children's quality of life. Older age at HCT was associated with poorer physical quality of life ($p = 0.002$); lower socioeconomic status ($p = 0.028$) and unrelated bone marrow HCT ($p = 0.010$) were associated with poorer psychosocial quality of life. Implications for screening and early intervention for children at risk for poorer cognitive and functional outcomes are described.

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"J.E. Wraith was deceased at the time of publication."

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## Introduction

Mucopolysaccharidosis type I (MPS I) is an inherited metabolic disorder caused by the absence or deficiency of lysosomal enzymes needed to degrade glycosaminoglycan (GAG). Progressive accumulation of GAG within the cells of various organs ultimately compromises their function. The severe form of MPS I (Hurler syndrome MPS-IH) usually presents in infancy. If left untreated, worsening neurological, cardiovascular, and respiratory problems result in death in early childhood. The standard of care for MPS-IH is treatment with hematopoietic cell transplantation (HCT) (Muenzer et al. 2009; Tolar et al. 2007).

While survival rates and short-term outcome are known to be improved by HCT, the long-term cognitive, adaptive, and quality of life outcomes of these children post transplant are not well understood. Additionally, genetic, demographic, and treatment-related factors that may influence these important functional outcomes have yet to be defined.

Prior reports on the cognitive and adaptive outcomes of children with Hurler syndrome have shown that most children continue to acquire cognitive skills after HCT, albeit at a slower rate compared to unaffected children. These studies suggest that, when performed early enough in the disease process, HCT improved or stabilized neurocognitive development and adaptive skills in most children, particularly in combination with enzyme replacement therapy, preventing progressive deterioration (Malm et al. 2008; Bjoraker et al. 2006; Eisengart et al. 2013). Nonetheless, the neurocognitive and adaptive outcomes after HCT for Hurler syndrome are highly variable (Aldenhoven et al. 2008). Several factors are suspected to play a role in this heterogeneity, including genotype, age at transplantation, graft source, and demographic factors, but their relative contributions have been incompletely studied (Grewal et al. 2003; Prasad and Kurtzberg 2010; Peters et al. 1998). A recent longitudinal multisite study (Aldenhoven et al. 2015) found that the neurodevelopmental outcome of patients with MPS-IH after HCT was determined in large part by the degree of central nervous system damage prior to transplant, with those showing higher baseline cognitive functioning and receiving early HCT showing better long-term outcomes.

The presence of a nonsense mutation on both IDUA (lysosomal enzyme alpha-L-iduronidase) alleles is known to cause severe Hurler syndrome (Matte et al. 2003). These nonsense mutations are believed to result in a complete lack of residual enzyme activity, causing rapid accumulation of lysosomal GAG storage, early onset of clinical signs, and rapid disease progression. Two of these mutations, W402X and Q70X, are particularly common, accounting for up to 70% of MPS I disease alleles, although there is considerable variation in frequency across racial/ethnic groups and countries (Terlato and Cox 2003). While the role of homozygous nonsense mutations in the clinical severity of Hurler syndrome is well established, their potential role in long-term cognitive and adaptive outcomes following transplantation has not been examined. Additionally, the role of other mutation types presumed to be severe (i.e., nonsense-deletion and deletion-deletion) in cognitive and functional outcomes is not known.

In this collaborative study between investigators in the United Kingdom and the University of Minnesota in the United States, we examined the cognitive status, adaptive functioning, and quality of life of 47 individuals with MPS-IH who were between 1 and 24 years status-post HCT. Additionally, we evaluated the relative influence of demographic, genetic, and transplant-related factors on these key outcomes.

## Materials and Methods

### Participants

#### *The United Kingdom*

Forty-nine participants with MPS-IH who were members of the Society for MPS and Related Diseases in the United Kingdom and previously transplanted at either the Royal Manchester Children's Hospital or Great Ormond Street Hospital were invited and agreed to participate in this study. The ethics board of these two participating medical centers reviewed and approved the protocol. A home visit was scheduled for interested families at which time informed consent was obtained and a psychologist administered the test battery described below. Medical background data related to transplant and treatments were obtained from the two participating medical centers. Two families were excluded because of incomplete data. One family with two siblings affected consented for only one child to participate. Two children were ultimately not able to participate due to significant health issues at the time of the study. Seven children were excluded from this analysis, as they were less than 1 year from HCT at the time of the study. Three additional children were excluded from analyses due to missing genetic mutation information. Thus, a total of 34 participants and their families from the United Kingdom were included in this research. Data were collected between 2004 and 2005.

#### *University of Minnesota (UMN), the United States*

Seventeen patients diagnosed with MPS-IH who were at least 1 year from having completed HCT and at least partially engrafted were selected from the pool of patients who were followed in our clinics after transplant. Written informed consent was obtained from parents at the time of the patient's assessment visit at the University of Minnesota Medical Center. Data were collected between 2004 and 2012. Cognitive and adaptive behaviors were collected as part of their clinical assessment, and quality of life assessments was collected as an additional research measure. Four participants were excluded due to lacking genetic mutation information, central for our study question.

Combined data from the United Kingdom and University of Minnesota yielded a total of 47 participants with MPS-IH that were at least 1-year post-HCT. Diagnosis of MPS-IH was made in accordance with the clinical guide-

lines at the time (Muenzer et al. 2009; Pastores et al. 2007), and all patients included in this study manifested early onset of severe symptoms prior to 2 years of age. All children were at least partially engrafted (i.e., 70% were > 90% engrafted; the remainder were 50–90% engrafted) and were transplanted between 1985 and 2007.

## Measures

### *Cognitive Functioning*

Children in the United Kingdom were administered the Griffiths Mental Development Scales (GMDS) (Griffiths 1996) for subjects from birth to 8 years of age, the Wechsler Intelligence Scale for Children Third Edition (WISC-III) (Wechsler 1991) for subjects 8 through 16 years of age, and the Wechsler Adult Intelligence Scale Third Edition (WAIS-III) for those ages 17 and over. The GMDS measures gross motor skills, personal-social development, hand and eye coordination, and performance, resulting in a general developmental quotient (GDQ) comparable to a Wechsler IQ (Luiz et al. 2001). Normative information for the GMDS is based on a national standardization sample representative of children between their second and eighth years of age in the United Kingdom (England, Wales, Scotland, and Northern Ireland) and Eire (Republic of Ireland). At the University of Minnesota, children under the age of 6 were given the Mullen Scales of Early Learning (Mullen 1995) ($n = 6$). Children older than 6 years of age were administered one of the Wechsler tests (WISC-IV or Wechsler Abbreviated Scale of Intelligence; $n = 9$) (Wechsler 1999) or were administered the Stanford-Binet Intelligence Scales Fifth Edition (Roid 2003) ($n = 8$; children who were generally more developmentally delayed). Full-scale IQ scores were collapsed across instruments to index cognitive ability with a mean of 100 and a standard deviation of 15 representing the average range of functioning and scores more than two standard deviations below the mean (i.e., <70) representing impairment.

### *Adaptive Behavior*

The Vineland Adaptive Behavior Scales (VABS) (Sparrow et al. 1984) were used to measure children's daily functioning. The VABS is a widely used norm-referenced parent-report measure of personal and social sufficiency in the areas of communication, daily living skills, socialization, and motor function. These domains are combined to form an adaptive behavior composite (ABC) score. Similar to IQ scores, domain areas and the composite score have a mean of 100 and a standard deviation of 15 with two standard deviations below the mean representing clinical impairment. Two editions of the VABS are available, with a second edition published in 2005 (Sparrow et al. 2005) offering a normative update and revisions to scale items. Due to differences in the availability of these instruments across centers and the timing of data collection, all UK participants received the first edition of the test and the majority of participants in Minnesota received the second edition.

### *Quality of Life*

The Child Health Questionnaire (CHQ) (Landgraf et al. 1996) PF-50 was administered to measure participant's physical and psychosocial well-being, as reported by parents. This 50-item survey has been widely used in studies of children with chronic illness and has established reliability and validity. While the CHQ is normed for parents of children 5–18 years of age, parents of all participants in the study completed this survey, given that none of our young adult participants ($n = 8$) were living independently and self-report ratings would have been questionable given estimates of their cognitive functioning. The CHQ assesses 14 physical and psychosocial domains: general health perceptions, physical functioning, role/social physical functioning, bodily pain, role/social-emotional functioning, role/social behavioral functioning, parent impact-time, parent impact-emotional, self-esteem, mental health, behavior, family activities, family cohesion, and change in health. Scales are transformed to a 0–100 scale, where 0 = the worst possible health state and 100 = the best possible health state. The individual scale scores are aggregated to derive two summary component scores: the physical functioning and psychosocial health summary scores. These scores are converted into norm-referenced *T*-scores with a mean of 50 and a standard deviation of 10. Poor quality of life has been defined as two standard deviations below the mean of the normative sample or a physical functioning or psychosocial health summary score <30.

### *Socioeconomic Status*

The Hollingshead and Redlich (2-factor) classification of socioeconomic status (SES) was used (Hollingshead, unpublished manuscript 1975; Hollingshead 1957). Two raters (E.S. and E.B.) independently classified both the UK and the US families based on parental occupation and education with 94% agreement. A consensus was reached on the two disagreements. SES was categorized as ≥ 4 ("lower middle to lower socioeconomic class") versus <4 ("middle to upper socioeconomic class").

### *Genotype*

Genotype was obtained from medical records and classified as known severe (homozygous for nonsense or deletion mutation or heterozygous for a combination of these) and

other (homozygous or heterozygous for missense mutation).

### Statistical Analysis

Descriptive characteristics were examined by mutation type and in aggregate. Unadjusted comparisons were based on a *t*-test with unequal variance and Welch degrees of freedom. Separate multiple linear regression models were used to examine the adjusted influence of demographic (SES, sex of the child), treatment factors (age at transplant, time since transplant, radiation treatment (yes/no), type of transplant (related versus unrelated marrow versus cord blood), number of transplants (one versus more than one) and genetic factors (severe versus not severe mutation type)) on cognitive (IQ), adaptive functioning composite (VABS ABC), physical quality of life, and psychosocial quality of life. All analyses were adjusted for treatment center (i.e., UK center or UMN) and regression analysis of adaptive behavior functioning was further adjusted for version type (Vineland I or II). Robust variance estimation was used for confidence intervals and *p*-values. All statistical analyses were performed using R v3.0.3 (Pinheiro et al. 2014).

## Results

### Participants

Descriptive statistics for the 47 patients with available information regarding mutation type (severe versus other) can be found in Table 1. Participants were between 2.2 and 25.4 years of age at the time of evaluation and were transplanted at a mean age of 18.6 months (range of 6–44 months). Given the time at which diagnosis and treatment took place, only two participants (both at the University of Minnesota) received enzyme replacement therapy (ERT) as part of their conditioning regimen. Twenty-three percent of the total sample received total body irradiation as part of their conditioning regimen (6 at the UMN and 5 in the United Kingdom). The majority of participating patients were found to have known severe mutations (66%), and the remainder (34%) had other types of mutations. The specific mutation types that comprise these groups are reported in Table 2. Children with severe mutations were older at the time of assessment and further from transplant than those with other known mutations. Overall cognitive ability for participants fell in the mildly impaired range, with similar level of impairment reported in their adaptive skills, consistent with prior reports in the literature. Children's physical quality of life was rated as poor by parents, with the sample mean falling more than two standard deviations below the general population mean. In contrast, parent ratings of children's psychosocial quality of life fell within the average range and were not discrepant from general population norms, suggesting that parents perceive their children to be functioning well from a social-emotional-behavioral perspective.

### Predictors of Cognitive and Adaptive Functioning

In multiple linear regression analyses, adjusted for demographic and treatment factors described above, overall cognitive ability was significantly associated with genotype, showing that those who had a known severe genotype scored more than one standard deviation lower (−16.76 points, 95% CI, −25.58 to −4.94, $p = 0.005$) on average for measures of IQ compared to those with a known other mutation. Specific transplant-related variables (i.e., type of transplant, number of transplants, age at transplant, time since transplant, total body irradiation treatment) and demographic factors (sex, SES) were not significant predictors in the multivariate model. Similarly, parent ratings of patient's adaptive functioning were also significantly associated with genotype, but not with demographic and treatment factors in multivariate analysis. Specifically, parents of patients with a severe mutation reported significantly lower adaptive functioning on average (−9.27 points, 95% CI, −18.33 to −0.20, $p = 0.045$).

### Predictors of Quality of Life

Age at transplant was significantly associated with physical quality of life, with older age at transplant associated with poorer physical functioning (−8.10, 95% CI −13.16 to −3.05, $p = 0.002$). Parents of patients who received total body irradiation as part of their transplant regimen reported better physical quality of life (e.g., better physical functioning, fewer limitations due to physical difficulties) than children who did not have total body irradiation (13.88, 95% CI 5.12–22.64, $p = 0.002$). Within the psychosocial domain of quality of life, children from lower SES families (−5.35, 95% CI −10.15 to −0.57, $p = 0.028$) and those who received unrelated bone marrow HCT (−7.73, 95% CI −13.62 to −1.83, $p = 0.010$) were reported to have poorer psychosocial functioning.

## Discussion

This study utilized a unique multi-institutional, international cross-sectional cohort of children with MPS-IH who were between 1 and 24 years post transplant to characterize the cognitive, adaptive, and quality of life outcomes of these patients. We investigated the role of mutation type, treatment factors, and demographic characteristics in these clinically important outcomes.

**Table 1** Participant characteristics by mutation type

| Covariate | Overall $N = 47$ *n* (%) | Severe mutation $N = 31$ *n* (%) | Other mutation $N = 16$ *n* (%) |
|---|---|---|---|
| United Kingdom | 34 (72.3) | 21 (67.7) | 13 (81.2) |
| UMN | 13 (27.7) | 10 (32.3) | 3 (18.8) |
| Female | 18 (38.3) | 12 (38.7) | 6 (37.5) |
| Male | 29 (61.7) | 19 (61.3) | 10 (62.5) |
| Transplant type | | | |
| HCT-related marrow | 26 (55.3) | 20 (64.5) | 6 (37.5) |
| HCT-unrelated marrow | 14 (29.8) | 8 (25.8) | 6 (37.5) |
| Cord blood | 7 (14.9) | 3 (9.7) | 4 (25.0) |
| Total body irradiation | 11 (23.4) | 7 (22.6) | 4 (25.0) |
| No GVHD | 15 (31.9) | 9 (29.0) | 6 (37.5) |
| Known GVHD | 18 (38.3) | 13 (41.9) | 5 (31.2) |
| Missing GVHD | 14 (29.8) | 9 (29.0) | 5 (31.2) |
| Engraftment | | | |
| <=90% | 9 (19.1) | 8 (25.8) | 1 (6.2) |
| >90% | 33 (70.2) | 20 (64.5) | 13 (81.2) |
| Missing | 5 (10.6%) | 3 (9.7%) | 2 (12.5%) |
| Single transplant | 32 (68.1) | 20 (64.5) | 12 (75.0) |
| Two transplants | 15 (31.9) | 11 (35.5) | 4 (25.0) |
| Vineland version I | 35 (74.5) | 22 (71.0) | 13 (81.2) |
| Vineland version II | 12 (25.5) | 9 (29.0) | 3 (18.8) |
| SES (Hollingshead) | | | |
| SES < 4 (middle to upper) | 23 (48.9) | 17 (54.8) | 6 (37.5) |
| SES >=4 (low-mid to low) | 24 (51.1%) | 14 (45.2) | 10 (62.5) |
| | **Mean (SD)** | **Mean (SD)** | **Mean (SD)** |
| Age at time of evaluation (year) | 10.5 (6.8) | 11.4 (7.1) | 8.9 (6.1) |
| Age at transplant (month) | 18.5 (8.2) | 18.8 (8.2) | 17.9 (8.2) |
| Time since transplant (year) | 9.0 (6.7) | 9.8 (7.0) | 7.4 (5.9) |
| IQ | 67.1 (22.3) | 61.1 (19.8) | 78.9 (22.9) |
| Vineland adaptive behavior | | | |
| Communication | 70.6 (23.9) | 64.4 (23.2) | 82.7 (21.0) |
| Daily living skills | 63.1 (24.4) | 61.3 (25.6) | 66.6 (22.2) |
| Socialization | 75.9 (20.7) | 72.9 (22.8) | 81.6 (14.8) |
| Adaptive composite | 64.8 (21.6) | 61.4 (21.8) | 71.3 (20.4) |
| CHQ: PHS | 24.1 (15.3) | 25.1 (15.5) | 22.3 (15.1) |
| CHQ: PSS | 45.0 (11.2) | 45.4 (11.6) | 44.1 (10.7) |

*Note*: *HCT* hematopoietic cell transplant, *GVHD* graft versus host disease, *SES* socioeconomic status (Hollingshead 2-factor), *IQ* intelligence quotient (from age-appropriate cognitive test), *CHQ* child health questionnaire, *PHS* physical summary scale, *PSS* psychosocial summary scale

Consistent with prior reports (Bjoraker et al. 2006; Souillet et al. 2003; Shapiro et al. 1995), the overall cognitive ability of our sample of children and young adults with MPS-IH was in the mildly impaired range, with a similar level of impairment reported in their adaptive skills. Mutation type was significantly and independently associated with both cognitive ability and adaptive skills, with those who had a known severe genotype scoring much lower on average than those with a known other mutation. Unlike prior reports (Aldenhoven et al. 2015; Peters et al. 1996; Guffon et al. 2009; Vellodi et al. 1997), age at transplant was not significantly associated with either IQ or adaptive functioning in this cohort. This may be due to restricted range of age at transplant as the majority of the

**Table 2** Distribution of specific genotypes representing severe and other non-severe mutations

| % | Severe mutation $n = 31$ Nonsense mutations or deletions | % | Other mutation $n = 16$ Missense mutations or one unknown |
|---|---|---|---|
| 45.2 | W402X/W402X | 25.0 | W402X/A327P |
| 10.0 | Q70X/Q70X | 6.2 | W402X/P533R |
| 23.0 | W402X/Q70X | 6.2 | W402X/S633L |
| 3.1 | W402X/R619X | 6.2 | W402X/T387R |
| 3.1 | W402X/R621X | 6.2 | A75T/A75T |
| 3.1 | W402X/Q561X | 6.2 | L490P/L490P |
| 3.1 | W402X/153delC | 6.2 | P533R/P533R |
| 3.1 | W402X/C49delC | 6.2 | Q70X/G208D |
| 3.1 | c.783delC/c.783delC | 6.2 | Q70X/A75T |
| 3.1 | Q70X/35del12 | 6.2 | T388R/W402X |
| | | 6.2 | Int9 2850g>t/A75T |
| | | 13.0 | W402X/unknown |

sample was transplanted at less than 2 years old, consistent with the modern standard of care. Surprisingly, this study did not replicate prior reports that have documented TBI as a risk factor for poor neurocognitive functioning. However, the absence of a relationship between this well-known risk factor and neurocognitive outcome is likely due to the relatively small size of the current sample and limited power for detecting such influences after adjusting for mutation type. Additionally, within this small sample of individuals who received TBI, some patients received brain-sparing techniques ($n = 2$), which may have further attenuated these relationships.

In examination of quality of life, individuals with MPS-IH appear to be doing well from a psychosocial standpoint, but are greatly affected physically. Mean physical quality of life fell more than two standard deviations below the general population mean, reflecting poor physical functioning and limitations in daily activities due to physical disability. In contrast, parent ratings of their children's psychosocial quality of life were average and not discrepant from the general population, suggesting that parents perceive their children to be functioning well from a social-emotional-behavioral perspective. Mutation type was not significantly associated with psychosocial or physical quality of life. Rather, specific demographic and treatment factors appeared to play a more prominent role. Even within the limited range of age at HCT in the current cohort, we found that every year older a child was at time of HCT was associated (on average) with almost one standard deviation poorer physical functioning. This is consistent with previous studies that have examined the relationship between age and health-related quality of life after HCT in children more broadly and may reflect developmental differences in the way in which both MPS and HCT are experienced and expressed by children as they age. Parents of children who had received total body irradiation as part of their transplant regimen were more likely to report better physical functioning than those who had not received this treatment, which may be secondary to better engraftment associated with use of total body irradiation conditioning in this cohort and consequently better disease and symptom management in the context of the available treatments and conditioning regimens during this time period. In more recent years, optimization of chemotherapy protocols has led to sustained donor-derived engraftment, reducing the need for total body irradiation for most children treated on modern treatment protocols, reducing the need for total body irradiation which has been consistently associated with poor neurodevelopmental outcomes.

Risk factors for poor psychosocial quality of life included lower socioeconomic status and having undergone an unrelated donor bone marrow HCT (as opposed to receiving bone marrow HCT from a donor relative). It should be noted that the significant contribution of socioeconomic status to psychosocial QOL remained even when adjusting for study center (UMN versus the United Kingdom) suggesting that SES is an important contributor to QOL in these children even after consideration of other contextual differences that exist between these samples (i.e., access to healthcare). The relationship between lower SES and parent/patient-reported poor quality of life has been well documented in other populations (Chen et al. 2006; Von Rueden et al. 2006; Kunin-Batson et al. 2014), but has not been examined in children with MPS disorders. Future prospective studies should examine the socioeconomic impact of MPS-IH on families to better understand whether socioeconomic disparities develop over the course of treatment and represent the economic toll of MPS-IH on quality of life. Such information may be useful for guiding intervention development and timing/delivery of interventions for at-risk families. Our findings regarding the role of transplant type (i.e., graft source) in quality of life are similar to some previous studies of children with hematologic malignancies (Phipps et al. 2002; Clarke et al. 2008), which have reported relatively poorer quality of life after unrelated donor bone marrow transplants when compared with recipients of transplants from matched sibling donors. While analyses were adjusted for GVHD, we did not have information about other potential complications that may differ between transplant types and may account for differences in quality of life after transplant.

Our results must be understood in the context of limitations. As this was a cross-sectional cohort including individuals from the United Kingdom, no information was available about cognitive functioning prior to transplant. A prospective, longitudinal design (including a pre-HCT assessment) would

have been needed to allow for a precise examination of genetic, treatment, and demographic factors influences changes over time in cognitive and adaptive functioning, as well as quality of life. We also lacked information on current health status (e.g., physical symptoms or neurological symptom severity) and physical mobility at the time of assessment and were thus not able to explore the role of such factors that are likely relevant to adaptive functioning quality of life after transplant. Such information would be important to include in future investigations of quality of life. While the CHQ is a validated and well-established measure for examining quality of life in children with chronic health conditions, use of an MPS-specific measure or health assessment tool (e.g., MPS Health Assessment Questionnaire) would have been beneficial to more precisely cover the diverse features and sequelae of MPS-IH. This is an important area for further study, and our team is actively working to develop and validate these tools at the University of Minnesota. It should also be noted that the majority of this cohort received bone marrow donor HCT, and few had received cord blood, consistent with the time frame during which transplants took place (i.e., 1985 and 2007). Given that cord blood transplants represent the current standard of care for children with MPS-IH, and there have been a number of advances in unrelated donor bone marrow transplant procedures since the time during which transplants took place for current study participants (e.g., advances in tissue type matching, enzyme delivery, and supportive care), our findings may not represent the long-term outcomes of children treated on these more modern treatment protocols. Nonetheless, our study has important strengths including our use of a multi-institution, international cohort from whom we have detailed information about treatment histories and mutation type, as well as performance-based cognitive testing. We also included caregiver ratings of functional adaptive skills and quality of life, important aspects of functioning that have been historically under reported in this population, and our sample includes a longer time frame for follow-up from transplant than most prior studies.

In summary, mutation type (i.e., homozygous for nonsense or deletion mutations or heterozygous for a combination of these) is significantly associated with both cognitive and functional adaptive outcomes post transplant, and thus mutation analysis may have relevance for early identification of children at risk for long-term severe neurocognitive impairment despite treatment. While recommendations for cognitive screening are beneficial for all children with MPS-IH, early assessment and routine monitoring appear particularly important for those with known severe mutations. Physical manifestations of MPS-IH appear to be a major hurdle in attaining good quality of life post transplant, whereas psychosocial functioning was consistent with population norms. Early intervention and adaptations for children's physical functioning are important, and research efforts aimed at developing efficacious interventions to improve the physical function of children with MPS-IH are needed. Further attention should also be paid to the assessment of socioeconomic risk factors to help at-risk families overcome barriers and access to resources needed for optimizing their child's psychosocial well-being.

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## Synopsis

Mutation type (i.e., homozygous for nonsense or deletion mutations or heterozygous for a combination of these) is significantly associated with both cognitive and functional adaptive outcomes post transplant and may have relevance for early identification of children at risk for severe long-term neurocognitive impairment despite treatment.

## Compliance with Ethics Guidelines

### Conflict of Interest

The authors declare that they have no conflict of interest.

### Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all participants included in the study.

### Animal Rights

This article does *not* contain any studies with animal subjects performed by any of the authors.

### Details of the Contributions of Individual Authors

A.S. Kunin-Batson, led manuscript writing and scientific conceptualization.

E.G. Shapiro assisted in writing paper and scientific conceptualization and assisted in obtaining Minnesota data.

K.D. Rudser statistical analysis, writing and editing.

C. Lavery scientific conceptualization; IQ, data collection in the United Kingdom, manuscript review and editing.

K.J. Bjoraker scientific conceptualization; data collection in Minnesota, manuscript review and editing.

S. Jones provided medical data and collaborated with Ms. Lavery in getting study accomplished, manuscript review and editing.

R. Wynn provided medical data regarding transplant and participated in manuscript review and editing.

A. Vellodi provided medical data regarding transplant, manuscript review and editing.

J. Tolar provided medical data regarding transplant, manuscript review and editing.

P. Orchard provided medical data regarding transplant, manuscript review and editing.

J.E. Wraith (deceased) collaborated with Ms. Lavery in getting study accomplished.

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