# Patient Reported Outcomes Measurement Information System and Quality of Life in Neurological Disorders Measurement System to Evaluate Quality of Life for Children and Adolescents with Neurofibromatosis Type 1 Associated Plexiform Neurofibroma

Jin-Shei Lai, PhD, OTR/L[1,2,3], Sally E. Jensen, PhD[1,4], Joel Charrow, MD[2,5], and Robert Listernick, MD[2,6]

**Objective** To assess the health-related quality of life of children with neurofibromatosis type 1-related plexiform neurofibromas (pNF) using a battery of patient-reported outcome measures selected based on a conceptual framework derived from input by patients, parents, and clinicians regarding the most important pNF symptoms and concerns.

**Study design** There were 140 children with pNF ages 8-17 years who completed the Patient-Reported Outcomes Measurement Information System (including domains anxiety, depressive symptom, psychosocial stress experiences, fatigue, pain interference, meaning and purpose, positive affect, peer relationships, physical function-mobility) and Quality of Life in Neurological Disorders measurement system (stigma) via an online platform. T-scores for each measure were compared with US population norms.

**Results** Children with pNF reported significantly worse scores than the population norms on 8 of 10 domains. Children with at least 1 family member having a diagnosis of neurofibromatosis type 1 and those having pain reported significantly worse symptoms and functioning on all domains. Boys reported significantly worse pain interference, stigma, meaning and purpose, mobility function, and upper extremity function than girls.

**Conclusions** Children with pNF experience significantly worse health-related quality of life on all but 1 domain, highlighting the importance of monitoring children's quality of life over time in clinical research and practice. Future research should evaluate the replicability of these findings and evaluate the validity of the Patient-Reported Outcomes Measurement Information System and Quality of Life in Neurological Disorders measurement system in relation to clinical characteristics among children with pNF. *(J Pediatr 2019;206:190-6).*

Neurofibromatosis type I (NF1) is an autosomal-dominant, tumor suppressor gene syndrome characterized by the development of multiple nerve sheath tumors in the central and peripheral nervous system and affects approximately 1 in 2700 individuals.[1] A subset of individuals with NF1 (25%-50%) develop plexiform neurofibromas (pNFs), benign peripheral nerve sheath tumors with expanded extracellular matrix that grow along the length of a nerve, involving its multiple fascicles and branches.[2-4] Generally congenital, pNFs vary in growth across the lifespan, with morbidity depending on their size and location.[5] Aside from their potentially significant effect on cosmesis, pNF may cause substantial morbidity to owing compression and invasion of organs and lead to pain or dysfunction ultimately conferring substantial decrements to quality of life (QOL).[4,6-8] Complete surgical resection is generally impossible because pNF tend to intertwine with surrounding tissue, but chemotherapy, previously unsuccessful, has begun to yield promising preliminary results.[2-4,9] The significant symptom burden of pNF highlights the importance of QOL in clinical research and practice.

The incorporation of patient-reported outcome measures into pNF trials may be particularly important, given that traditional primary endpoints such as tumor size may not fully capture intervention effects. Although a pediatric NF1-specific patient-reported outcome measure was recently developed,[10] no published pediatric measure for pNF-specific concerns currently exists, making it challenging to know whether their concerns were addressed and their needs met.

| | |
|---|---|
| CAT | Computerized adaptive test |
| HRQOL | Health-related QOL |
| Neuro-QoL | Quality of Life in Neurological Disorders measurement system |
| NF1 | Neurofibromatosis type I |
| pNF | Plexiform neurofibroma |
| PROMIS | Patient-Reported Outcomes Measurement Information System |
| QOL | Quality of life |

From the [1]Department of Medical Social Sciences; [2]Department of Pediatrics, Northwestern University Feinberg School of Medicine; [3]Division of Hematology, Oncology, Neuro-Oncology & Stem Cell Transplantation, Ann & Robert H. Lurie Children's Hospital of Chicago; [4]Department of Surgery, Northwestern University Feinberg School of Medicine; [5]Division of Genetics, Birth Defects and Metabolism, Ann & Robert H. Lurie Children's Hospital of Chicago; and [6]Division of Academic General, Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, IL

This work was supported by an Agreement from the Johns Hopkins University School of Medicine and the Neurofibromatosis Therapeutic Acceleration Program (NTAP). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the Johns Hopkins University School of Medicine. The study sponsor provided consultation regarding study design and assistance with recruitment for data collection. The study sponsor was not involved in the analysis/interpretation of data, the writing of the report, or the decision to submit the manuscript for publication. The authors declare no conflicts of interest.



https://doi.org10.1016/j.jpeds.2018.10.019

Recent research used interviews with pediatric patients, parents, and clinicians to develop a conceptual framework including 5 domains important to include when assessing pNF outcomes: pain, social functioning, physical function impact, stigma, and emotional distress[6]; instruments to measure these domains are available in Patient-Reported Outcomes Measurement Information System (PROMIS),[11] and Quality of Life in Neurological Disorders measurement system (Neuro-QoL),[12] This article reports the results from our study to evaluate QOL reported by children with pNF using the PROMIS and Neuro-QoL.

## Methods

Eligible participants were recruited from 3 sources: (1) the Children's Tumor Foundation NF Patient Registry (NF registry) by identifying eligible patients in the database, (2) the regional NF1 organizations across the country by posting the invitation to participate on their websites and their social media communication channels, and (3) the Ann & Robert H. Lurie Children's Hospital of Chicago by placing study flyers in the clinic as well mailing invitation letters to eligible patients. Eligible patients were ages 8-17 years old, had a confirmed diagnosed of NF1, had at least 1 pNF in any location (symptomatic or asymptomatic), and were fluent in English. Parents of eligible participants needed to be fluent in English to provide informed consent. Children aged 12-17 were required to provide assent. This study was approved by the Ann & Robert H. Lurie Children's Hospital Institutional Review Board.

Participants were provided a custom link to complete questionnaires. Children completed pediatric measures from the PROMIS, including domains anxiety,[13] depressive symptoms,[13] psychosocial stress experiences,[14] fatigue,[15] pain interference,[16] meaning and purpose,[17] positive affect,[18] peer relationships, physical function-mobility,[19] and physical function—upper extremity function[19] via computerized adaptive tests (CAT).[20,21] Participants also completed an 8-item stigma[22] from the Neuro-QoL measurement system and a single 0-10 rating for pain intensity. Positive (eg, meaning and purpose) and negative (eg, pain interference) worded measures were grouped separately and were randomly administered to balance order effect. Parents provided demographic and clinical information of their children and rated their children's symptom burden using a 9-item PROMIS global health.[23] These measures were chosen to capture key concerns addressed by children with pNF, their parents, and experts in pNF.[6] All these measures demonstrated acceptable psychometric properties and were available for CAT administration. In CAT, all participants first completed a screening item. An initial score was estimated based on the response using the preprogrammed algorithm and the next most informative item around the estimated score on the measurement continuum was administered by the algorithm, following which the score was reestimated based on the participant's response to that item. This iterative estimation process continued until the stopping rule was met. As a result, precise estimation could be achieved by using just a few items because only the most informative item was chosen.[20,24-26] CATs were used in this study to capture children's health-related QOL (HRQOL) in a comprehensive manner without adding too much respondent burden. Scores were reported using a T-score metric with a norm of 50 and SD of 10. Thus, the scores from these measures can be compared with the US general population as well as other pediatric patient populations, providing a standard benchmark for the interpretation of scores. Higher scores represent worse functioning on measures of stigma, anxiety, depression, psychosocial stress experiences, fatigue, and pain interference. For other measures, higher scores represent better functioning.

### Statistical Analyses

We compared patients' HRQOL with the US general population using means with 95% CIs. Test-statistics and analysis ANOVA were used to evaluate whether there were significantly different HRQOL scores between sex and the family history of a NF1 diagnosis (yes/no); and whether HRQOL discriminated patients based on (1) the presence or absence of pain or itch, (2) age at diagnosis (<5, 5-9, and 10-17 years old), (3) numbers of café-au-lait spots (0, ≤6, 6-20, and >20), (4) reported cognition (no problems, learning problems, attention problems, and both learning and attention problems), and (5) other clinical characteristics. ANOVA was also used to evaluate how well HRQOL discriminates children's health as measured by using parent-reported PROMIS Global Health measuring general health, overall QOL, physical health, mental health, sadness, peer relationships (having fun with friends), family communications (your child feels that you listen to his or her ideas), fatigue, and trouble sleeping owing to pain.

## Results

Data from 140 children with pNF were analyzed. Their demographic and clinical information are shown in **Table I**. Mean age was 12.5 years (SD, 2.7), 64.3% were boys, 62.3% were white, 32.3% attended mainstream schools without receiving an individualized educational program, and 44.3% had at least 1 family member who was diagnosed having NF1. The average number of missed school days in the past month was 3.94 (SD, 5.58). More than 50% received a pNF diagnosis when they were younger than 5 years old; 48.6% had 6-20 and 37.9% had more than 20 café-au-lait spots; 35.6% reported having chronic itch; and 67.1% had pain. The top 5 locations that children reported their pNFs located were back (42.9%), neck (31.4%), head (29.3%), chest (22.1%), and legs (21.4%).

### Analyses

The **Figure** and **Table I** show descriptive information and score distributions of the HRQOL measures. The **Figure** depicts patient-reported HRQOL scores compared with norms using T-scores metric (50; SD, 10). **Figure**, A shows domains in which higher scores represent worse functioning and

**Table I. Patient demographic and clinical information**

| Variables | Mean (SD) or % |
|---|---|
| Age (years) | 12.53 (2.7) |
| Days missed school in the past month | 3.94 (5.58) |
| Sex | |
| Boy | 64.29 |
| Girl | 35.71 |
| Type of classroom attending | |
| Mainstream classroom, no IEP | 32.03 |
| Mainstream classroom, with IEP | 55.47 |
| Special education classroom within a regular school | 4.69 |
| Special education school | 2.34 |
| Home school | 5.47 |
| Race | |
| White | 64.29 |
| Black or African American | 30.00 |
| Family history of NF1 | |
| None | 47.14 |
| Yes | 44.29 |
| Not sure | 8.57 |
| Age at diagnosis (years) | |
| <5 | 57.14 |
| 5-9 | 26.43 |
| 10-17 | 16.43 |
| Café-au-lait spots: how many? | |
| No | 0.71 |
| Yes: ≤6 | 12.86 |
| Yes: 6-20 (inclusive) | 48.57 |
| Yes: >20 | 37.86 |
| pNF(s): how many? | |
| No | 4.29 |
| Yes: 1 | 39.29 |
| Yes: 1-5 | 42.86 |
| Yes: ≥5 | 6.43 |
| Don't know/not sure | 7.15 |
| Chronic itching | |
| No | 58.57 |
| Yes | 38.57 |
| Unsure | 2.86 |
| Received chronic itching treatment | |
| No treatment | 62.96 |
| Yes | 37.04 |
| Pain | |
| No | 32.86 |
| Yes | 67.14 |
| pNF locations | |
| Head | 29.29 |
| Neck | 31.43 |
| Chest | 22.14 |
| Arms | 15.71 |
| Legs | 21.43 |
| Abdomen | 12.14 |
| Spine | 19.29 |
| Back | 42.86 |
| Not sure | 3.57 |
| Treatment received | |
| Drug | 37.86 |
| Radiation | 10.00 |
| Surgery | 17.86 |
| No treatment | 45.71 |
| Not sure | 0.71 |
| Any learning or attention problems in school | |
| No | 12.50 |
| Learning problems | 37.50 |
| Attention problems | 11.67 |
| Both learning and attention problems | 36.67 |
| Not sure | 1.67 |

*IEP*, individualized education plan.

**Figure**, B depicts domains in which higher scores represent better functioning. Respondents reported significantly worse scores than the norms on 8 of 10 domains. Patients reported fatigue (mean, 50.3) and pain interference similar to that which was reported by the general population. Patients reported 1 SD (10 T-scores) worse meaning and purpose (mean, 40.1) and upper extremity function (mean, 39.7) than the norm, 0.5 SD (5 T-scores) worse than the norm on psychological stress experience (mean, 56.8), mobility (mean, 40.9), and peer relationships (mean, 43), and 0.25 SD (2.5 T-scores) worse than the norm on anxiety (mean, 53.2), depressive symptoms (mean, 53.5), stigma (mean, 53.3), and positive affect and well-being (mean, 46.4). As shown in **Table I**, the number of items administered by CAT ranged from 5.2 (meaning and purpose) to 8 (upper extremity function).

The top 3 concerns reported by parents regarding their children were sadness (29.45% always or often), physical health (23.94% poor or fair), and trouble sleeping when the child had pain (23.45% often or almost always). The least frequently reported concerns were listening to the child's ideas (7.57% never or rarely), general health (13.01% poor or fair), and having fun with friends (14.48% never or rarely). All HRQOL measures significantly differentiated participants with different levels of health as measured by parents' responses to the PROMIS Pediatric Global Health measure, with $P < .001$ on all comparisons (health, QOL, physical health, mental health, feeling really sad, having fun with friends, listening to child's ideas, pain), except "my child got tired easily" on meaning and purpose ($P < .05$), peer relationships ($P < .05$), and positive affect and well-being ($P < .01$).

ANOVA and test statistics results are summarized in **Table II**. A post hoc analysis (Tukey test) indicated that boys reported worse pain interference, stigma, meaning and purpose, mobility, and upper extremity function than girls. Children with at least 1 family member having a diagnosis of NF1 and those having pain reported significantly worse symptoms and functioning on all HRQOL domains. Children with chronic itch reported worse peer relationships. Children who were diagnosed under age 5 (vs 5-9 years and 10-17 years of age) reported fewer symptoms and better functioning on all HRQOL domains except peer relationships. Children with 1-5 pNFs (vs only 1) reported worse depressive symptoms, fatigue, and pain interference. Unexpectedly, children with more than 20 café-au-lait spots reported better meaning and purpose, mobility, and upper extremity function than those with 6 or fewer café-au-lait spots. Children with learning problems reported worse anxiety, depressive symptoms, fatigue, stigma, pain interference, psychological stress experiences, mobility, and upper extremity function than those who did not report either learning or attentional problems. Children with both learning and attentional problems reported worse depressive symptoms, fatigue, stigma, psychological stress experiences, mobility, peer relationships, and upper extremity function. Significant upper extremity function scores were found on all comparisons, except between children with attentional problems vs those with both learning and attentional problems. There were no significantly

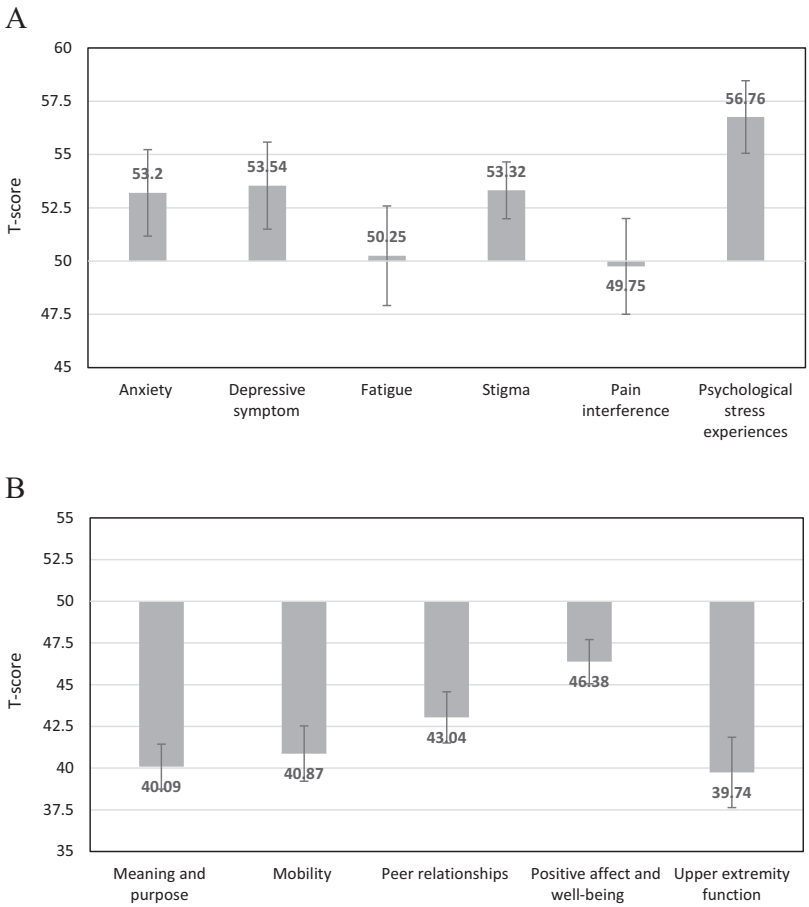


**Figure.** Child-reported HRQOL compared with those of the norming sample, in which the mean is 50 and the SD is 10. Error bars represent 95% CIs. **A,** Measures with higher scores represent worse functioning (mean, 53.2, 53.54, 50.25, 53.32, 49.75, and 56.76 for anxiety, depressive symptom, fatigue, stigma, pain interference, and psychological stress experiences, respectively). **B,** Measures with higher scores represent better functioning (mean = meaning and purpose, mobility, peer relationship, positive affect and well-being, and upper extremity function, respectively).

different HRQOL scores found on other demographic and clinical characteristics.

## Discussion

Children with NF1 are likely to experience poorer HRQOL than their peers in multiple domains, such as motor, cognitive, social functioning, self-esteem, positive and negative emotions, and psychological adjustment.[27-30] Although children with NF1 who have pNF have been considered to experience relatively inferior HRQOL, most studies have been performed in children with NF1 irrespective of pNF status. To fill this gap, we evaluated HRQOL reported by children with pNF. Our results indicate that children with NF1 with pNF report worse scores in almost all domains when compared with a normative sample of the pediatric PROMIS measures. Fatigue and pain interference were the only domains in which children with pNF did not differ from the normative sample on average. However, both measures had medians of 52 and the 75th percentile were about 62 (**Table III**), suggesting that some children experienced worse fatigue and pain interferences; however, their scores were averaged out by those who did not. Because children likely experience symptoms throughout their lifespan owing to the noncurable nature of pNF and their HRQOL remains affected into adulthood,[31,32] exploring potential factors influencing their HRQOL could assist in developing interventions to alleviate the negative impact from pNFs.

Pain, family history, and age at diagnosis were the 3 most prominent factors contributing to children's functioning. Sixty-seven percent of our sample reported having pain, which was higher than reported in the literature.[33,34] This finding was expected because previous studies included a mixed sample of NF1 and pNF, and our sample was restricted to only children with pNF. The finding that pain negatively affected children's HRQOL was not surprising and has previously been recognized in the literature.[28,31,35,36] In contrast, children with a family history of NF1 unexpectedly reported worse functioning and well-being than those who did not. Because there is no extant literature on the impact of NF1 family history on patients'

**Table II. Comparisons of HRQOL scores on demographic and clinical characteristics**

| | Sex | Family w/NF1 besides your child | Chronic itch | Pain | Age at diagnosis | Number of café-au-lait spots | Number of pNFs | Attention or learning problems |
|---|---|---|---|---|---|---|---|---|
| Anxiety | NS | <.0001 | NS | <.0001 | 0.0004 | NS | NS | .0293 |
| Depressive symptoms | NS | <.0001 | NS | <.0001 | <.0001 | NS | .0097 | .0071 |
| Fatigue | NS | <.0001 | NS | <.0001 | .0013 | NS | .0126 | .0094 |
| Stigma | .0123 | <.0001 | NS | <.0001 | .0118 | NS | NS | .007 |
| Pain | .0065 | <.0001 | NS | <.0001 | .0004 | NS | .0293 | .0331 |
| Psychological stress experiences | NS | <.0001 | NS | <.0001 | .0003 | NS | NS | .0115 |
| Meaning and purpose | .0018 | .0249 | NS | <.0001 | <.0001 | .031 | NS | NS |
| Mobility | .0011 | <.0001 | NS | <.0001 | <.0001 | .0151 | NS | .0004 |
| Peer relationships | NS | .0232 | .0468 | .0022 | NS | NS | NS | NS |
| Positive affect and well-being | NS | .0001 | NS | .0033 | .0154 | NS | NS | NS |
| Upper extremity function | .0017 | <.0001 | NS | <.0001 | <.0001 | .0134 | NS | <.0001 |

*NS*, not significant.
Age at diagnosis: <5 years old (n = 80); 5 (inclusive) to 10 (n = 37); 10 (inclusive) to 17 years (n = 23).
Number of café-au-lait spots: ≤6 (1-6, n = 18; no, n = 1); 6-20 (n = 68); >20 (n = 53).
Number of pNF: no (n = 6); 1 (n = 55); 1-5 (n = 60); > 5 (n = 9).
Attention or learning problems: no problem (n = 15); attentional problem only (n = 14); learning problems only (n = 45); both attentional and learning problems (n = 44).

HRQOL, replication of this finding is warranted to explore its underpinnings. Another unexpected finding was how numbers of café-au-lait spots impacted patient-reported meaning and purpose, mobility, and upper extremity function. Similar to the NF1 family history, future studies with a large and representative sample are needed to understand the relationship between numbers of café-au-lait and patients reported QOL.

Deficits in cognitive functioning, attention skills, language development, and behavioral regulation have all been associated with poorer social competence and outcomes in children and adolescents with NF1.[28-30,37,38] Gutmann et al further suggest that attention deficit/hyperactivity disorder and social perception problems are perhaps the most devastating complications of NF1 in childhood.[39] Our results showed that children with attentional and/or learning problems report worse symptoms and functioning on most domains, including stigma; however, no significant differences were found on peer relationships, meaning and purpose, or positive affect and well-being.

This study has several strengths as well as limitations. This study used CATs to measure HRQOL reported by children with pNF. Because CATs provide precise estimation with few informative items, we were able to obtain more comprehensive HRQOL information by administering multiple PROMIS measures without increasing substantial response burden to children.[40] Instead of exclusively recruiting children from local NF1 clinics, we expanded our recruitment nationwide via supportive organizations, such as the Children's Tumor Foundation. As a result, we were able to obtain a relatively large and more diverse sample compared with those in current available literature. However, we relied on parents' report of their children's clinical information because we were unable to access medical records. Past studies have compared clinical information obtained from self-report and extracted from medical chart review with various conclusions. For example, Gupta et al studied data from more than 5000 patients with breast cancer and found high validity for patient self-reported information for a variety of disease and treatment-related variables.[41] Conversely, Caterino and Graham found that patients in the emergency department identified more antimicrobial resistance risk factors by themselves than chart review.[42] Information reported by our study sample was similar to those variables documented in the literature (eg, pain, family history, etc), which enhanced the validity of clinical characteristics reported by our sample. We used the same clinical form used by the Children's Tumor Foundation registry to ensure

**Table III. HRQOL score distributions among patients surveyed**

| | | | | 95% CI | | Score distribution (in percentile) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| HRQOL measure | No. of items (SD)* | Mean | SD | Lower bound | Upper bound | Minimum | 25th | 50th | 75th | Maximum |
| Anxiety | 7.2 (2.8) | 53.2 | 12.2 | 51.2 | 55.2 | 31.9 | 43.9 | 54.3 | 62.9 | 83.2 |
| Depressive symptoms | 6.7 (2.9) | 53.5 | 12.2 | 51.5 | 55.6 | 31.8 | 45.4 | 55.0 | 64.7 | 82.1 |
| Fatigue | 7.3 (2.7) | 50.2 | 14.0 | 47.9 | 52.6 | 25.6 | 41.7 | 51.4 | 61.9 | 84.0 |
| Meaning and purpose | 5.2 (1.1) | 40.1 | 7.7 | 38.7 | 41.5 | 20.0 | 35.6 | 37.7 | 45.6 | 64.3 |
| Mobility | 6.2 (2.8) | 40.9 | 9.8 | 39.2 | 42.5 | 22.4 | 32.5 | 38.5 | 46.8 | 61.7 |
| Pain interference | 7.3 (3.2) | 49.8 | 13.4 | 47.5 | 52.0 | 32.0 | 35.4 | 51.7 | 61.8 | 82.3 |
| Peer relationship | 5.9 (2.2) | 43.0 | 9.1 | 41.5 | 44.6 | 19.2 | 38.4 | 40.5 | 46.4 | 66.0 |
| Positive affect and well-being | 5.3 (1.1) | 46.4 | 7.6 | 45.1 | 47.7 | 27.2 | 42.2 | 43.6 | 49.1 | 69.7 |
| Psychological stress response | 5.7 (2.0) | 56.8 | 9.8 | 55.1 | 58.5 | 34.6 | 48.7 | 57.9 | 64.7 | 76.2 |
| Upper extremity function | 8.0 (3.3) | 39.7 | 12.4 | 37.6 | 41.9 | 16.0 | 26.8 | 37.7 | 50.9 | 57.3 |
| Stigma* | 8 (0) | 53.3 | 8.0 | 52.0 | 54.7 | 37.1 | 48.5 | 55.0 | 59.1 | 70.1 |

*Number of items administered in CAT. Stigma was assessed using an 8-item short-form.

consistency between the 2 databases for future studies. Information such as socioeconomic status was not available and we were unable to evaluate contributions from environment or family factors to children's HRQOL. Future studies should take these factors into accounts.

In conclusion, we found that children with NF1 with pNFs experience significantly worse HRQOL on all but 2 domains when compared with the normative sample, highlighting the importance of monitoring children's HRQOL over time during their follow-up visits so as to provide prompt interventions. We have developed a guide to select appropriate measures for evaluating HRQOL for children with pNF (http://www.healthmeasures.net/applications-of-healthmeasures/guidance/recommended-healthmeasures). Studies are needed to evaluate the replicability of our findings and to evaluate the validity of the PROMIS measures in relation to clinical characteristics. PROMIS CATs provide precise estimates of HRQOL without adding substantial response burden and has been integrated into the EPIC medical record system (2017 version or later), which allow for systematically monitoring patients' symptoms from childhood into adulthood. ■

*We thank all the patients and parents who participated in the study. We also thank Ms Pamela Knight from the Children's Tumor Foundation, who assisted with recruitment, as well as the following organizations who partnered with the study team to recruit participants: NF Upper Midwest, NF Midwest, NF Network, Texas NF Foundation, NF California, NF Northeast, The NF Team, NF Mid-Atlantic, Littlest Tumor Foundation, Cure NF with Jack, European NF Group, Washington State Neurofibromatosis Families, BC Neurofibromatosis Foundation, The Neuro Foundation, Childhood Tumour Trust, NF Central Plains, NF Arizona, NF Michigan.*

Submitted for publication Jun 27, 2018; last revision received Sep 11, 2018; accepted Oct 9, 2018

Reprint requests: Jin-Shei Lai, PhD, OTR/L, Department of Medical Social Sciences and Pediatrics, Feinberg School of Medicine at Northwestern University, 633 N St Clair, 19th Floor, Chicago, IL 60611. E-mail: js-lai@northwestern.edu

## References

1. Evans DG, Howard E, Giblin C, Clancy T, Spencer H, Huson SM, et al. Birth incidence and prevalence of tumor-prone syndromes: estimates from a UK family genetic register service. Am J Med Genet A 2010;152a:327-32.
2. Korf BR. Plexiform neurofibromas. Am J Med Genet 1999;89:31-7.
3. Mautner VF, Asuagbor FA, Dombi E, Funsterer C, Kluwe L, Wenzel R, et al. Assessment of benign tumor burden by whole-body MRI in patients with neurofibromatosis 1. Neuro Oncol 2008;10:593-8.
4. Vranceanu AM, Merker VL, Park ER, Plotkin SR. Quality of life among children and adolescents with neurofibromatosis 1: a systematic review of the literature. J Neurooncol 2015;122:219-28.
5. Dombi E, Solomon J, Gillespie AJ, Fox E, Balis FM, Patronas N, et al. NF1 plexiform neurofibroma growth rate by volumetric MRI: relationship to age and body weight. Neurology 2007;68:643-7.
6. Lai J-S, Jensen SE, Patel ZS, Listernick R, Charrow J. Using a qualitative approach to conceptualize concerns of patients with neurofibromatosis type 1 associated plexiform neurofibromas (pNF) across the lifespan. Am J Med Genet A 2016;173:79-87.
7. Wolkenstein P, Zeller J, Revuz J, Ecosse E, Leplège A. Quality-of-life impairment in neurofibromatosis type 1: a cross-sectional study of 128 cases. Arch Dermatol 2001;137:1421-5.
8. Page PZ, Page GP, Ecosse E, Korf BR, Leplege A, Wolkenstein P. Impact of neurofibromatosis 1 on quality of life: a cross-sectional study of 176 American cases. Am J Med Genet A 2006;140A:1893-8.
9. Dombi E, Baldwin A, Marcus LJ, Fisher MJ, Weiss B, Kim A, et al. Activity of selumetinib in neurofibromatosis type 1-related plexiform neurofibromas. N Engl J Med 2016;375:2550-60.
10. Nutakki K, Varni JW, Swigonski NL. PedsQL Neurofibromatosis Type 1 module for children, adolescents and young adults: feasibility, reliability, and validity. J Neurooncol 2018;137:337-47.
11. Cella D, Riley W, Stone A, Rothrock N, Reeve B, Yount S, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. J Clin Epidemiol 2010;63:1179-94.
12. Gershon R, Lai J, Bode R, Choi S, Moy C, Bleck T, et al. Neuro-QOL: quality of life item banks for adults with neurological disorders: item development and calibrations based upon clinical and general population testing. Qual Life Res 2012;21:475-86.
13. Irwin DE, Stucky B, Langer MM, Thissen D, Dewitt EM, Lai JS, et al. An item response analysis of the pediatric PROMIS anxiety and depressive symptoms scales. Qual Life Res 2010;19:595-607.
14. Bevans KB, Gardner W, Pajer KA, Becker B, Carle A, Tucker CA, et al. Psychometric evaluation of the PROMIS® pediatric psychological and physical stress experiences measures. J Pediatr Psychol 2018;43:678-92.
15. Lai J-S, Stucky B, Thissen D, Varni J, DeWitt E, Irwin D, et al. Development and psychometric properties of the PROMIS® pediatric fatigue item banks. Qual Life Res 2013;22:2417-27.
16. Varni JW, Stucky B, Thissen D, Dewitt EM, Lai JS, Dewalt DA, et al. PROMIS pediatric pain interference scale: an item response theory analysis of the pediatric pain item bank. J Pain 2010;11:1109-19.
17. Forrest CB, Devine J, Bevans KB, Becker BD, Carle AC, Teneralli RE, et al. Development and psychometric evaluation of the PROMIS Pediatric Life Satisfaction item banks, child-report, and parent-proxy editions. Qual Life Res 2017;27:217-34.
18. Forrest CB, Ravens-Sieberer U, Devine J, Becker BD, Teneralli RE, Moon J, et al. Development and evaluation of the PROMIS® pediatric positive affect item bank, child-report and parent-proxy editions. J Happiness Stud 2017;1-20.
19. DeWitt EM, Stucky BD, Thissen D, Irwin DE, Langer M, Varni JW, et al. Construction of the eight-item Patient-Reported Outcomes Measurement Information System pediatric physical function scales: built using item response theory. J Clin Epidemiol 2011;64:794-804.
20. Lai J-S, Beaumont JL, Nowinski CJ, Cella D, Hartsell WF, Han-Chih Chang J, et al. Computerized adaptive testing in pediatric brain tumor clinics. J Pain Symptom Manage 2017;54:289-97.
21. Cella D, Gershon R, Lai J-S, Choi S. The future of outcomes measurement: item banking, tailored short-forms, and computerized adaptive assessment. Qual Life Res 2007;16(Suppl 1):133-41.
22. Lai JS, Nowinski C, Victorson D, Bode R, Podrabsky T, McKinney N, et al. Quality-of-life measures in children with neurological conditions: pediatric Neuro-QOL. Neurorehabil Neural Repair 2012;26:36-47.
23. Forrest C, Tucker C, Ravens-Sieberer U, Pratiwadi R, Moon J, Teneralli R, et al. Concurrent validity of the PROMIS® pediatric global health measure. Qual Life Res 2015;25:739-51.
24. Lai J-S, Butt Z, Zelko F, Cella D, Krull K, Kieran M, et al. Development of a parent-report cognitive function item bank using item response theory and exploration of its clinical utility in computerized adaptive testing. J Pediatr Psychol 2011;36:766-79.
25. Lai JS, Cella D, Choi SW, Junghaenel DU, Christodolou C, Gershon R, et al. How item banks and their application can influence measurement practice in rehabilitation medicine: a PROMIS Fatigue item bank example. Arch Phys Med Rehabil 2011;92:S20-7.
26. Pilkonis PA, Choi SW, Reise SP, Stover AM, Riley WT, Cella D. Item banks for measuring emotional distress from the Patient-Reported Outcomes Measurement Information System (PROMIS):depression, anxiety, and anger. Assessment 2011;18:263-83.
27. Barton B, North K. The self-concept of children and adolescents with neurofibromatosis type 1. Child Care Health Dev 2007;33:401-8.

28. Barton B, North K. Social skills of children with neurofibromatosis type 1. Dev Med Child Neurol 2004;46:553-63.
29. Noll RB, Reiter-Purtill J, Moore BD, Schorry EK, Lovell AM, Vannatta K, et al. Social, emotional, and behavioral functioning of children with NF1. Am J Med Genet A 2007;143:2261-73.
30. Domon-Archambault V, Gagnon L, Benoît A, Perreault S. Psychosocial features of neurofibromatosis type 1 in children and adolescents. J Child Neurol 2018;33:225-32.
31. Krab LC, Oostenbrink R, de Goede-Bolder A, Aarsen FK, Elgersma Y, Moll HA. Health-related quality of life in children with neurofibromatosis type 1: contribution of demographic factors, disease-related factors, and behavior. J Pediatr 2009;154:420.e1-5.e1.
32. Vranceanu AM, Merker VL, Park E, Plotkin SR. Quality of life among adult patients with neurofibromatosis 1, neurofibromatosis 2 and schwannomatosis: a systematic review of the literature. J Neurooncol 2013;114:257-62.
33. Kim A, Gillespie A, Dombi E, Goodwin A, Goodspeed W, Fox E, et al. Characteristics of children enrolled in treatment trials for NF1-related plexiform neurofibromas. Neurology 2009;73:1273-9.
34. Nguyen R, Kluwe L, Fuensterer C, Kentsch M, Friedrich RE, Mautner V-F. Plexiform neurofibromas in children with neurofibromatosis type 1: frequency and associated clinical deficits. J Pediatr 2011;159:652-5, e2.
35. Wolters PL, Burns KM, Martin S, Baldwin A, Dombi E, Toledo-Tamula MA, et al. Pain interference in youth with neurofibromatosis type 1 and plexiform neurofibromas and relation to disease severity, social-emotional functioning, and quality of life. Am J Med Genet A 2015;167a:2103-13.
36. Oostenbrink R, Spong K, de Goede-Bolder A, Landgraf JM, Raat H, Moll HA. Parental reports of health-related quality of life in young children with neurofibromatosis type 1: influence of condition specific determinants. J Pediatr 2007;151:182-6, 6.e1-6.e2.
37. Lehtonen A, Howie E, Trump D, Huson SM. Behaviour in children with neurofibromatosis type 1: cognition, executive function, attention, emotion, and social competence. Dev Med Child Neurol 2013;55:111-25.
38. Huijbregts S, Jahja R, De Sonneville L, De Breij S, Swaab-Barneveld H. Social information processing in children and adolescents with neurofibromatosis type 1. Dev Med Child Neurol 2010;52:620-5.
39. Gutmann DH, Ferner RE, Listernick RH, Korf BR, Wolters PL, Johnson KJ. Neurofibromatosis type 1. Nat Rev Dis Primers 2017;3:17004.
40. Lai J-S, Zelko F, Krull K, Cella D, Nowinski C, Manley P, et al. Parent-reported cognition of children with cancer and its potential clinical usefulness. Qual Life Res 2014;23:1049-58.
41. Gupta V, Gu K, Chen Z, Lu W, Shu XO, Zheng Y. Concordance of self-reported and medical chart information on cancer diagnosis and treatment. BMC Med Res Methodol 2011;11:72.
42. Caterino JM, Graham L. Discordance between patient report and chart review of risk factors for antimicrobial resistance in ED patients. Am J Emerg Med 2013;31:1397-401.