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Using PROMIS® to create clinically meaningful profiles of nephrotic syndrome patients

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Abstract

OBJECTIVE—Nephrotic syndrome (NS) is a kidney disease known to adversely impact health-related quality of life (HRQOL). Patient-reported outcome (PRO) measures are commonly used to characterize HRQOL and the patient disease experience. This study aims to improve the interpretability and clinical utility of the Patient-Reported Outcomes Measurement Information

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System® (PROMIS®) by identifying distinct meaningful HRQOL profiles in children and adults with NS.

METHODS—Patients were from two prospective NS cohort studies (PROMIS-II: 121 children; NEPTUNE: 40 children and 219 adults) with data from six PROMIS domains. Latent Profile Analysis was used to identify subgroups of patients based on PROMIS score patterns. A 3-step analysis of latent profile predictors was used to determine how clinical parameters predicted HRQOL profile membership.

RESULTS—We identified three HRQOL profiles (Good, Average, and Poor) with strong indicators of membership classification (entropy>0.86). Complete proteinuria remission, reduction in symptoms, and shorter disease duration, were significant predictors of better HRQOL profile membership.

CONCLUSIONS—Patients with NS can be classified by HRQOL into clinically meaningful categories. Integrating this approach into clinic may help in the identification of individuals with poor HRQOL will help clinicians better manage their symptoms and researchers study the causes and possible interventions for these patients. PROMIS HRQOL profiles were reproducible in replication cohorts.

INTRODUCTION

Nephrotic syndrome (NS) is characterized by relapsing and remitting episodes of proteinuria, hypoalbuminemia, and edema (Gipson et al., 2009). Disease complications and therapies may include an increased risk for severe infections, sleep disturbances, mood swings, as well as frequent hospitalizations, and end-stage kidney disease (Hodson & Alexander, 2008; Hoyer, Vester, & Ulrich Becker, 2008). Both the natural disease course and immunosuppressive treatments of NS are related to poorer health-related quality of life (HRQOL) (Perrone, Coons, Cavanaugh, Finkelstein, & Meyer, 2013), i.e., the impact that a disease has on mental, physical and/or social well-being (D. F. Cella, 1995). This is especially important given that HRQOL is increasingly recognized as a patient centered marker of clinical efficacy. (Beitz, 1999; Beitz, Gnecco, & Justice, 1996; FDA.GOV)

Patient-reported outcomes (PRO) measures have become an accepted method to assess HRQOL and now PROs serve as accepted study endpoints for clinical trials (Murthy & Wood, 2015). In addition to the clinical measures of disease activity, PRO assessment can assist in understanding the patient experience and function to improve clinical care and trials (Gipson et al., 2013). Although PROs have become accepted endpoints, continuous PRO scores are difficult to interpret in clinical practice and more work is needed to define specific categories of high and low HRQOL to focus care and research.

The Patient-Reported Outcomes Measurement Information System® (PROMIS®) provides a dynamic assessment of HRQOL for both adults and children (www.HealthMeasures.net). PROMIS was designed for use across clinical diseases, and is comprised of a broad range of measures of mental, physical and social aspects of HRQOL. Furthermore, a significant amount of work has been done to validate PROMIS pediatric measures in children with kidney disease. Specifically, PROMIS measures are sensitive to markers of disease activity in children with NS and chronic kidney disease (CKD) in cross-sectional investigations

(Buckner et al., 2014; Selewski et al., 2014; Selewski et al., 2015). Convergent validity has previously been established through significant correlations between the PROMIS and PedsQL instruments (Selewski, et al., 2015). PROMIS domains have demonstrated both high test-retest reliability (0.727-0.883) and Cronbach's alpha (0.906-0.991) (Bartlett et al., 2015). These domains also show measurement invariance by age and gender (Kim, Chung, Amtmann, Revicki, & Cook, 2013). Despite this work, there remain knowledge gaps that limit full adoption of these measures in clinical and research arenas.

An important step in increasing the clinical utilization of PRO instruments is to improve the interpretability of PRO measures by providing clinicians and researchers the ability to identify NS patients at risk for poor HRQOL or those who would potentially benefit from intervention. For example, PRO measurements such as PROMIS generally yield numeric values, often between 0 and 100, indicating their HRQOL. These continuous values may be practical for researchers, but could be difficult for clinicians to interpret and guide patient care. For example, researchers can use these detailed PRO scores in statistical models measuring within-patient change in PRO over time. However, it is harder for clinicians to act on these continuous numeric values without clear categories of poor or good PRO, and clinicians may benefit from tools that summarize PRO scores into clinically distinct categories.

In order for PROs to be clinically meaningful, it is important to have clear methods of determining if a patient has good, average, or poor HRQOL. To date there is limited data on establishing meaningful clinical profiles for PROMIS measures in other clinical populations. For example, clinical profiles have been developed for PROMIS in rheumatology (Nagaraja et al., 2018) and juvenile idiopathic arthritis (Morgan et al., 2017). This work has employed a benchmarking approach to establish clinically meaningful cut-points (i.e., an adaptation of a bookmark standard-setting procedure in which clinical vignettes are reviewed by clinical experts in order to derive consensus-driven cut scores).

An alternative method for developing clinically meaningful profiles is to use a latent profile analysis (LPA). Briefly, LPA is a type of latent measurement model which uses observed continuous variables to assign patients into categories of an unobserved, or "latent", variable (Heinen, 1993; Lazarsfeld & Henry, (1968).; B. O. Muthen, 2002). These "latent categories" are referred to as profiles. Previous studies have used LPA to identify patterns of HRQOL scores and the association between categories of HRQOL severity and co-occurring symptoms and functional impairments (Buckner, et al., 2014; Fenton, Grey, Armstrong, McCarroll, & Von Gruenigen, 2013). An advantage of using an LPA is that it categorizes patients into discrete groups based on their common HRQOL experiences that can be further evaluated to determine what clinical and patient characteristics are associated with each group (HRQOL profile). LPA has been successfully used with PROMIS measures in children with cancer and adults with chronic pelvic pain (Buckner, et al., 2014; Fenton, Grey, Armstrong, et al., 2013; Fenton, Grey, Reichenbach, McCarroll, & Von Gruenigen, 2013). In each of these analyses researchers identified clinical characteristics that placed patients at risk of membership in Poor HRQOL profiles. LPA has not yet been performed in patients with NS and represents an important step in the clinical deployment of the PROMIS instrument.

The primary goal of this study is to use an LPA to define clinically distinct HRQOL profiles in patients with NS. In clinical practice, this technique could be used to summarize information from multiple PRO instruments and provide a summary HRQOL to the clinician. We hypothesized that meaningful HRQOL profiles can be identified for NS and that profile membership will change over time in response to changes in disease status.

METHODS

Study design and participants

The data in this analysis come from two longitudinal cohorts of NS patients, PROMIS-II and NEPTUNE (Gadegbeku et al., 2013; Selewski, et al., 2015). Each participating center of the two cohort studies obtained Institutional Review Board (IRB) approval, and informed consent was obtained from all individual participants included in the studies (see Author Note for complete list of sites). In both PROMIS II and NEPTUNE, patients were consented at their pediatric nephrology visit. The consent was thoroughly explained in language such that the child was able to understand. All questions from the parent(s) and child were answered, and children over the age of 10 were asked to provide either verbal or written assent to participate in the study, depending on their ability level. In the PROMIS II study, we also employed an online consent, where parents were asked to check either “I accept” or “I do not accept”. The consent was then verbally verified when the study coordinator called to confirm eligibility. In the case of online consent, a waiver of assent was obtained from the University of Michigan IRB.

The PROMIS-II study enrolled children age 8-17 years old with active NS across 14 sites in the United States of America (USA) and Canada (12 from the Midwest Pediatric Nephrology Consortium and 2 additional participating centers in the USA). The inclusion criteria and study design have been previously described (Gadegbeku, et al., 2013; Selewski, et al., 2015). Patients completed three visits with PROMIS assessments, one at baseline and two at follow-up visits within a year after their initial visit. The first follow-up visit occurred either once the patient reached remission of proteinuria or three months after their initial visit if remission was not achieved. The second follow-up visit occurred 12 months after the initial visit.

NEPTUNE patients were enrolled at the time of first clinically indicated kidney biopsy. The details of the NEPTUNE study have been previously published (Gadegbeku, et al., 2013). After biopsy, patients returned for a baseline visit and then follow-up visits every four months for the first year and every six months thereafter. The NEPTUNE study sample selected for this analysis included children age 8-17 years and for the adult sample ages ≥ 18 years with at least three PROMIS assessments collected.

The PROMIS-II cohort was used to initially identify and develop the latent profiles. Independent profile development was then performed on the NEPTUNE pediatric cohort and adult cohorts.

PRO Measures

We examined the following child and adult PROMIS domains: Fatigue, Pain Interference, Anxiety and Depression. Each of these four domains used different questions for children and adults. In children, we also examined Mobility, and Peer Relationships, and in adults we examined Physical Function and Satisfaction with Social Roles and Activities. PROMIS measures were limited to the PROMIS domains available and validated in children with nephrotic syndrome at the launch of the PROMIS-II and NEPTUNE studies. As there were little data on PRO in adults with nephrotic syndrome at that time, similar and comparable PROMIS adult domains were selected among existing instruments We used the PROMIS Assessment Center online interface with a computer adaptive test design (www.assessmentcenter.net) to administer questionnaires and collect patient-reported data. Each item was asked in reference to "In the past 7 days." Responses included five options ranging from "never" to "almost always" in the majority of domains and from "with no trouble" to "not able to do" for the physical functioning measures. Each domain generates a *T*-score as an aggregate score of multiple questionnaire items with a mean of 50 and a standard deviation of 10. For the adult measures, *T*-scores are relative to the general population while calibration samples included both members of the general population and from clinical settings (D. Cella et al., 2010; DeWitt et al., 2011; Hinds et al., 2013; Irwin et al., 2012; Liu et al., 2010; Rothrock et al., 2010; Varni et al., 2010). A higher score indicates higher levels of the domain consistent with the measure's name. For example, a higher Physical Functioning score indicates better physical functioning (e.g., better outcome) while a higher Anxiety score indicates higher anxiety (e.g., worse outcome).

Outcomes

HRQOL latent profiles were the outcomes of interest. We hypothesized predictors of HRQOL profile membership included proteinuria remission status, edema, number of symptoms, number of medications, health care utilization, and co-existing conditions.

Statistical analysis

LPA profile selection—LPA (Heinen, 1993; Lazarsfeld & Henry, (1968).; B. O. Muthen, 2002), a posterior membership probability modeling approach, was used to identify categorical subgroups of NS patients based on their scores on six PROMIS HRQOL domains. First, the optimal number of latent profiles was selected by running a series of models with an increasing number of latent profiles. The optimal model was selected using a combination of empirical model fit indices and profile interpretability using the following selection indices: Akaike, Bayesian, and adjusted Bayesian information criterion; Lo-Mendell-Rubin likelihood ratio test; adjusted Lo-Mendell-Rubin likelihood ratio test; and the bootstrap likelihood ratio test (Lo, Mendell, & Rubin, 2001; McCutcheon, 1987). The quality of profile assignment was examined using entropy statistic and the average posterior probability of profile membership stratified by assignment to the most likely latent profile. Model selection was done first using the PROMIS-II cohort and then model selection was repeated separately for the NEPTUNE pediatric and adult samples for confirmation. NEPTUNE samples were not used to formally validate or confirm the exact model used in

the PROMIS sample and are instead used as an independent derivation cohort. Additionally, we explored using an LPA with a combined PROMIS-II and NEPTUNE pediatric sample.

Predictors of profile membership—Longitudinal predictors of profile membership were tested in the PROMIS-II cohort using the number of profiles favored from the exploratory, cross-sectional LPA analyses. LPA analyses were repeated on all 314 study visits across 121 patients. Equality restrictions were imposed on the means and variances of each profile to ensure all profiles were defined identically at each study visit and to match the baseline LPA assessment. All multinomial logistic regressions of class membership used a 3-step approach for latent profile predictors. In this approach, the latent categorical variable is used as the distal outcome. First, the most likely profile membership of each assessment are obtained from the posterior probabilities of the LPA along with the uncertainty rate. For example, these models do not assign participants to profiles with complete certainty, and the specific outcome is the probability the observation belongs to each of the profiles. 3-step LPA first classifies observations and then analyzes the most likely membership together with covariates and accounts for measurement error in the most likely assigned latent profile (Asparouhov & Muthen, 2014; Vermunt, 2010).

The following covariates were tested: disease duration (≥6 months vs. <6 months), steroid exposur, other immunosuppressive therapy exposure (treated vs. untreated at the time of study visit), obesity (based on BMI percentile and BMI at the time of study visit for children and adults respectively), edema (at the time of study visit assessed by clinician assessment), number of symptoms (a list of reportable symptoms are included in Appendix 1), number of other medical conditions (condition list included in Appendix 1), number of medications, health care utilization in the six months before the study visit (any emergency room visits or hospitalization in the 6 months prior to study visit), proteinuria remission status, urine protein: creatinine ratio (UP:C), estimated glomerular filtration rate (eGFR), and serum albumin. eGFR was estimated using the CKD-Epi equation for adults age ≥18 years and the CKiD formula for children and represents overall kidney function with lower number representing poorer function (Levey et al., 2009; Schwartz et al., 2009). Any factor that was a significant predictor of profile membership in the univariate analysis at α=0.25 was included for multivariable backward selection. After fitting the multivariable model, the variable with the highest non-significant p-value at α=0.05 was removed and the model was refit. This process was repeated until all remaining variables were significant at α=0.05.

LPAs were conducted using M*plus* 8.0, while descriptive statistics and data visualizations were completed using SAS 9.4 (L. K. Muthen & Muthen, 1998-2012; SASInstituteInc, 2014).

RESULTS

Baseline characteristics of each cohort are described in Table 1. The PROMIS-II cohort included 56 incident (disease duration at baseline <30 days) and 65 prevalent (disease duration at baseline ≥30 days) pediatric cases. The NEPTUNE cohort included 87 incident and 172 prevalent cases. The PROMIS-II cohort was more likely to have edema compared to the NEPTUNE pediatric (74% vs. 35%, p<0.01) and adult cohorts (74% vs. 56%, p<0.01).

Additionally, the PROMIS-II cohort showed higher degrees of proteinuria than the NEPTUNE pediatric cohort (median urine protein: creatinine ratio [g/g] 5.2 [IQR=2.2, 8.6] vs. 2.6 [1.6, 7.3], p=0.02).

PROMIS Scores

Baseline PROMIS HRQOL score distributions are shown for the different cohorts in Figure 1. While the median domain scores for most domains were near the standardized mean of 50, there was a wide range of scores crossing 1 (+/- 10 points) and 2 (+/- 20 points) standard deviations distance from the standardized mean.

Latent Profile Selection

Model selection indices used to determine the proper number of latent profiles from each cohort are presented in Table 2. Better model fit is indicated by lower akaike, Bayesian, and adjusted Bayesian information criteria, higher entropy values, and significant p-values for the Vuong-Lo-Mendell-Rubin, adjusted Vuong-Lo-Mendell-Rubin, and parametric bootstrapped likelihood ratio tests; bolded values in Table 2 indicate better values for each of these characteristics. Four of the seven tests in the PROMIS-II cohort (the Bayesian information criterion, Vuong-Lo-Mendell-Rubin likelihood ratio test, adjusted Vuong-Lo-Mendell-Rubin likelihood ratio test, and entropy statistic) favored the three profile model. Four of the seven tests also favored the three profile model in the NEPTUNE pediatric and adult cohorts as well. While certain tests favored a two or four profile model, the majority of tests across each sample indicated strongest fit with the three profile model. Model interpretability and usefulness also favored a three profile solution which we labeled as “Good”, “Average”, and “Poor” HRQOL.

The mean PROMIS HRQOL scores by each of the three latent profiles in the PROMIS-II cohort are shown in Figure 2. The three profile model clearly sorted patients into the three profiles, Good, Average, and Poor levels of HRQOL with the Average profile being the most populous (20%, 49%, and 31% of PROMIS-II participants, respectively). The Average profile had mean domain scores close to the reference value of 50, while the Poor and Good profiles tended to have mean scores shifted by at least 1 standard deviation from the average profile (score shift was in the expected direction for all PROMIS measures).

Following identification of the latent profiles, the findings were replicated in independent pediatric and adult NS samples. The pediatric and adult NEPTUNE cohorts also favored the three profile solution. Entropy statistics were equally strong in the pediatric (0.91) and adult (0.88) NEPTUNE samples compared to the PROMIS-II cohort (0.87). Posterior assignment probabilities for each sample are presented in Table 3. All probabilities were ≥0.90 and indicated very strong membership classification. For example, the posterior classification probabilities indicated that a PROMIS-II patient was assigned to the Good HRQOL profile, with 96% certainty according to the model.

The PROMIS-II and NEPTUNE cohorts all showed strong separation among profiles by symptom severity (Figure 2a-2d). Both pediatric cohorts showed very similar mean domain scores (Figures 2a and 2b) as did the combined pediatric cohort (Figure 2d). Peer relationships did not discriminate profile membership as strongly as other domains for

children. This is seen by the overlapping 95% confidence intervals for the PROMIS-II and pediatric NEPTUNE samples. However, among the adult NEPTUNE sample, there was strong separation in mean scores across all domains between the three latent profiles (Figure 2c).

Predicting Profile Membership

The unadjusted and adjusted multinomial logistic regression results predicting latent profile membership are shown in Table 4. Significant unadjusted (i.e., univariate) predictors of profile membership included disease duration, edema, obesity, health care utilization, number of symptoms, number of medical conditions, number of medications, proteinuria remission, and serum albumin. The final adjusted model determined that disease duration, number of symptoms, and proteinuria remission were each independently associated with profile membership. A higher number of symptoms was associated with a decreased likelihood of belonging to the Good HRQOL (OR=0.7 [95%CI=0.6, 0.8]) profile compared to Poor HRQOL profile. When a patient reached complete remission, they were more likely to be in the Good than Poor profile (OR=5.6 [95%CI=2.0, 15.3]). Prevalent patients were also less likely to belong to the Good compared to the Poor profile (OR=0.3 [95%CI=0.1, 0.7]).

Change in Profile Membership Over Time

Transitions between profile membership over time for the 121 PROMIS-II patients with complete PRO data at all visits are described in Table 5. Between visit 1 and 2 (median of 3 months apart), 57% of the 107 patients with visits 1 and 2 were estimated to remain in the same profile while the remaining 43% transitioned. Patients in the Poor profile were more likely to transition: 80% (28/35) of those in Good profile at visit 1 remained in that profile compared to 48% (25/52) of Average remaining in Average, and 40% (8/20) of Poor remaining in the Poor profile. A similar trend was found for transitions between visit 2 and 3.

Changes in latent profile were not always associated with significant changes in all six PROMIS domain scores. For example, one patient who transitioned from Poor to Good had large improvements in Anxiety (−20.2), Fatigue (−27.8) and Mobility (18.3), and minimal change in Depression (−1.0) and Pain Interference (0.3), whereas another patient had large improvements in Depression (−17.1) and Pain Interference (−19.9), but minimal change in Mobility (2.4).

DISCUSSION

PRO measures provide clinicians and researchers the ability to understand and track the impact that chronic conditions, such as NS, and their treatments, have on patients' HRQOL. NS represents a chronic condition in which a significant amount of work has been done to validate and apply PRO measures (Gipson, et al., 2013; Gipson et al., 2011; Selewski, et al., 2014; Selewski, et al., 2015). Adoption of PRO measures into clinical or research arenas as endpoints requires both validation and the ability to clinically interpret HRQOL scores. Our study shows that clinically meaningful subgroups of patients can be identified using

HRQOL data from PROMIS. Specifically, three distinct profile groups were supported by the data and included patients with NS with “Poor,” “Average,” or “Good” HRQOL. These subgroups were predicted by disease characteristics including proteinuria remission, disease duration, and symptom burden.

In chronic disease management, clinicians recognize that each patient’s perception and experience of disease is unique and, as a result, identifying disease characteristics that impact PRO in chronic disease can be challenging. Designing processes for reporting results and identifying aids to facilitate score interpretation are integral steps to the incorporation of PRO measures into clinical care (Snyder et al., 2012). We envision these latent profiles being used in practice to stratify patients into clinically actionable groups. For example, patients in the Poor HRQOL profile might be stronger candidates for targeted interventions and require additional resources. Nephrologists already measure and interpret clinically meaningful strata of other laboratory markers of disease activity and progression such as eGFR, serum albumin, and UP:C when treating patients with NS, and we expect patient-reported markers may reach the same level of utility.

Some practices have incorporated other HRQOL measures into electronic medical health records (Carlson, Waller, Groff, Zhong, & Bultz, 2012; Clark, Bardwell, Arsenault, DeTeresa, & Loscalzo, 2009; DeWalt et al., 2015; Wagner et al., 2015). HRQOL has been identified as a significant predictor of hospital readmission, (Abernethy et al., 2009; Johnston et al., 2015; M. Kopp, Kaur, & Hanson, 2015), and LPA may prove useful to improve the integration of HRQOL results into a simple indicator for use in clinical practice.

This study offers two potential applications for clinicians interested in identifying patients with poor HRQOL. The first is minor: our final multivariable model indicated that number of symptoms, disease duration, and proteinuria remission were the strongest independent predictors of HRQOL, and that other tested covariates, such as steroid use or obesity, were not significant after adjustment for number of symptoms. While unsurprising, this finding emphasizes the importance of symptom management in HRQOL. A broader p of these results are the implications of using this type of latent variable model in clinic. In our experience, nephrologists struggle to use several different HRQOL measurements on continuous uncertain scales. However, if all patients within a clinic completed the same domain assessments, an LPA could be fit on all data available to that practice and inform the clinician if this patient has “Good”, “Average”, or “Poor” HRQOL. The domain scores themselves would of course be available as well. This approach could be improved by pooling data from many nephrology clinics, and perhaps the study data collected in these studies. This would give the clinician the option of creating the profiles referent to all pooled data, or just the patients seen in their clinic.

While this study offers important contributions to the NS literature utilizing PROs, it is also important to acknowledge several study limitations. First, the adult and pediatric PROMIS physical functioning and social functioning item banks are not perfectly aligned in their content and structure. While the Pain Interference, Fatigue, Depression and Anxiety domains are intended to measure the same construct with slightly different questions for pediatric and adult participants, the differences in the pediatric Peer relationships domain and the adult

Social functioning domains reflect differences in content greater than differently worded questions. Consequently, the NEPTUNE pediatric and adult samples were given slightly different domains (i.e., Peer relationships vs. Social functioning, and Physical functioning – mobility vs. Physical functioning). This difference did not prevent the successful segregation of PRO profiles, and both the adult and pediatric domains favored a three profile model. Second, although parent proxy forms are now available for measuring HRQOL in children under 8 years old, these were not at the time this study was implemented. The PROMIS domains used were also limited to those available at the time the studies began. Additionally, this study was limited to English speaking participants as the PROMIS instruments had not yet been translated and validated for other languages at the time of data collection.

With respect to the methods used, latent variable analyses such as latent profile models, traditionally require a minimum of 200 subjects or 10 subjects per observed variable to guarantee stability in the model estimates (Bollen, 1989; Tein, Coxe, & Cham, 2013). Both of our pediatric samples do not meet the 200 subject requirement, and while our assignment probabilities for these models appear strong (≥0.9), we still highlight this as a limitation to the generalizability and stability of our results. Another methodological problem related to our sample size was our inability to power and fit latent transition analysis (Lanza & Collins, 2008) given there were only 121 PROMIS-II patients, and ony 82 PROMIS-II patients with complete data at all study visits.

Despite these limitations, this study also exhibits several strengths. First, this analysis included an independent comparison samples including both children and adults. Second, the multi-center participation in PROMIS-II and NEPTUNE supports the generalizability of findings to the US and Canada. Finally, this is one of the only longitudinal analyses on PRO in patients with NS.

PROMIS can be used to reliably classify both children and adults with NS into three distinct clinically interpretable and meaningful HRQOL profiles. In addition, HRQOL profile membership was responsive to markers of NS disease status. Taken together, these findings provide support for the clinical utility of PROs (i.e., PROMIS) in NS and represent a critical step in the mobilization of HRQOL measures into the clinical and research realms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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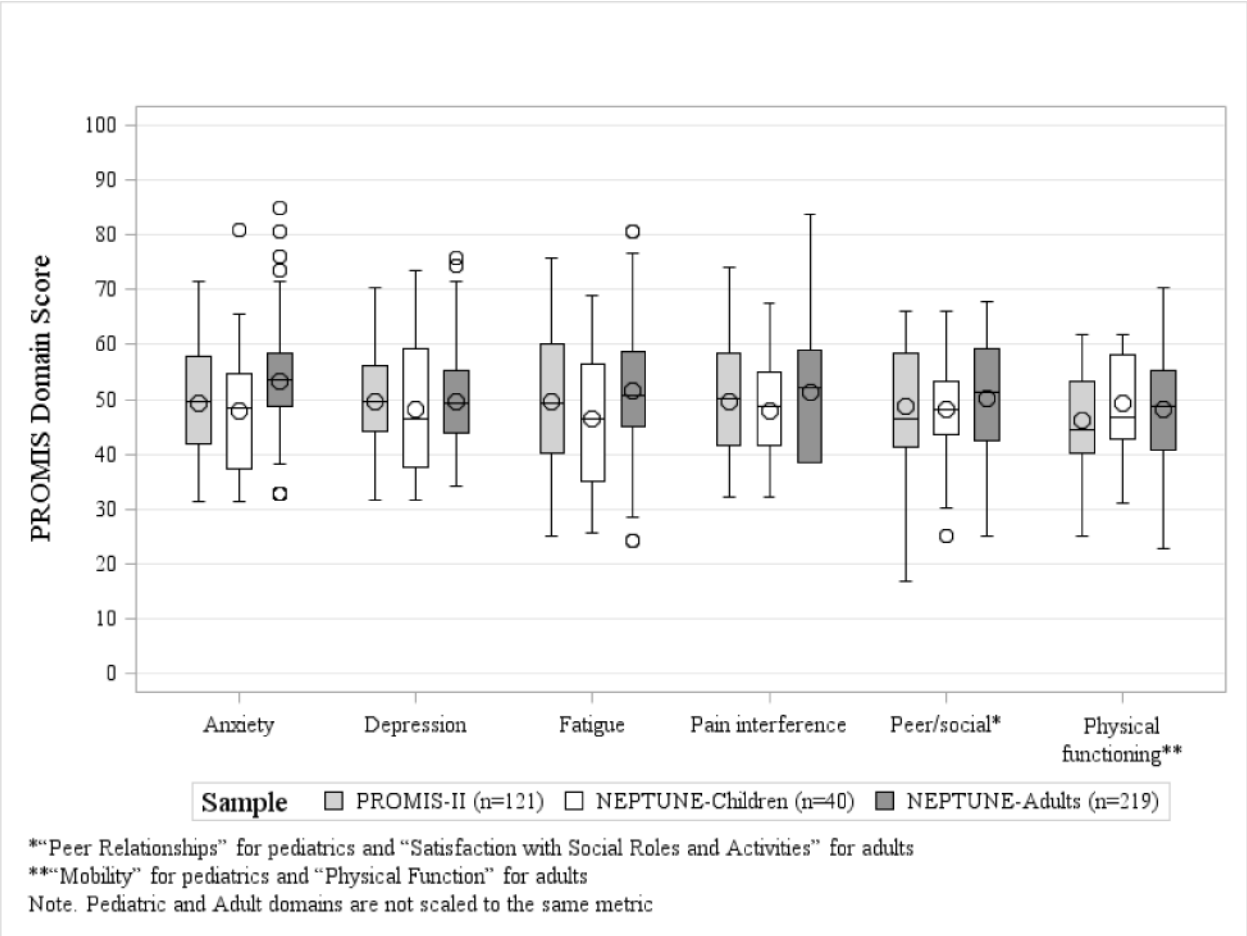

Figure 1.
Baseline PROMIS domain scores the PROMIS-II and NEPTUNE cohorts

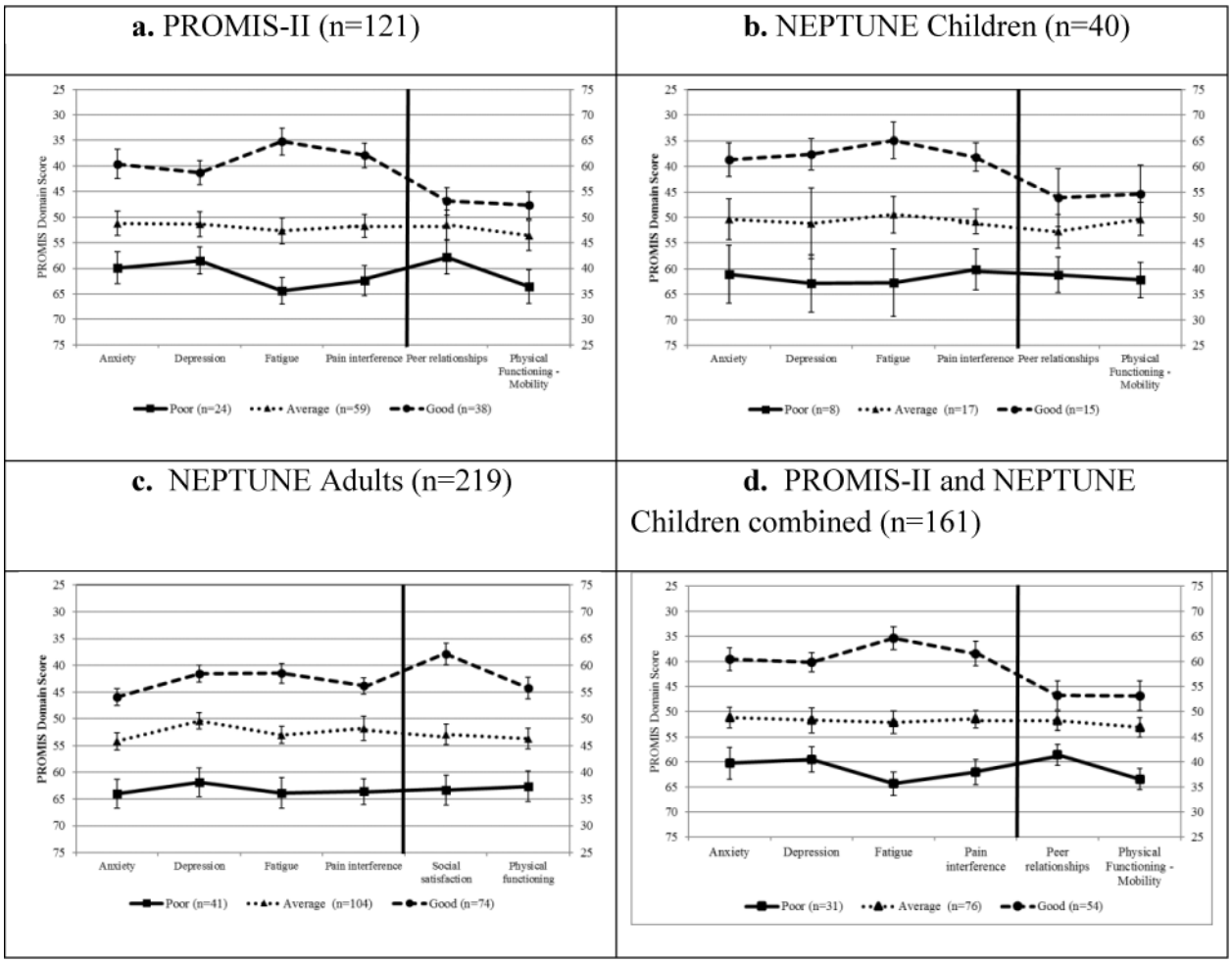

Figure 2. PROMIS domain scores of three latent profiles from by cohort. Mean and 95% confidence intervals are plotted

*Anxiety, Depression, Fatigue, and Pain interference are plotted using the left Y-axis; Peer relationships and Physical functioning – mobility are plotted using the right Y-axis

Table 1

Baseline demographic and clinical characteristics of the PROMIS-II and NEPTUNE cohorts

	PROMIS-II Cohort N=121	NEPTUNE Pediatric Cohort N=40	NEPTUNE Adult Cohort N=40
Sex			
Male, n (%)	79 (65)	24 (60)	137 (63)
Female, n (%)	42 (35)	16 (40)	82 (37)
Age (years)			
8-12, n (%)	65 (54)	9 (23)	0 (0)
13-17, n (%)	56 (46)	31 (77)	0 (0)
≥18, n (%)	0 (0)	0 (0)	219 (100)
Race			
Caucasian, n (%)	64 (53)	15 (38)	132 (60)
Black/African American, n (%)	33 (28)	20 (50)	31 (14)
Asian, n (%)	14 (12)	1 (3)	39 (18)
Other, n (%)	10 (8)	4 (10)	17 (8)
Hispanic or Latino ethnicity, n (%)	10 (8)	7 (18)	27 (12)
Disease duration			
Incident (<30 days), n (%)	56 (46)	15 (38)	72 (33)
Prevalent (≥30 days), n (%)	65 (54)	25 (62)	147 (67)
Urine protein: creatinine ratio (g/g), median (IQR)	5.2 (2.2, 8.6)	2.6 (1.6, 7.3)	4.1 (1.9, 6.8)
eGFR ml/min/1.73m2, median (IQR)	110 (83, 134)	88 (69, 108)	65 (43, 96)
Edema present, n (%)	90 (74)	14 (35)	124 (56)
Diagnosis			
Minimal change disease, n (%)	19 (16)	12 (30)	28 (13)
Focal segmental glomerulosclerosis, n (%)	19 (16)	18 (45)	69 (32)
Membranous nephropathy, n (%)	1 (1)	1 (3)	57 (26)
Other glomerular disease, n (%)	16 (13)	9 (23)	65 (30)
Nephrotic Syndrome, not otherwise classified*, n (%)	66 (55)	0 (0)	0 (0)

Counts presented as n (%), Continuous variable presented as Median (Interquartile range)

*In children, nephrotic syndrome is commonly treated based on clinical signs in the absence of a kidney biopsy informed diagnosis

Table 2

Model selection indices comparing 1, 2, 3 and 4 PRO latent profile models

	AIC	BIC	ABIC	LMR LR	ALMR LR	BLRT	Entropy
PROMIS-II Cohort (n=121)							
Number of profiles							
1-Profile solution	5494	5528	5490	---	---	---	---
2-Profile solution	5287	5340	5280	<0.01	<0.01	<0.01	**0.87**
3-Profile solution	5237	**5310**	5228	**<0.01**	**<0.01**	<0.01	**0.87**
4-Profile solution	**5223**	5315	**5211**	0.62	0.63	**<0.01**	0.85
NEPTUNE Pediatric Cohort (n=40)							
Number of profiles							
1-Profile solution	2490	2515	2477	---	---	---	---
2-Profile solution	2379	2417	2357	<0.01	**<0.01**	<0.01	**0.91**
3-Profile solution	2346	**2398**	**2316**	0.39	0.40	**<0.01**	**0.91**
4-Profile solution	**2337**	2403	2326	0.26	0.26	0.06	0.89
NEPTUNE Adult Cohort (n=219)							
Number of profiles							
1-Profile solution	11337	11379	11341	---	---	---	---
2-Profile solution	10765	10832	10771	0.02	0.02	<0.01	0.85
3-Profile solution	10548	10640	**10557**	**<0.01**	**<0.01**	<0.01	**0.88**
4-Profile solution	**10504**	**10621**	10566	0.67	0.68	**<0.01**	0.86
PROMIS-II and NEPTUNE Pediatric Combined Cohort (n=161)							
Number of profiles							
1-Profile solution	7308	7345	7307	---	---	---	---
2-Profile solution	6999	7057	6997	<0.01	<0.01	<0.01	0.88
3-Profile solution	**6919**	**6999**	6917	**<0.01**	**<0.01**	<0.01	**0.89**
4-Profile solution	6972	7004	**6899**	0.35	0.36	**<0.01**	0.84

AIC=Akaike information criterion; BIC=Bayesian information criterion; ABIC=Sample-size adjusted Bayesian information criterion; LMR LR= Vuong-Lo-Mendell-Rubin likelihood ratio test; AMR LR= Adjusted Vuong-Lo-Mendell-Rubin likelihood ratio test; BLRT=Parametric bootstrapped likelihood ratio test. Better model fit is indicated by lower akaike, Bayesian, and adjusted Bayesian information criteria, higher entropy values, and significant p-values for the Vuong-Lo-Mendell-Rubin, adjusted Vuong-Lo-Mendell-Rubin, and parametric bootstrapped likelihood ratio tests; bolding indicates better values for each of these characteristics

Table 3

Latent profile assignment probabilities using the three-category profile LPA models in the PROMIS-II and NEPTUNE cohorts

	PROMIS-II Cohort (n=121)		
	Poor	**Average**	**Good**
Poor (n=24)	**0.90**	0.10	0.00
Average(n=59)	0.04	**0.94**	0.02
Good (n=38)	0.00	0.04	**0.96**
NEPTUNE Pediatric Cohort (n=40)			
	Poor	Average	Good
Poor (n=8)	**0.91**	0.09	0.00
Average (n=17)	0.01	**0.98**	0.01
Good (n=15)	0.00	0.01	**0.99**
NEPTUNE Adult Cohort (n=219)			
	Poor	Average	Good
Poor (n=41)	**0.99**	0.01	0.00
Average (n=104)	0.04	**0.93**	0.03
Good (n=74)	0.00	0.04	**0.96**
PROMIS-II and NEPTUNE Pediatric Combined Cohort (n=161)			
	Poor	Average	Good
Poor (n=31)	**0.92**	0.08	0.00
Average (n=76)	0.04	**0.94**	0.02
Good (n=54)	0.00	0.04	**0.96**

Note. Bolding indicates agreement with prediction and assignment in each sample.

Table 4

Longitudinal predictors of latent profile membership in the PROMIS-II from unadjusted and adjusted multinomial logistic regression models

	Unadjusted Models			Final Multivariable Adjusted Model		
	OR_{Good}	**$OR_{Average}$**	**OR_{Poor}**	**OR_{Good}**	**$OR_{Average}$**	**OR_{Poor}**
Prevalent	**0.3 (0.1, 0.8)**	0.9 (0.4, 2.2)	REF	**0.3 (0.1, 0.7)**	0.9 (0.4, 2.1)	REF
Steroid exposure	1.1 (0.5, 2.4)	0.9 (0.4, 2.0)	REF			
Other therapy	**0.1 (0.1, 0.8)**	1.1 (0.3, 4.0)	REF			
Obese	**0.4 (0.1, 0.9)**	0.5 (0.2, 1.3)	REF			
Edema	**0.3 (0.2, 0.8)**	0.9 (0.4, 1.9)	REF			
Number of symptoms	**0.6 (0.5, 0.7)**	**0.8 (0.7, 0.9)**	REF	**0.7 (0.6, 0.8)**	0.9 (0.7, 1.0)	REF
Number of medical conditions	**0.7 (0.6, 0.9)**	**0.8 (0.7, 0.9)**	REF			
Number of medications	**0.7 (0.6, 0.9)**	**0.8 (0.7, 0.9)**	REF			
ER/hospital visits	0.5 (0.2, 1.1)	**0.4 (0.2, 0.9)**	REF			
Proteinuria remission	**7.8 (3.0, 20.7)**	**2.8 (1.1, 7.0)**	REF	**5.6 (2.0, 15.3)**	2.6 (1.0, 6.7)	REF
eGFR ml/min/1.73m^2 (per 30)	1.1 (0.7, 1.7)	0.9 (0.5, 1.5)	REF			
UP:C g/g (per 1)	0.9 (0.9, 1.0)	1.0 (0.9, 1.0)	REF			
Serum Albumin g/dL (per 1)	**1.5 (1.0, 2.1)**	1.0 (0.7, 1.5)	REF			

Analysis was limited to 121 individuals (314 observations); Maternal education=maternal education≥ college degree; obese=BMI percentile>95th percentile; ER/hospital visits=any emergency room or hospital visits 6th months before the baseline visit or before the previous visit for follow-up visits; UP:C=urine protein:creatinine ratio

Note. Bolding indicates $p<0.05$

Table 5

Transitions between latent profiles among PROMIS-II patients. Class counts and proportions based on most likely class pattern.

	Visit 2 Profile			
Visit 1 Profile	**Poor (n=12) n (row %)**	**Average (n=36) n (row %)**	**Good (n=59) n (row %)**	**Missed Visit (n=14) n (row %)**
Poor (n=24)	8 (33)	4 (17)	8 (33)	4 (17)
Average(n=59)	4 (7)	25 (42)	23 (39)	7 (12)
Good (n=38)	0 (0)	7 (18)	28 (74)	3 (8)
	Visit 3 Profile			
Visit 2 Profile	Poor (n=9) n row (%)	Average (n=31) n (row %)	Good (n=46) n (row %)	Missed Visit (n=35) n (row %)
Poor (n=12)	1 (8)	5 (42)	5 (42)	1 (8)
Average(n=36)	9 (25)	14 (39)	1 (3)	12 (33)
Good (n=59)	33 (56)	12 (20)	2 (3)	12 (20)
Missed Visit (n=14)	3 (7)	0 (0)	1 (7)	10 (71)