Validation of the Phenylketonuria-Symptom Severity and Impact Scale (PKU-SSIS) in adults with PKU

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Background

- Phenylketonuria (PKU) is a rare inherited metabolic disorder resulting in elevated blood and brain phenylalanine (Phe)
- Elevated Phe is linked to cognitive, psychological, and emotional symptoms that reduce health-related quality of life
- Persistent neuropsychological symptoms remain common despite current treatments
- The Phenylketonuria Symptom Severity and Impacts Scale (PKU-SSIS; **Figure 2**) was developed as a disease-specific patient-reported outcome (PRO) measure to assess PKU-related symptoms and their impact on daily life (Quinn et al, 2022)

Objective

To evaluate the psychometric properties of the PKU-SSIS Adult Version in adults with PKU

Methods

Sample

Adults with PKU aged ≥ 18 years were recruited from the United States, Canada, and Ireland through health care professionals, patient advocacy groups, PKU clinics, and third-party recruiters

Study Design

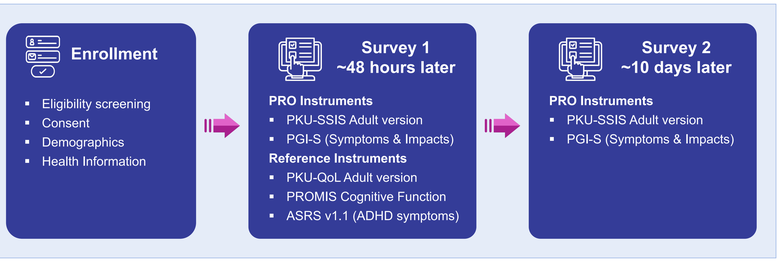
A prospective, non-interventional study was conducted using online surveys administered at two timepoints. Adult participants completed the PKU-SSIS Adult version and additional PRO measures (**Figure 1**)

Participants completed two surveys:

- Survey 1: within 48 hours of consent and enrollment
- Survey 2: approximately 10 days after Survey 1

Invitations were sent at the 10-day mark and participants had up to 1 week to complete each survey.

Figure 1. Study design and assessment schedule



Abbreviations: ASRS = Adult ADHD Self-Report Scale v1.1, PGI-S = Patient Global Impression of Severity - Symptoms and Impacts, PKU-QoL = Phenylketonuria Quality of Life Adult version, PKU-SSIS = Phenylketonuria Symptom Severity and Impacts Scale Adult version, PROMIS Cognitive Function Short Form-8a

PKU-SSIS Adult Version

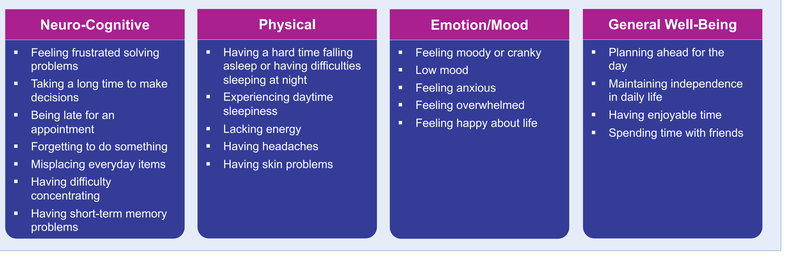
Concepts developed by Quinn et al. (2022) created a 22-item patient-reported instrument designed to evaluate neuropsychological symptoms and daily life impacts associated with PKU (**Figure 2**)

Higher scores indicate great symptom severity and impact

Response options included:

- Never, Rarely, Occasionally, Frequently, Very Frequently
- Very Dissatisfied, Dissatisfied, Neutral, Satisfied, Very Satisfied

Figure 2. PKU-SSIS adult version concepts



Results

Population

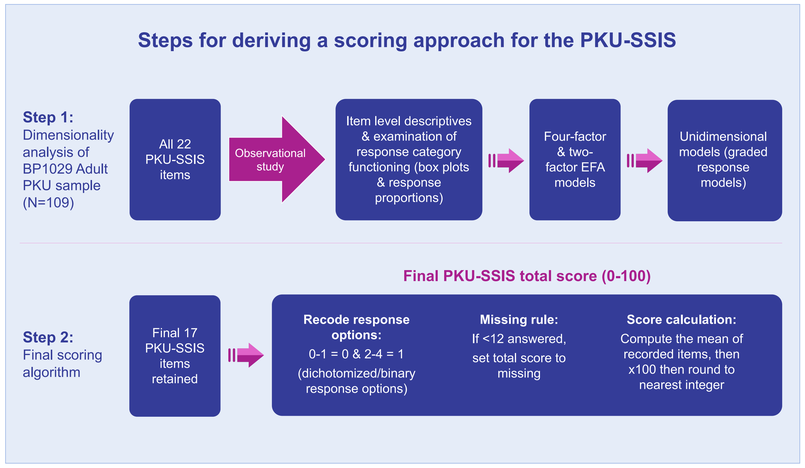
The study included **109 adults:**

- Adults had a **mean age of 34.6 years** (SD = 10.7)
- Most participants identified as **female (64.2%)**, **White (95.3%)**
- All adults reported at least one strategy for PKU management including:
  - **Phe-restricted diet (n = 77, 71%)**
  - **Medication prescribed specifically for PKU (n = 47, 43%)**
  - **Receiving treatment as part of clinical trail (n = 2, 2%)**

Dimensionality and Scoring Approach

Scoring of the PKU-SSIS Adult Version was informed by a series of analyses to assess dimensionality and to derive a scoring algorithm (**Figure 3**)

Figure 3. Analytic flow for evaluation of PKU-SSIS structure



Step 1:

- Four-factor and two factor EFA models did not generate sufficient fit statistics due to multiple item cross-loadings (**Table 1**)
- Moved towards a unidimensional approach since factor structure could not be resolved. Results showed a weaker than expected fit indicating the structure was inadequate
- Graded response model parameters were inspected and results indicated that collapsing some response categories might improve the model fit and scoring, though poor fit statistics remained
- A final GRM was examined using a binary scoring approach which was the best fit overall to balance model fit with model parsimony

Step 2:

- The final scoring approach focused on the PKU-SSIS total score, with higher scores indicating greater symptom severity and impact

Table 1. Dimensionality analysis fit statistics across the various proposed PKU-SSIS structures

Model	C2	Degrees of Freedom	PR(C_2)	RMSEA	Lower Limit 90% CI	Upper Limit 90% CI	SRMSR	TLI	CFI
4 factor	107.7814	74	0.0063	0.065	0.0353	0.0901	0.0463	0.9763	0.9871
2 factor	159.9217	103	3e-04	0.0715	0.0487	0.0921	0.0614	0.9714	0.9783
Unidimensional model	269.1464	119	0	0.1081	0.0905	0.1247	0.0857	0.9346	0.9428
Collapsed responses GRM	254.7651	119	0	0.1028	0.085	0.1196	0.0828	0.937	0.9449
Binary Response GRM	189.8363	119	0	0.0742	0.0535	0.0931	0.0812	0.9453	0.9521

Scale-Level Analysis

Psychometric properties of the PKU-SSIS total score included construct validity, item-total correlations, internal consistency reliability, and test-retest reliability. (**Table 2** and **Table 3**)

Table 2. Construct validity of PKU-SSIS total score

Concept	Measure	r	Interpretation
Cognitive	PROMIS Cognitive Function	0.715	Strong
	Lack of concentration[1]	0.647	Moderate
	Slow thinking[1]	0.664	Moderate
Emotional	Moodiness / sadness / anxiety[1]	0.617–0.745	Moderate–Strong
	Irritability / aggressiveness[1]	0.473–0.593	Moderate
Physical	Tiredness / headache / stomach ache[1]	0.326–0.664	Moderate
ADHD-related	Inattention / Hyperactivity (ASRS)	0.562–0.665	Moderate
Disease Impact	PKU overall impact[1]	0.558	Moderate
	PKU diet impact[1]	0.441	Moderate
	Dietary adherence[1]	0.194	Weak
Global (PRO)	PGI-S Symptom / Impact	0.628–0.758	Moderate–Strong

[1]PKU-QoL Adult domain scores
[2]The magnitude of correlations was interpreted in line with FDA recommendations: less than 0.3 = weak, between 0.3 and 0.7 = moderate, between 0.7 and 0.9 = strong, and above 0.9 = very strong

Table 3. Psychometric analyses and criteria for evaluation of the PKU-SSIS adult version

Psychometric Property	Description	Results
Item-total correlations	Item correlations with the PKU-SSIS total score. Acceptable correlations r ≥ 0.40	Item 14 had a low correlation with the total score (r = 0.387); all other items above threshold (r = 0.44 – 81)
Internal consistency reliability	Assessed using Kuder–Richardson Formula 20 (KR-20). KR-20 is a special case of alpha for dichotomous data	KD-20 = 0.88
Test–retest reliability	Assessed using ICC among stable participants across two survey timepoints using change in the PGI-S ratings	ICC = 0.86 (PGI-S Symptoms) ICC = 0.88 (PGI-S Impacts)

Conclusions

PKU-SSIS scale structure confirmed 17 items generate a total score from 0 to 100, with higher scores representing greater symptom severity and impact of PKU

Psychometric properties were strong:

- Reliability: **good internal consistency** and **excellent test-retest reliability**
- Concurrent validity: Score **monotonically increases** based on severity ratings
- Convergent validity: **Moderate to strong correlations with similar constructs** like cognitive functioning and emotional symptoms
- Divergent validity: **Smaller correlations to unrelated constructs** like diet adherence

The PKU-SSIS Adult version is a reliable and valid measure of symptom burden and impacts in adults with PKU

Further research in larger and more diverse samples is warranted to confirm dimensional structure and support broader application

To view a copy of this poster, scan this QR code.

Reference: Quinn J, Georgiadis A, Lewis HB, Jurecki E. Measuring burden of illness in phenylketonuria (PKU): development of the PKU symptom severity and impacts scale as a robust patient-reported outcome. *Advances in Therapy*. 2022;39(2):971-991.

Disclosures: Disclosures: DA, ED, KD are employees and shareholders of BioMarin Pharmaceutical Inc. and HO was employed by BioMarin at the time of the analysis. AH, IA, TB, KC are employees of Clinical Outcomes Solutions who was contracted by BioMarin Pharmaceutical Inc. to conduct the study.

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