# Measuring phenylketonuria burden of illness:

## Development of the Phenylketonuria Symptom Severity and Impacts Scale as a robust patient reported outcome

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### Background

- Phenylketonuria (PKU) is a rare genetic metabolic disorder caused by deficient activity of the hepatic enzyme phenylalanine hydroxylase (PAH), an essential enzyme for metabolizing the amino acid phenylalanine (Phe) to tyrosine
- PKU can result in abnormally high concentrations of Phe in the blood and the brain and often affects patients' health related quality of life (QoL), even in those with better metabolic control<sup>1</sup>
- The management of PKU is complex, requiring life-long adherence to a severely protein restricted diet and an unpalatable, amino acid fortified medical food, along with regular visits to PKU clinics, including collection of blood samples and food diaries to monitor metabolic control
- To date, current Patient Reported Outcome (PRO) instruments are not sensitive for assessing the neuropsychological symptoms in addition to determining impact of dietary management and other treatments on patients' QoL
- Herein we describe the development of the PKU Symptom Severity and Impacts Scale (PKU-SSIS), a PRO instrument designed to evaluate symptoms and impacts on the lives of early-treated PKU patients

#### Methods

- A draft PKU-SSIS consisting of 24 questions assessing six domains (emotional, cognitive, behavioral, physical functioning, general well-being, and self-care) was developed previously based on a targeted literature review, PKU expert physician interviews, and an advisory board consisting of patients with PKU
- Combined concept elicitation and cognitive interviewing was conducted in a US PKU population in 10 PKU patients (age ≥15 years old) with self-reported blood Phe levels from <120 to >1200 µmol/L, to elicit further qualitative data on the neuropsychological symptoms and impacts of PKU on patients' QoL and perform cognitive debriefing on the draft PKU-SSIS
- A separate, supplementary set of 20 adult and adolescent patients with PKU, with self-reported blood Phe levels of <120 to >1200 µmol/L, completed the draft PKU-SSIS in a paper survey format, to enable preliminary item-level descriptive assessment of responses on the instrument
- Data were analyzed using qualitative and quantitative methods as appropriate
- A content and thematic analytic approach was used in the analysis of the concept elicitation interviews by two researchers to ensure consistency in the application of codes

## Results

- A conceptual model was developed and refined (Figure 1) upon completion of the patient interviews. Patient interviews elicited four key symptom themes, namely: neurocognitive function, emotional and behavioral, physical functioning, and physical health. Four impact themes were also identified: social function, physical health, emotions, and level of independence
- The most frequently reported symptoms (i.e., reported in ≥70% of patients) were anxiety, headaches, difficulty sleeping, fatigue/low energy and difficulty focusing/concentrating (Table 1)
- Overall participants' responses to the items included in the instrument were equally distributed among the available response options
- Using the cognitive debriefing data, 7 items were deleted and 5 items were added, and 15 items were revised into questions to improve clarity. The qualitative data showed that the final instrument had good content validity; it included 22 items, covering three symptom domains (1. Emotional, Mood, and Psychological; 2. (Neuro)-Cognitive, Executive and Intellectual Function; and 3. Physical Health), and four impact domains (1. Social Relations; 2. Level of Independence; 3. General Well-being; and
- 4. Self-Care). Initial item-level analyses showed good response variability, with no indication of floor or ceiling effects observed for any of the items in the instrument

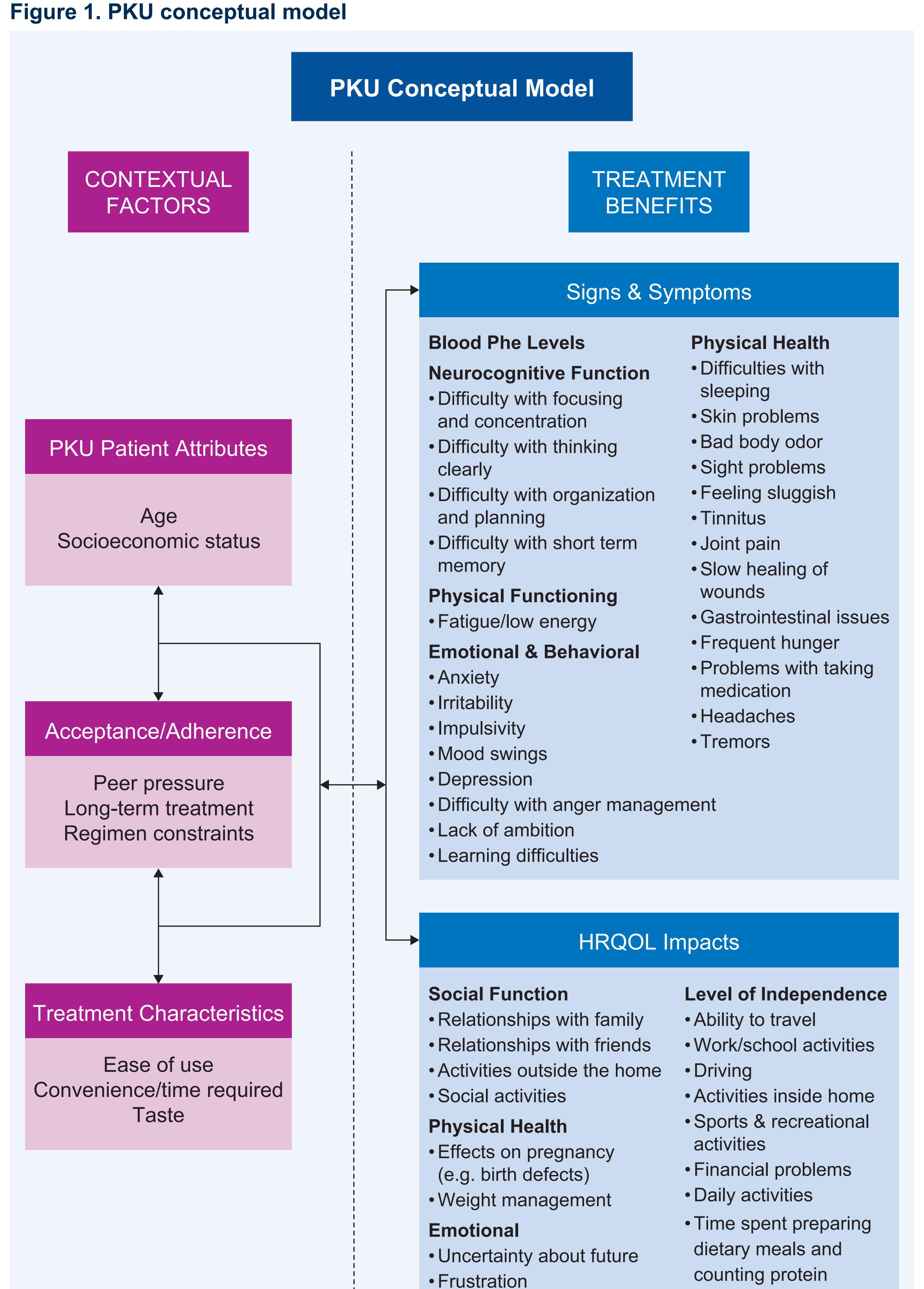


Table 1. Summary of spontaneously reported and probed symptoms

Symptoms <sup>1</sup>	Spontaneously reported n (%)	Probed <sup>2</sup> n (%)	Total report n (%)
Anxiety	2 (20%)	7 (70%)	9 (90%)
Headaches	5 (50%)	4 (40%)	9 (90%)
Difficulties with sleeping	0	8 (80%)	8 (80%)
Fatigue/low energy	4 (40%)	4 (40%)	8 (80%)
Difficulty focusing/concentration	2 (20%)	5 (50%)	7 (70%)
Irritability	4 (40%)	2 (20%)	6 (60%)
Skin problems	1 (10%)	5 (50%)	6 (60%)
Difficulties with thinking clearly	3 (30%)	3 (30%)	6 (60%)
Difficulties with organization/planning	1 (10%)	5 (50%)	6 (60%)
Tremors	2 (20%)	3 (30%)	5 (50%)
Impulsivity	0	4 (40%)	4 (40%)
Mood swings	1 (10%)	3 (30%)	4 (40%)
Depression	1 (10%)	3 (30%)	4 (40%)
Difficulties with short-term memory	4 (40%)	0	4 (40%)
Difficulties with anger management	0	2 (20%)	2 (20%)
Gastrointestinal issues	1 (10%)	0	1 (10%)
Slow healing of wounds	1 (10%)	0	1 (10%)
Problems with taking medication	1 (10%)	0	1 (10%)
Cannot gain muscles	1 (10%)	0	1 (10%)
Learning difficulties	1 (10%)	0	1 (10%)
Lack of ambition	1 (10%)	0	1 (10%)
Frequent hunger	1 (10%)	0	1 (10%)
Joint pain	1 (10%)	0	1 (10%)
Tinnitus	1 (10%)	0	1 (10%)
Sight problems	1 (10%)	0	1 (10%)

symptom has not been not included in the results. 2If a participant mentioned a symptom spontaneously before probing and talked about it after probing, the mention was counted as spontaneous only

### Conclusions

- This study aimed to examine the content validity of a PKU disease-specific PRO instrument, the first that focuses mainly on neuropsychological symptoms and impacts of the disorder on patients' lives
- Results demonstrate promising value of the new instrument to measure burden of PKU due to both the qualitative feedback from patients on the high relevance and comprehensibility of domains/ items to patients and the lack of floor/ceiling effects
- The PKU-SSIS allows the comprehensive assessment of neuropsychological function, including major physical health symptoms and functioning, such as fatigue/low energy, difficulties with sleeping and skin problems
- Even though the measurement properties of the new instrument have not yet been tested extensively, the PKU-SSIS has the potential to address an important gap in the evaluation of the impact on QoL of existing and future treatments for PKU
- The PKU-SSIS is equally applicable to clinical or real-world studies and will enhance the understanding of the factors that may influence the symptoms and impacts of PKU and help clinical teams to monitor the efficacy/effectiveness of existing and new pharmacological interventions

References 1. Vockley J et al. Genet Med. 2014;16(2):188-200.

**Disclosures** 

EJ and JQ are employees and stockholders of BioMarin. AG and HBL are employees of ICON.