Assessment of the Treatment and Management LAndScape of phenylketonuria: ATLAS survey study in Japan

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On behalf of the ATLAS Japan study group

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(BioMarin)

Background

- PKU is caused by PAH enzyme deficiency, resulting in elevated Phe in the blood and tissues that can cause depression, anxiety, memory problems, headaches, and other neurological and psychiatric symptoms[1]
- In Japan, prevalence is estimated at 1:125,000 and incidence at 1:46,000–70,000 live births[2-4]
- PKU is managed primarily through MNT, which is the severe restriction of natural protein intake with addition of Phe-free medical food; however, strict adherence to MNT is challenging and impacts QOL in patients with PKU[5]
- 2 pharmacological treatments are available to lower blood Phe:
  - Sapropterin is used in conjunction with a Phe-restricted diet in responsive individuals
  - Pegvaliase is an enzyme substitution therapy that was approved in Japan in 2023 for patients aged ≥15 years
- Treatment and management practices have changed as therapeutic options have become more readily available
  - A 2015 survey of PKU clinics in the USA reported that adherence to treatment and frequency of Phe measurement decreased with age[6]
  - However, there is limited understanding of management practices within Japan

MNT, medical nutrition therapy; PAH, phenylalanine hydroxylase; Phe, phenylalanine; PKU, phenylketonuria; QOL, quality of life

1. van Spronsen FJ et al. *Nat Rev Dis Primers*. 2021;7(1):36. **2.** Aoki K. *Southeast Asian J Trop Med Public Health*. 2003;34 Suppl 3:19-23. **3.** Shibata N et al. *Mol Genet Metab Rep*. 2018;16:5-10. **4.** Hillert A et al. *Am J Hum Genet*. 2020;107(2):234-250. **5.** Cazzorla C et al. *Mol Genet Metab Rep*. 2018;16:39-45. **6.** Jurecki ER et al. *Mol Genet Metab*. 2017;120(3):190-197.

Objective

- The objective of the Assessment of the Treatment and Management LAndScape of phenylketonuria (ATLAS) study was to better understand the global treatment landscape of patients with PKU across different countries and regions
- ATLAS was a global HCP web-based survey to describe management practices, patient adherence, and the use of QOL questionnaires and neurocognitive assessments for the management of patients with PKU
- Herein we report the findings of the survey respondents from Japan

HCP, healthcare professional; PKU, phenylketonuria; QOL, quality of life

Methods

- A web-based survey of HCPs who treat patients with PKU in Japan was conducted from May to July 2024
- The protocol was approved by local ethical review boards in compliance with regulations in each country
- Eligible clinics were those that managed ≥5 active patients with PKU, defined as patients seen by the clinic virtually or in person in the past 3 years
- Sites were identified by the study sponsor, and 1 HCP per clinical site was invited to complete the survey
- No individual patient-level data were collected; however, HCP participants were asked to review and aggregate information from the medical records in response to the questions
- Responses to survey questions in Japan aimed to reflect management practices prior to pegvaliase launch (May 24, 2023)
- Participants were compensated upon survey completion

HCP, healthcare professional; PKU, phenylketonuria

Results: Clinic and patient characteristics

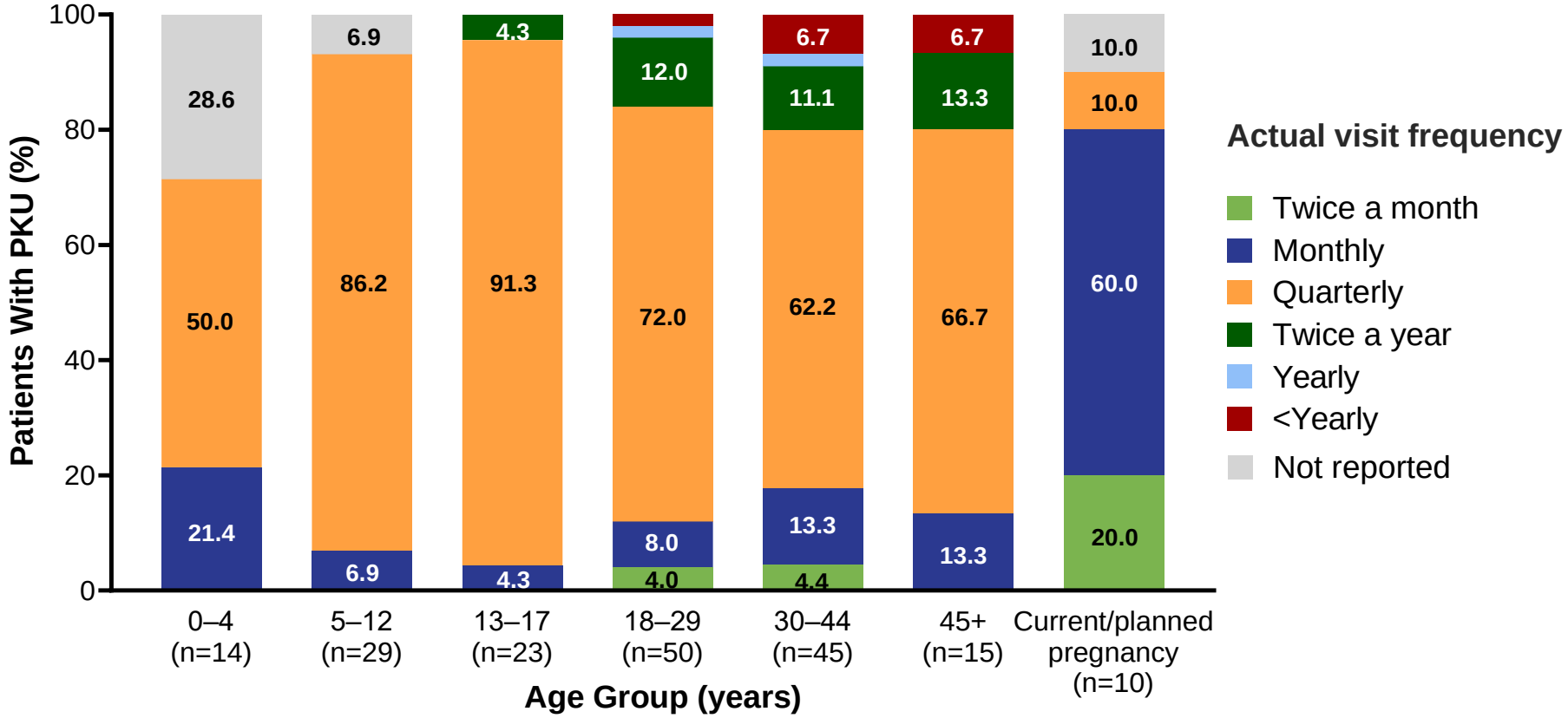
Clinic characteristic	All participating clinics (N=8)
Years managing patients with PKU	
Mean (SD)	21.6 (11.87)
Median (min, max)	21.5 (3.0, 40.0)
Practice setting, n (%)	
Academic	8 (100.0)
Clinic FTE provider type, mean (min, max)	
Physician	3.2 (0.0, 6.5)
Dietitian	1.9 (0.0, 7.0)
Social worker	0.2 (0.0, 1.0)
Psychologist/neuropsychologist/psychiatrist	0.5 (0.0, 1.1)
Nurse/nurse practitioner	4.4 (0.0, 17.0)
Genetic counselor	1.1 (0.0, 4.0)
Patients with PKU	*n=210, all clinics*
Mean (SD)	26.3 (33.97)
Median (min, max)	12.5 (6.0, 105.0)
Active* patients with PKU	*n=176, all clinics*
Mean (SD)	22.0 (29.30)
Median (min, max)	9.0 (6.0, 90.0)
Inactive patients with PKU	*n=34, all clinics*
Mean (SD)	4.3 (5.23)
Median (min, max)	3.0 (0.0, 15.0)

*Defined as patients seen by the clinic (in person or virtually) within the past 3 years

FTE, full-time equivalent; max, maximum; min, minimum; PKU, phenylketonuria; SD, standard deviation

- 8 clinics met criteria for inclusion and completed the survey
- Clinics were all academic practices and had a median of 21.5 years managing patients with PKU
- Across all clinics surveyed, there were 210 patients with PKU
  - 34 inactive
  - 176 active*

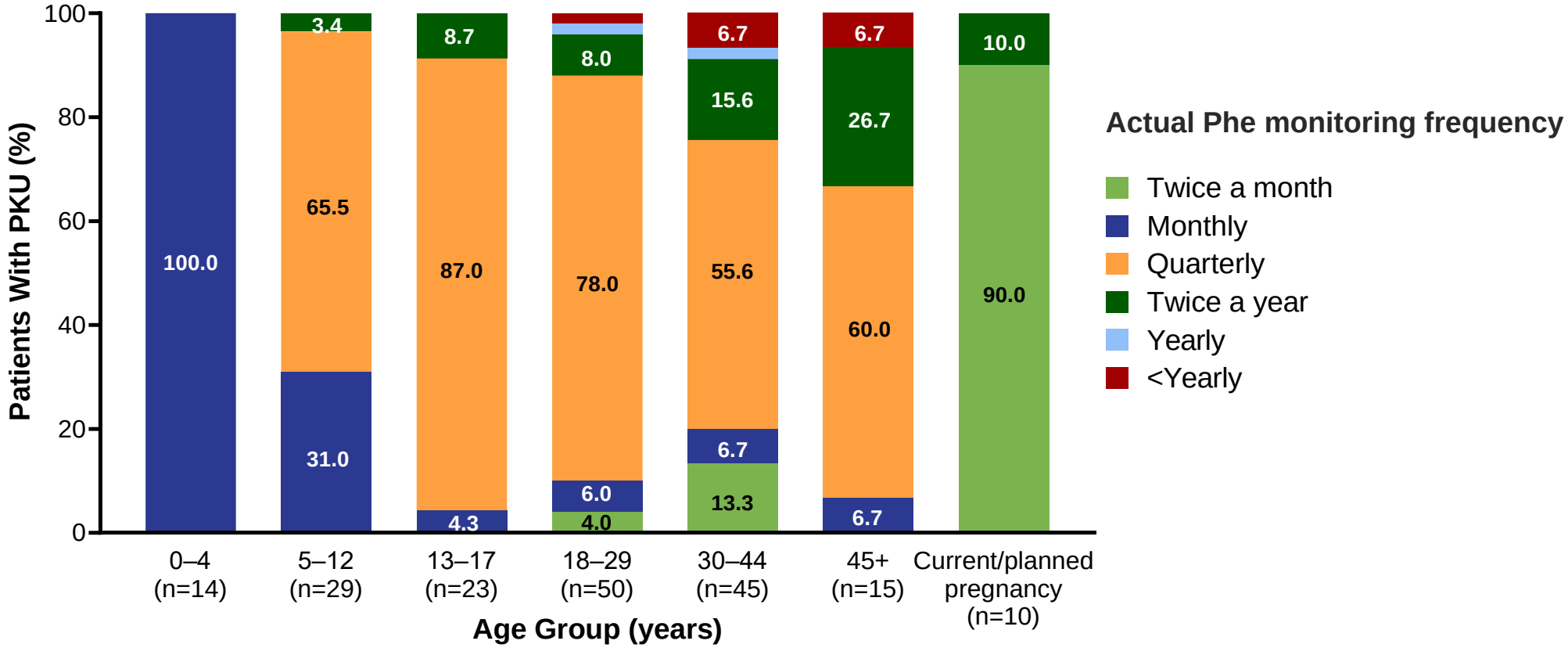
Frequency of clinic visits (active patients)



	0–4 (n=14)	5–12 (n=29)	13–17 (n=23)	18–29 (n=50)	30–44 (n=45)	45+ (n=15)	Current/planned pregnancy (n=10)
Recommended visits/year, mean (min, max)*	12.0 (12.0, 12.0)	5.5 (4.0, 6.0)	5.0 (4.0, 6.0)	5.0 (4.0, 6.0)	5.0 (4.0, 6.0)	5.0 (4.0, 6.0)	15.0 (12.0, 24.0)

*Centers with recommendations for visit frequency (n=4)
max, maximum; min, minimum; PKU, phenylketonuria

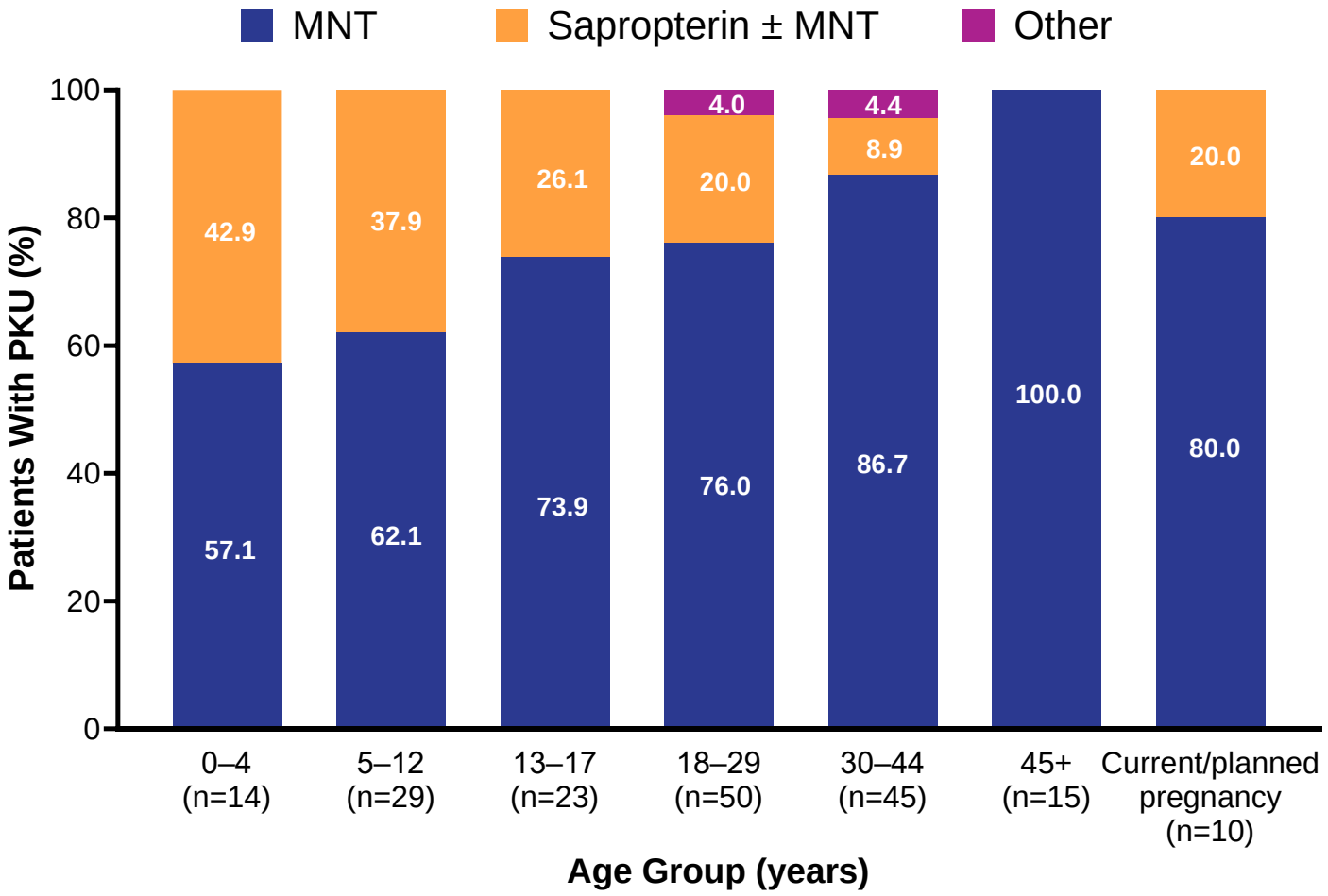
Frequency of Phe monitoring (active patients)



	0–4 (n=14)	5–12 (n=29)	13–17 (n=23)	18–29 (n=50)	30–44 (n=45)	45+ (n=15)	Current/planned pregnancy (n=10)
Recommended Phe tests/year, mean (min, max)*	10.0 (8.0, 12.0)	7.5 (6.0, 12.0)	5.5 (4.0, 6.0)	5.0 (4.0, 6.0)	7.0 (4.0, 12.0)	5.0 (4.0, 6.0)	24.0 (24.0, 24.0)

*Centers with recommendations for Phe monitoring frequency (n=4)
max, maximum; min, minimum; Phe, phenylalanine; PKU, phenylketonuria

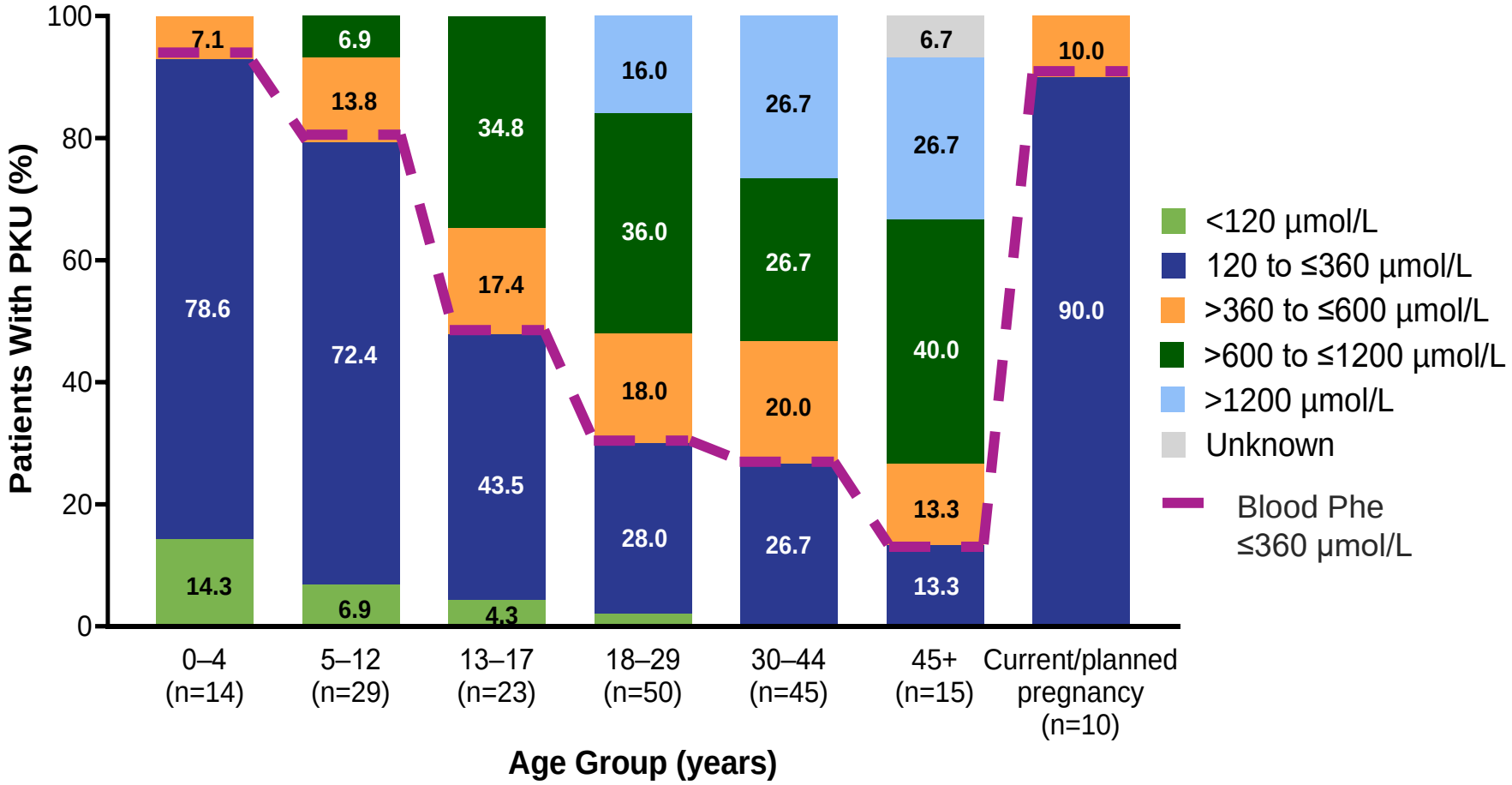
PKU treatment by age (active patients)



- The majority (76.7%, 135/176) of active patients across the lifespan were managed with MNT alone
- Sapropterin ± MNT was more commonly used in younger patients

MNT, medical nutrition therapy; PKU, phenylketonuria

Blood Phe level by age (active patients)

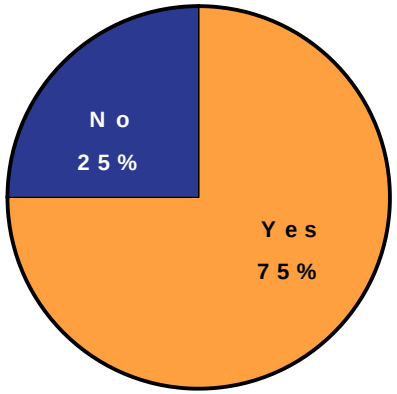


- Blood Phe was in the recommended guideline range of 120–360 µmol/L for most patients aged 0–12 years
- The percentage with blood Phe in this range declined from adolescence onward

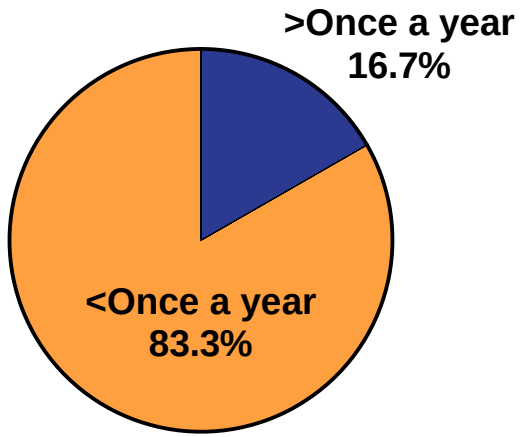
Phe, phenylalanine; PKU, phenylketonuria

Neurocognitive testing

- 75% of clinics (n=6) administered neurocognitive assessments
  - Reasons for non-administration included time constraints, lack of trained staff, and lack of patient willingness
- A range of age-appropriate scales were used, with the most common being the Wechsler Intelligence Scale for Children, 4th edition
- Most common reported frequency of neurocognitive assessment was less than once a year (83.3%)
- No QOL questionnaires were administered



Clinics administering neurocognitive assessments



Frequency of neurocognitive assessments

QOL, quality of life

Conclusions

This was the **first survey of PKU management practices in Japan** and presented results for **176 active patients** from 8 academic clinics, representing management practice before pegvaliase was available

Most active patients had **quarterly visits and Phe measurements**, but these were more frequent in those aged 0–4 years and those with current/planned pregnancy

Most active patients were managed **solely with MNT; a minority of patients,** mostly aged <18 years, **received sapropterin**

Achievement of **target Phe levels** was greatest in younger patients, with a **minority of active adults within target range**

There is an **unmet need**, particularly in older adolescents and adults, **for treatment options that do not rely on MNT** to help patients achieve target blood Phe levels

MNT, medical nutrition therapy; Phe, phenylalanine; PKU, phenylketonuria

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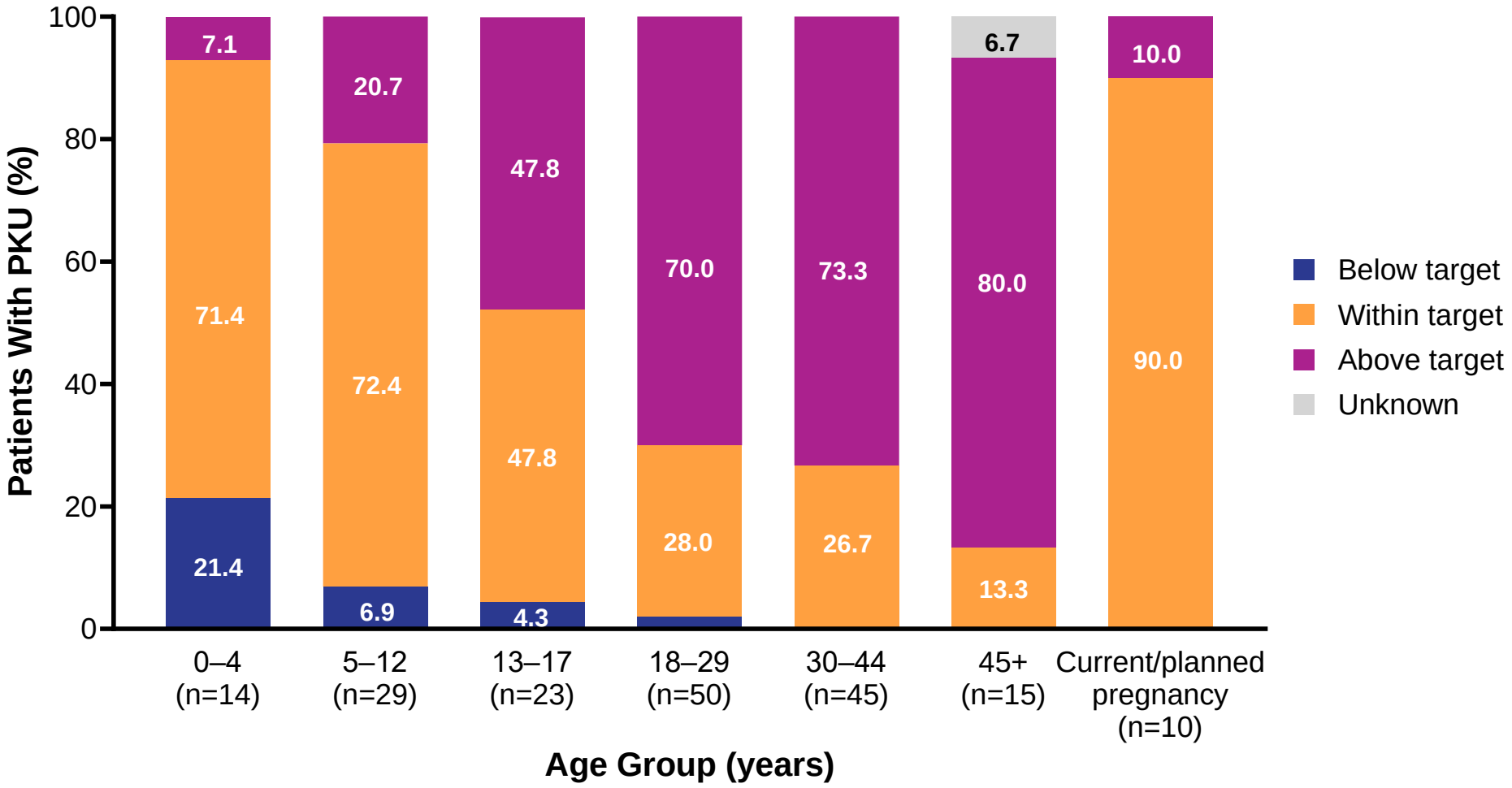
Achievement of clinic's Phe target by age (active patients)



Phe, phenylalanine; PKU, phenylketonuria