CO177

Blood Phenylalanine (Phe) Levels in Individuals with Phenylketonuria (PKU): A United States Electronic Health Records (US EHR) and Medical Notes Study

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1. Background & Objectives:

Phenylketonuria (PKU) is a rare genetic disorder that results in the accumulation of blood phenylalanine (Phe).[1]

High blood Phe levels interfere with normal brain function.[1] As such, early diagnosis and management is crucial to mitigate the progression to developmental delays and ultimately, irreversible intellectual disability.[2]

Management of PKU involves the lifelong restriction of dietary Phe, which is burdensome from the perspective of both individuals with PKU and their caregivers.[3,4]

Currently approved pharmacological therapies for PKU include oral sapropterin dihydrochloride and the subcutaneously administered pegvaliase.[5,6]

These therapies are not suitable for all individuals with PKU owing to limited responsiveness, hypersensitivity reactions, or indication limited to specific age groups only.[7,8]

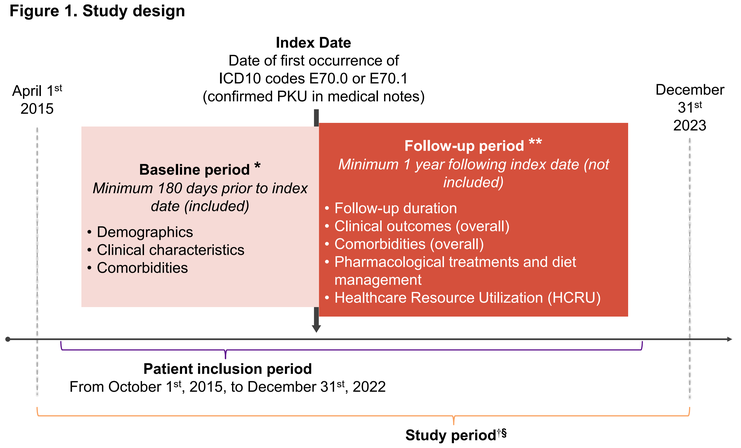
The objective of this study is to describe real-world clinical characteristics and treatment patterns of individuals with PKU in the US.

2. Methods:

Study design

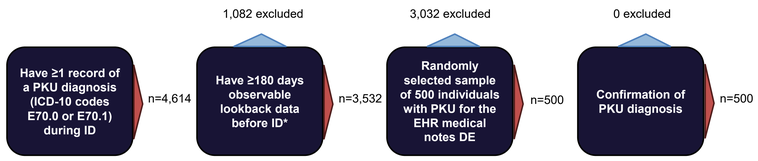
- This is a retrospective noninterventional longitudinal study using data from the Oracle US EHR and medical notes.
- The study period (01/APR/2015–31/DEC/2023) encompassed a 180-day pre-index baseline period, index date (i.e., date of first recorded PKU diagnosis), and at least 1 year of follow-up (**Figure 1**).

Figure 1. Study design



* **Baseline period** is only applicable for individuals older than 1 year of age at index date.
** **Follow-up period** is allowed but not required for all included individuals. End of follow-up reasons: death, end of study period, disenrollment from the database.
† **Study period begins** 6 months earlier than beginning of inclusion period to allow **for minimum baseline period of 6 months** for individuals included on October 31st, 2015;
§ **Study period ends** 6 months after end of inclusion period to allow for a **minimum follow-up period of 1 year** for individuals included on December 31st, 2022

Inclusion criteria



Outcomes of interest

- Demographics and clinical characteristics at PKU diagnosis index date
- Treatment use and discontinuation of prescribed pharmacological treatments
- Blood Phe levels across age categories, including proportion of individuals with blood Phe >360 µmol/L

3. Results:

Demographics and clinical characteristics at PKU diagnosis index date

- **4.5** average years of follow-up
- **53%** were female
- Mean (SD) age was **16.5 (17.7)** years; **64%** were younger than 18 years
- Mean (SD) number of **Phe-level records** during follow-up was **10.9 (17.8)**
- **Pegvaliase treatment duration:** Median (Q1; Q3): **801** (183;1338) days
- **Sapropterin treatment duration:** Median (Q1; Q3): **710** (280;1454) days

Abbreviations: EHR, electronic health records; Phe, phenylalanine; Q, quarter; SD, standard deviation

Table 1. Treatment use and treatment discontinuation within the study population

Treatment subgroups	N (% among 500)
Individuals only managed by diet	221 (44.2%)
Sapropterin-treated individuals	179 (35.8%)
Individuals with no recorded treatment/diet management	56 (11.2%)
Pegvaliase-treated individuals	24 (4.8%)
Individuals who switched from sapropterin to **pegvaliase**	18 (3.6%)
Individuals who switched from pegvaliase to **sapropterin**	2 (0.4%)

→ 181 **sapropterin-treated** individuals
→ 42 **pegvaliase-treated** individuals

Discontinuation subgroups	N (% of treated)
Discontinued **sapropterin**	79 (43.6%)
Discontinued **pegvaliase**	16 (38.1%)

Note: Among those with available data, reasons for discontinuation included lack of response or no benefit, and side effects/tolerability issues, though data were limited.

Blood Phe levels across age categories

- Differences in annual average blood Phe levels between age groups were statistically significant, with older individuals having higher annual average blood Phe (**Figure 2**).
- More blood Phe tests were conducted for younger (mean [SD]: 17.1 [25.1] samples/year, age <5 years) compared to older individuals (4.6 [5.4] samples/year, age ≥18 years).
- When compared to younger age groups, older age groups have a higher proportion of individuals whose most frequently reported Phe levels are above 360 µmol/L (i.e., individuals with uncontrolled PKU; **Figure 3**).

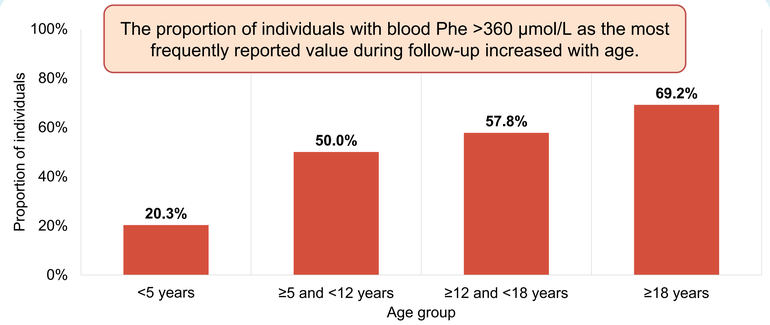
Figure 2. Annual average blood Phe level distribution, by year of follow-up and age category (µmol/L)

	Overall		Age <5 years		Age ≥5 and <12 years		Age ≥12 and <18 years		Age ≥18 years	
Number of individuals	**394**		**138**		**72**		**64**		**120**	
	Annual average	*SD*	*Annual average*	*SD*	*Annual average*	*SD*	*Annual average*	*SD*	*Annual average*	*SD*
During baseline*	420.14	377.77	361.25†	366.21	333.58	254.84	503.05	227.33	689.7	527.61
Year 1 during follow-up	342.46	297.06	245.69	179.69	369.89	275.12	564.72	353.57	581.67	437.17
Year 2 during follow-up	455.16	519.03	335.14	254.32	415.54	287.52	616.17	361.27	683.69	970.61
Year 3 during follow-up	432.07	308.1	344.55	223.28	394.86	281.42	524.85	328.75	650.27	392.8
Year 4 during follow-up	436.93	336.89	342.43	174.12	434.76	290.97	492.55	397.5	679.09	529.61

* 180 days pre-index; † May include blood Phe at diagnosis
Abbreviations: Phe, phenylalanine; SD, standard deviation

3. Results (cont'd):

Figure 3. Proportion of individuals with >360 µmol/L as the most frequent blood Phe value



Note: Most frequent Phe level refers to the most frequently reported value during the patient's follow-up as an indicator of whether or not the patient was controlled over time. If a patient had more than one most frequently reported value, the median was used (or the average of two medians if the patient had an even number of values).

4. Discussion & Conclusions:

This study demonstrated that individuals with PKU continued to have blood Phe levels above target therapeutic range despite the availability of diet and pharmacological therapies. In particular, elevated blood Phe was reported more frequently as age increased.

Moreover, high rates of discontinuing pharmacologic treatment were observed.

Notably, the study population was composed primarily of younger individuals with PKU (64% were under 18 years of age). As such, the unmet needs highlighted in this study exist even in the context of parents' and caregivers' close monitoring of their child's disease management, especially their diet.

Strengths of the study include:
- The use of a large, real-world, US dataset which allowed for the identification of a substantial number of individuals with PKU for robust analyses.
- Additionally, this study leveraged the review of medical notes to support and validate data identified from EHR.

Limitations mainly reflect the nature of EHR, namely that the data may not be representative of the entire US population and coverage may vary across different states. Additionally, difficulty in ascertaining level of diet control and extent/duration of sapropterin dihydrochloride or pegvaliase use through EHR limits the potential to account for the impact of these factors.

Given the rarity of PKU, the available data from this study provide valuable insights to better understand the burden of this disease, in particular remaining unmet needs with current treatments.

Findings from this study highlight the limitations of currently available pharmacological treatments and diet management strategies for PKU and indicate that novel therapies are needed to control blood Phe levels and address unmet needs.

5. References:

1) van Spronsen et al. Nat Rev Dis Prim. 2021;7(1):36. **2)** Cabello et al. Philadelphia, PA: Lippincott Williams & Wilkins; 2003. **3)** Rose et al. Mol Genet Metab Rep. 2019 Oct 16;21:100523. **4)** Ford et al. Mol Genet Metab Rep. 2018 Oct 18;17:57-63. **5)** Lichter-Konecki U, Vockley J. Drugs. 2019;79(5):495-500. **6)** Sanford M, Keating GM. Drugs. 2009;69(4):461-76. **7)** Longo et al. Genetics in medicine. 2019;21(8):1851-1867. **8)** Qu et al. British journal of clinical pharmacology. 2019;85(5):893-9

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