January 9, 2026

PHEFREE Consortium Update

As we begin 2026, we wanted to share an update with our PHEFREE research participants and other members of the PKU community.

The PHEFREE Consortium's goal is to collect a wide variety of information over time from people with PKU to understand how they are doing and what needs still remain despite currently available treatments. To do this, seven study sites around the United States, with the assistance of our patient advocacy group, The National PKU Alliance (NPKUA), have recruited people with PKU to join our longitudinal natural history study.

Study participants and data collected:

Between 2022 and 2025, about 250 people signed up for the longitudinal study. About 175 participants have completed their first study visit, with many returning for their second, third, or even fourth annual visit! The study participants range from 0 to 60 years old and are fairly evenly split between males (49%) and females (51%).

Here is a sample of the information the study has gathered thanks to the participants and their families:

- The largest set of detailed neuropsychological test data from people with PKU so far! Many participants have completed this testing at more than one visit, meaning we will be able to look at how people's test results change over time.
- Bone density scans on both children and adults
- Detailed diet records from participants of all ages who use a variety of treatments
- Patient-reported outcomes, including quality-of-life questionnaires
- Genotypes for participants who had never had genetic testing done for their PKU
- More than 19, 000 Phe levels!

The researchers are hard at work analyzing and writing up the information that has been collected. Some articles based on PHEFREE data have already been published. A list is at the end of this newsletter.

Funding and what's next:

The PHEFREE Consortium has been funded by a Rare Disease Consortium grant from the National Institutes of Health (NIH) for the last several years as one of several groups studying rare diseases. These grants usually last about five years at a time. Starting in September 2025, PHEFREE entered what is called a 'no-cost extension' year. We have a limited budget, which means we have had to pause study visits for now. We want to keep the longitudinal study going, so the consortium has applied for another five years of grant funding. We will find out later in 2026 if PHEFREE will receive another grant.

Our research on PKU is only possible because of the time and effort given by research participants and their families! Thank you from all the members of the PHEFREE Consortium.

<u>List of articles based on data from PHEFREE projects:</u>

Singh S, Kluen L, Curtis K, Norel R, Agurto C, Grinspoon E, Hawks Z, Christ S, Waisbren S, Cecchi G, Germine L. **Leveraging Cognitive and Speech Ecological Momentary Assessment in Individuals With Phenylketonuria: Development and Usability Study of Cognitive Fluctuations in a Rare Disease Population.** *JMIR Form Res*. 2025 Jun 3;9:e63644. doi: 10.2196/63644.

Harding CO, Arnold G, Berry GT, Christ SE, Grange DK, Jurecki E, Levy H, Lichter-Konecki U, Longo N, McNutt M, Meachum P, Sacharow S, Shayota B, Thomas J, Vucko E; Members of the PHEFREE Consortium. **Phenylketonuria in adults: we know plenty, but there is much more to learn.** *Am J Clin Nutr*. 2025 Mar;121(3):741-743. doi: 10.1016/j.ajcnut.2024.12.024. Epub 2025 Jan 24.

Holmes BM, Hollander S, Sacharow S. **Perspectives and Insights Into Phenylketonuria: Patient Narratives About the Early Years Following Newborn Screening.** *Am J Med Genet C Semin Med Genet*. 2024 Sep 17:e32110. doi: 10.1002/ajmg.c.32110. Epub ahead of print. PMID: 39285733.

Waisbren SE, Christ SE, Bilder DA, Bjoraker KJ, Bolton S, Chamberlin S, Grant ML, Janzen DM, Katz R, Lubliner E, Martin A, McQueen K, Moshkovich O, Nguyen-Driver M, Shim S, Stefanatos AK, Wilkening G, Harding C. **Neurocognitive assessment platform for clinical trials in PKU: White paper developed by the NPKUA neurocognitive workgroup**. *Mol Genet Metab*. 2024 Sep-Oct;143(1-2):108555. doi: 10.1016/j.ymgme.2024.108555. Epub 2024 Jul 25.

Christ SE, Arnold G, Lichter-Konecki U, Berry GT, Grange DK, Harding CO, Jurecki E, Levy H, Longo N, Morotti H, Sacharow S, Thomas J, White DA. **Initial results from the PHEFREE longitudinal natural history study: Cross-sectional observations in a cohort of individuals with phenylalanine hydroxylase (PAH) deficiency**. *Mol Genet Metab*. 2024 Jul 22;143(1-2):108541. doi: 10.1016/j.ymgme.2024.108541. Epub ahead of print. PMID: 39059270.

Sacharow S, Zhu E, Hollander S. **The challenge of adults with phenylketonuria who have been lost to care; a single center's attempt to reach those diagnosed with PKU over 60 years of newborn screening.** *Mol Genet Metab Rep*. 2024 Jun 8;40:101099. doi: 10.1016/j.ymgmr.2024.101099.