The PK/PD nomogram explores the relationship between PK/PD variables, blood Phe, and diet[1,2]

BIOMARIN

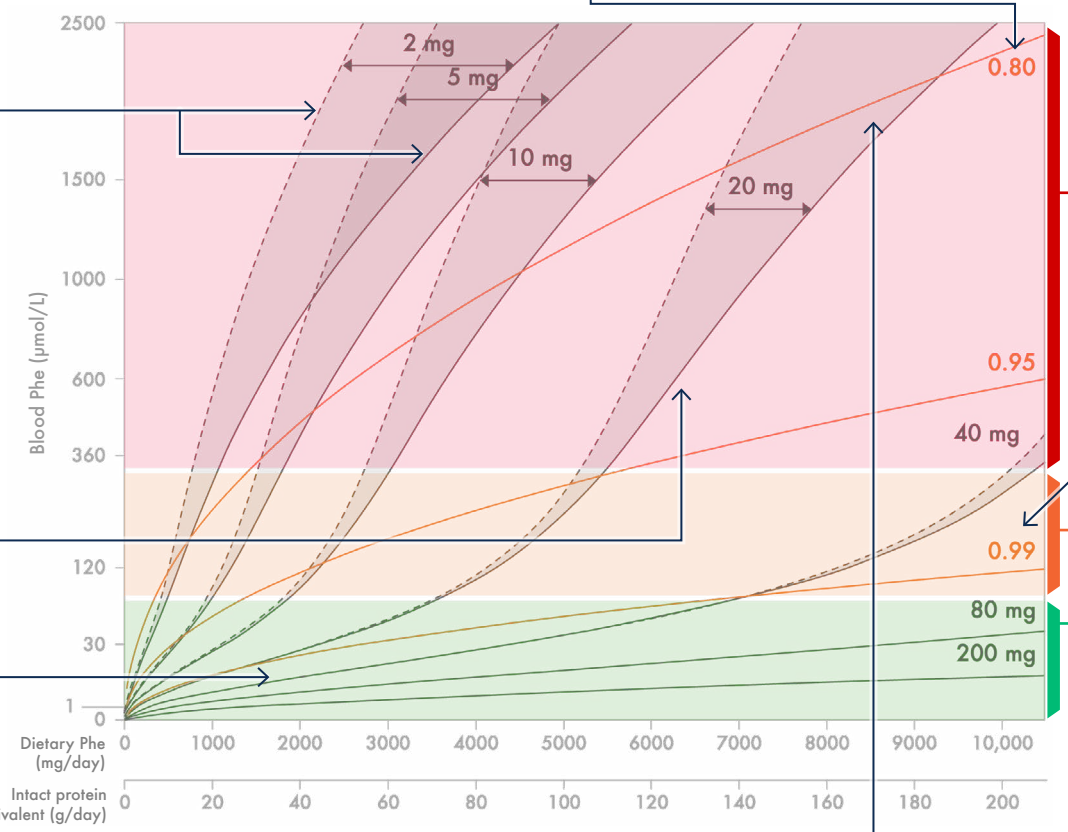
1 Orange lines: Proportion of Phe metabolism by pegvaliase (γ)

- **γ=0.80:** **80%** of Phe metabolism is driven by pegvaliase (drug clearance ↑)
- **γ=0.99:** **99%** of Phe metabolism is driven by pegvaliase (drug clearance ↓)

2 Solid and dashed gray lines:
Pegvaliase plasma exposure

3 Slope of gray lines:
Sensitivity of blood Phe to dietary Phe intake (β)
(↑ β = ↑ sensitivity)

- **Steeper line = ↑ β = high sensitivity of blood Phe to dietary Phe intake**
  Small increases in dietary Phe may cause a substantial increase in blood Phe
  ↑ β is associated with ↓ γ
- **Flatter line = ↓ β = low sensitivity of blood Phe to dietary Phe intake**
  Substantial changes in dietary Phe have a minimal effect on blood Phe
  ↓ β is associated with ↑ γ



4 Shaded area: Individual variability in baseline Phe metabolism* (α) *e.g., the range of endogenous PAH activity in individuals with PKU*

As γ ↑ (more Phe metabolism is being driven by pegvaliase), the shaded area (α) ↓
No shaded area = variability in baseline metabolism no longer matters

5 Overlays of three key zones† to help with interpretation:[2]

Red zone:
- Four variables are affecting blood Phe (clearance, exposure, endogenous PAH activity, and dietary Phe)
- Response is difficult to predict

Orange zone:
- ↑ % of Phe metabolism is driven by pegvaliase = blood Phe is more predictable than in the red zone
- Approaching a homeostatic situation: immune system tolerization ↑, drug clearance ↓

Green zone:
- γ is ↑ = more certainty about dose and clearance, and a more predictable blood Phe
- As β is ↓, blood Phe and dietary Phe are uncoupled, and changes in dietary Phe will have minimal impact on blood Phe

*Represents the interval between the 25th and 75th percentiles of observed dietary Phe tolerance. †Overlays and annotations have been added to the original figure to assist interpretation. Limitations: While years of additional learnings were used to better understand patterns of response in the PRISM dataset used for the model, a clinical trial may not reflect real-world use. Additionally, in the PK model, pegvaliase lifetime was treated as constant without adjustment for potential influencing factors such as body composition and site rotation. α, individual variability in baseline Phe metabolism; β, sensitivity of blood Phe to dietary Phe intake; γ, proportion of Phe metabolism by pegvaliase; PAH, phenylalanine hydroxylase; PD, pharmacodynamics; Phe, phenylalanine; PK, pharmacokinetics; PKU, phenylketonuria.

1. Harding CO, et al. *Genet Med* 2025;27:101459; 2. BioMarin. Data on file.

Scan to view the Harding publication

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