

# Clinical monitoring practices among adult patients with pyruvate kinase deficiency who have never been transfused

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## BACKGROUND

- Pyruvate kinase (PK) deficiency is a rare, congenital, hemolytic anemia caused by a glycolytic defect, characterized by deficient PK enzyme activity in red blood cells (RBCs)<sup>1,2</sup>
- Patients with PK deficiency are at risk of both acute symptoms and long-term complications, including anemia and chronic hemolysis, low bone mineral density, and iron overload<sup>1,2</sup>
- Iron overload may be associated with serious disease complications and can occur in all patients with PK deficiency, including those who have never received a RBC transfusion<sup>2</sup>
- The long-term complications of PK deficiency can negatively affect patient-reported health-related quality of life and may lead to increased risk of early mortality<sup>3-5</sup>
- In 2024, the first international expert guidelines for managing PK deficiency were published and included recommendations for never transfused (NT) patients<sup>2</sup>

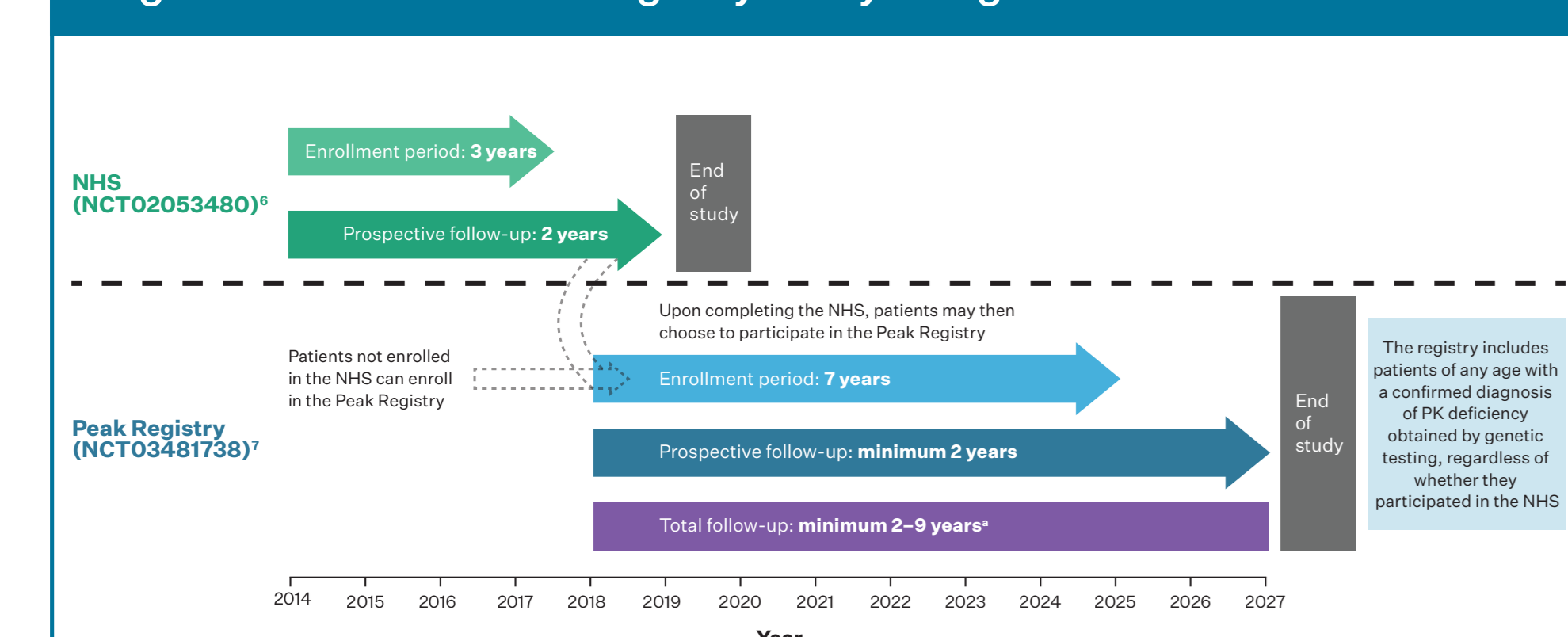
## OBJECTIVE

- To describe (1) reasons provided by clinicians for not transfusing patients with PK deficiency who were never transfused and (2) disease monitoring activities in these patients, using data from 2 real-world studies: the PK deficiency Natural History Study (NHS) and Peak Registry

## METHODS

- The NHS (NCT02053480)<sup>6</sup> and Peak Registry (NCT03481738)<sup>7</sup> were designed as global, longitudinal, observational studies to address the knowledge gaps in PK deficiency and the variability and severity of disease complications
- The registries enrolled patients with PK deficiency (NHS 2014–2017, Peak Registry 2018–ongoing [data cutoff: 15May2023])
  - Study design details are displayed in **Figure 1** and the country study sites are shown in **Supplemental figure 1**
- This descriptive analysis used merged data from both studies and included patients aged ≥18 years (at last documented visit), with a confirmed diagnosis of PK deficiency, who were NT (defined as no lifetime history of blood transfusions before/during study follow-up)
- Details of the inclusion and exclusion criteria and the study population are shown in **Figure 2**

Figure 1. NHS and Peak Registry study design and duration



\*Participants in the Peak Registry who were originally included in the NHS from 2014 to 2017 and for whom data are integrated within the Peak Registry may have a cumulative follow-up exceeding 11 years. NHS, PK deficiency Natural History Study; PK, pyruvate kinase

Figure 2. Study population

Key inclusion/exclusion criteria	
<b>Inclusion</b>	
• ≥18 years of age (at last documented visit)	
• Confirmed diagnosis of PK deficiency	
• <b>Peak:</b> Patients with a confirmed diagnosis of PK deficiency via genetic testing*	
• <b>NHS:</b> Patients with biochemically or genetically diagnosed PK deficiency OR patients with a hemolytic anemia AND a family member with genetically diagnosed PK deficiency	
• <b>NT:</b> No lifetime history of blood transfusions before/during study follow-up	
<b>Exclusion</b>	
• Patients homozygous for p.R479H	
• Unknown transfusion status	
• Patients whose participation in mitapivat interventional trials overlapped with registry participation*	
<b>Study population</b>	
<b>Overall NT group</b>	
• All adult NHS and Peak NT patients	
• <b>NT 12M+ subgroup:</b> Patients with ≥12 months of retrospective data	
• <b>Anemia not very severe/symptomatic (as reason for not transfusing) subgroup:</b> Documented treatment decision of "Anemia not very severe" OR "Anemia not symptomatic" for not transfusing (either or both reasons could be selected) (Peak Registry only)	

\*Clinical features consistent with PK deficiency together with the presence of 2 or more PKLR gene mutations. For novel or indeterminate PKLR gene mutations, patients are deemed eligible if, in the opinion of the investigator, the reported PKLR gene mutations are sufficient to support a diagnosis of PK deficiency. \*To prevent confounding factors from interventional trials impacting real-world study data. NHS, PK deficiency Natural History Study; NT, never transfused; PK, pyruvate kinase

An analysis of monitoring practices was performed on the following groups of patients:

- All adult NHS and Peak Registry patients who were NT
  - Subgroup of patients with ≥12 months of retrospective data (to permit adequate time for monitoring in line with guidelines<sup>2</sup>)
  - Subgroup of patients with reason for not being transfused reported as "Anemia not very severe/symptomatic" (clinically relevant indicator for patient management)
- Results were evaluated relative to pertinent recommendations from the PK deficiency international expert guidelines<sup>2</sup>

## RESULTS

### Patient disposition and characteristics

- A total of 55 adult NT patients were included in the analysis: patients enrolled in NHS only: 10 (18.2%); patients in Peak Registry only: 31 (56.4%); patients in both registries: 14 (25.5%) (**Table 1; Supplemental table 1** [QR code])
  - Median age (min, max) at the last visit was 39 years (18, 81); 24 patients (43.6%) were female
  - 42 patients (76.4%) had ≥12 months of retrospective data
  - Regional variations in the lifetime prevalence of NT patients were observed, with the greatest proportion residing in Southern Europe (24 patients [43.6%])
- PKLR genotype distribution was 62% missense/missense (M/M), 34% missense/non-missense (M/NM), and 4% non-missense/non-missense (NM/NM)
- Median (quartile [Q1], Q3) lab results at last patient visit included hemoglobin 11.4 g/dL (10.3, 12.2), absolute reticulocyte count 207.0 10<sup>9</sup>/L (134.3, 300.0), and ferritin 312.0 ng/mL (176.0, 404.0) (**Table 2; Supplemental Table 2** [QR code])
- Overall, 93 adult patients, who did not meet the criteria of never having received a transfusion, were excluded from the analysis (**Supplemental table 3** [QR code])
- Reasons for non-transfusion of patients are shown in **Figure 3**

Table 1. Patient demographics

	NT* (N=55)	NT 12M+ subgroup* (N=42)	Anemia not very severe/symptomatic subgroup* (N=34)
<b>Age at last documented visit, median (min, max), years</b>	39.0 (18.0, 81.0)	35.0 (18.0, 75.0)	40.0 (20.0, 75.0)
<b>Female, n/N (%)</b>	24/55 (43.6)	19/42 (45.2)	17/34 (50.0)
<b>Race, n/N (%)</b>			
Asian	2/50 (4.0)	2/39 (5.1)	0/30
Black or African American	3/50 (6.0)	2/39 (5.1)	1/30 (3.3)
American Indian or Alaska Native	1/50 (2.0)	0/39	0/30
White	43/50 (86.0)	35/39 (89.7)	29/30 (96.7)
Other	1/50 (2.0)	0/39	0/30
<b>Ethnicity, n/N (%)</b>			
Not Hispanic or Latino	44/49 (89.8)	33/38 (86.8)	24/29 (82.8)
Hispanic or Latino	5/4	4/3	3/23
<b>Age at PK deficiency diagnosis, n</b>	54	41	35
Median (min, max), years	21.5 (0.0, 76.0)	22.0 (2.0, 55.0)	28.0 (2.0, 55.0)
<b>Time from symptom onset to diagnosis, n</b>	10	8	8
Median (min, max), months	291 (0.0, 252.8)	4.6 (0.0, 219.2)	4.6 (0.0, 252.8)

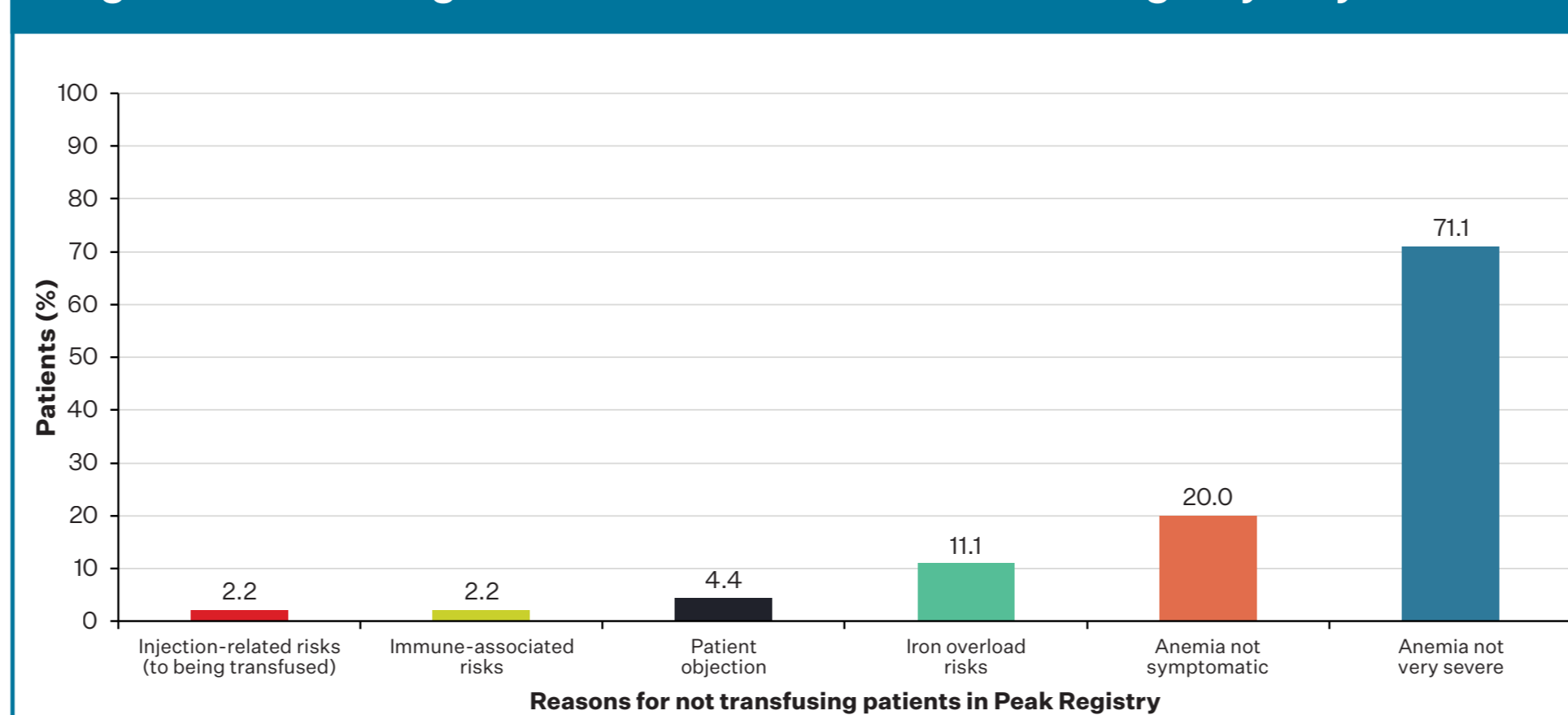
N represents the number of patients with data available. \*NT = subject has never been transfused up to data cutoff date; \*NT 12M+ = NT with ≥12 months of retrospective data; \*Anemia not very severe/symptomatic = NT with documented rationale of "Anemia not very severe" and/or "Anemia not symptomatic"; only common terms reported in both the Peak Registry and NHS were included; \*Including 2 scenarios: complete date; year and month are available with day as missing. NHS, PK deficiency Natural History Study; NT, never transfused; PK, pyruvate kinase

Table 2. Laboratory parameters at last documented visit

Laboratory values	NT* (N=55)	NT 12M+ subgroup* (N=42)	Anemia not very severe/symptomatic subgroup* (N=34)
<b>Hemoglobin, n</b>	47	40	30
Median (Q1, Q3), g/dL	11.4 (10.3, 12.2)	11.3 (10.2, 12.1)	11.3 (10.3, 12.1)
<b>Absolute reticulocyte count, n</b>	32	31	25
Median (Q1, Q3), 10 <sup>9</sup> /L	207.0 (134.3, 300.0)	210.0 (138.0, 302.9)	204.0 (138.0, 297.0)
<b>Indirect bilirubin, n</b>	38	33	25
Median (Q1, Q3), mg/dL	2.0 (1.1, 3.5)	2.0 (1.1, 3.3)	1.9 (1.2, 3.3)
<b>Lactate dehydrogenase, n</b>	40	37	26
Median (Q1, Q3), U/L	221.0 (165.5, 327.0)	206.0 (165.0, 301.0)	204.0 (164.0, 288.0)
<b>Ferritin, n</b>	39	37	25
Median (Q1, Q3), µg/L	312.0 (176.0, 404.0)	312.0 (179.3, 404.0)	280.5 (176.0, 360.0)
<b>Ferritin in males, n</b>	22	21	12
Median (Q1, Q3), µg/L	318.2 (240.0, 671.0)	317.0 (240.0, 671.0)	298.8 (209.7, 535.0)
<b>Ferritin in females, n</b>	17	16	13
Median (Q1, Q3), µg/L	278.0 (163.0, 362.0)	287.0 (163.5, 383.0)	278.0 (163.0, 360.0)

N represents the number of patients with data available. \*NT = subject has never been transfused up to data cutoff date; \*NT 12M+ = NT with ≥12 months of retrospective data; \*Anemia not very severe/symptomatic = NT with documented rationale of "Anemia not very severe" and/or "Anemia not symptomatic"; only common terms reported in both the Peak Registry and NHS were included. NHS, PK deficiency Natural History Study; NT, never transfused; PK, pyruvate kinase; Q, quartile

Figure 3. Reasons given for non-transfusion\* (Peak Registry only)

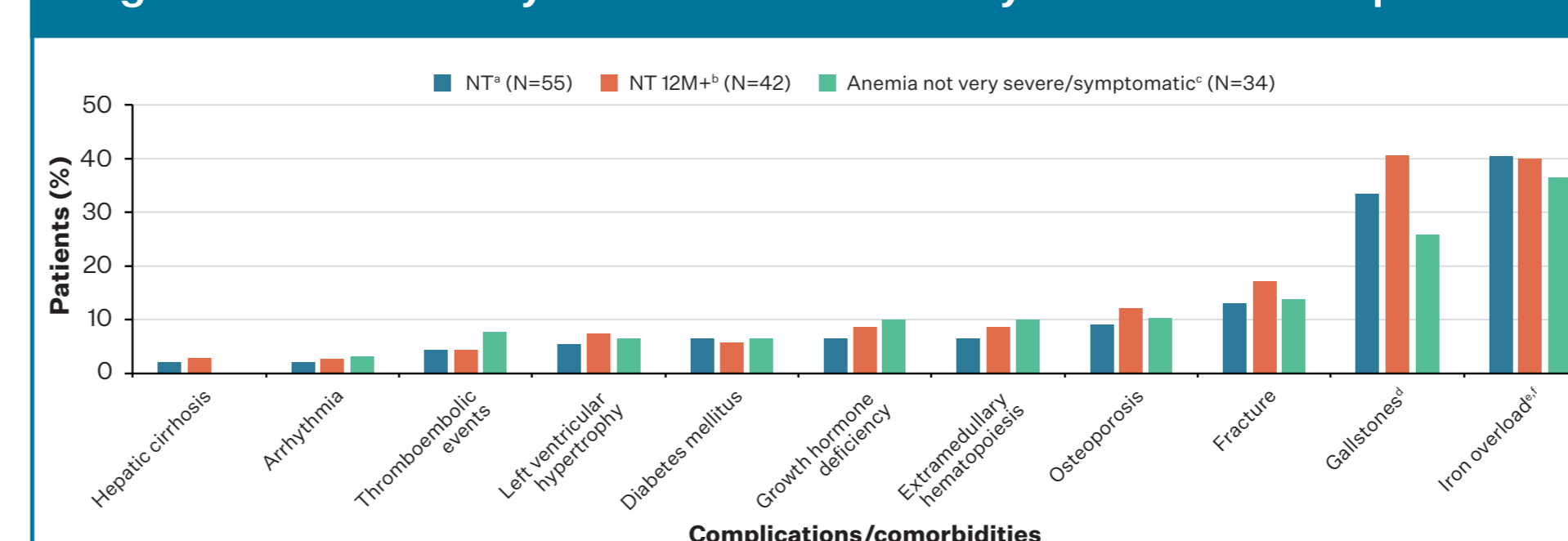


\*Data were only collected in the Peak Registry (N=45), with multiple reasons for non-transfusion permitted per patient

### Medical complications

- Among the 42 NT patients with ≥12 months of retrospective data, the most commonly observed complications included iron overload (40.0%) and osteoporosis (12.1%) (**Figure 4**)
- All complications, except hepatic cirrhosis, were also observed in the subgroup reporting anemia not very severe and/or not symptomatic (**Figure 4**)
- Further data on medical complications are displayed in **Supplemental table 4** (QR code)
- Disease management**
- Among NT patients, 18.9% had previously undergone splenectomy (**Table 3**)
- Despite never receiving transfusions, the number of interventions received among patients with ≥12 months of retrospective data was high, with 31.7% receiving cholecystectomy and 20.0% receiving splenectomy

Figure 4. PK deficiency-related medical history and medical complications



\*NT = subject has never been transfused up to data cutoff date; \*NT 12M+ = NT with ≥12 months of retrospective data; \*Anemia not very severe/symptomatic = NT with documented rationale of "Anemia not very severe" and/or "Anemia not symptomatic"; only common terms reported in both the Peak Registry and NHS were included; \*Pooled gallstones and asymptomatic gallstones; \*Iron overload was defined as: having ever received chelation/phlebotomy for the removal of iron OR had any of the following (for Peak Registry participants): ferritin >1000 ng/mL; liver MRI (including Ferriscan®) >3 mg Fe/g dry weight; cardiac T2 MRI ≤20 ms OR had any of the following (for NHS participants): ferritin >1000 ng/mL in the 12 months prior to enrollment; liver MRI (including Ferriscan®) >3 mg Fe/g dry weight; cardiac T2 MRI ≤20 ms; Iron overload occurred in 4.3% (13/30) of males and 38.4% (13/22) of females in the NT group. MRI, magnetic resonance imaging; NHS, PK deficiency Natural History Study; NT, never transfused; PK, pyruvate kinase

Table 3. Disease management among NT patients with PK deficiency

Intervention, n/N (%)	NT* (N=55)	NT 12M+ subgroup* (N=42)	Anemia not very severe/symptomatic subgroup* (N=34)
<b>Cholecystectomy</b>	18/54 (33.3)	13/41 (31.7)	11/33 (33.3)
<b>Chelation treatment</b>	14/52 (26.9)	10/40 (25.0)	7/33 (21.2)
<b>Alternative treatments**</b>	6/24 (25.0)	6/24 (25.0)	4/13 (30.8)
<b>Splenectomy</b>	10/53 (18.9)	8/40 (20.0)	4/32 (12.5)
<b>Phlebotomy treatment</b>	8/53 (15.1)	6/41 (14.6)	4/32 (12.5)
<b>Ever treated with mitapivat†</b>	4/55 (7.3)	2/42 (4.8)	3/34 (8.8)
<b>Other treatments</b>			
Folic acid‡	37/55 (67.3)	31/42 (73.8)	24/34 (70.6)
Anxiolytics and/or antidepressants	9/55 (16.4)	7/42 (16.7)	7/34 (20.6)
Vitamin D and analogs§	6/45 (13.3)	4/32 (12.5)	4/34 (11.8)

N represents the number of patients with data available. \*NT = subject has never been transfused up to data cutoff date; \*NT 12M+ = NT with ≥12 months of retrospective data; \*Anemia not very severe/symptomatic = NT with documented rationale of "Anemia not very severe" and/or "Anemia not symptomatic"; only common terms reported in both the Peak Registry and NHS were included; \*Alternative, non-traditional, or investigational therapies, stem cell transplant; †Data from NHS registry only; ‡Number from clinical trials (n=3); number from commercial use (n=1); §Due to a lack of evidence, international expert guidelines for PK deficiency do not include a recommendation on folic acid use; †Data available from Peak Registry only. NHS, PK deficiency Natural History Study; NT, never transfused; PK, pyruvate kinase

### Monitoring among the 42 patients who were NT with ≥12 months of retrospective data

- Clinical monitoring received during registry participation (and recent pre-baseline history) included lab assessments for hemoglobin (97.6%), reticulocytes (85.7%), and ferritin (95.2%) (**Table 4**)
- Bone health was monitored via 25-hydroxyvitamin D levels (23.8%) and DEXA scan (12.9% [only assessed in the Peak Registry])
- Cardiovascular monitoring occurred in 37.5% and 19.4% of NHS and Peak Registry patients, respectively
- MRI for iron assessment (liver and/or cardiac) was performed for 28.6% of patients (NHS and Peak Registry pooled data)
- Among 5 patients with ongoing chelation therapy (treatment durations ranged from 2.3 to 6.1 years), all had registry documentation of ferritin monitoring, and none had a liver iron concentration evaluation via MRI

Table 4. Disease monitoring among NT patients with PK deficiency (1/2)

Disease monitoring* (documented during registry participation)	NT* (N=55)	NT 12M+ subgroup* (N=42)	Anemia not very severe/symptomatic subgroup* (N=34)
<b>Iron assessment, n/N (%)</b>			
Any of the iron assessments	51/55 (92.7)	40/42 (95.2)	34/34 (100.0)
<b>Iron assessment details, n/N (%)</b>			
Ferritin	48/55 (87.3)	40/42 (95.2)	31/34 (91.2)
MRI for iron assessment	14/55 (25.5)	12/42 (28.6)	10/34 (29.4)
Transferrin saturation†	22/45 (48.9)	20/32 (62.5)	21/34 (61.8)
<b>Cardiovascular, n/N (%)</b>			
Echocardiogram‡	9/24 (37.5)	9/24 (37.5)	6/13 (46.2)
Cardiac assessment (ECG, MUGA, other)§	7/43 (16.3)	6/31 (19.4)	6/33 (18.2)
<b>Bone health, n/N (%)</b>			
25-hydroxyvitamin D levels	11/55 (20.0)	10/42 (23.8)	8/34 (23.5)
DEXA scan¶	4/44 (9.1)	4/31 (12.9)	3/33 (9.1)

N represents the number of patients with data available. \*Data only available from 1 registry for some monitoring procedures; †NT = subject has never been transfused up to data cutoff date; \*NT 12M+ = NT with ≥12 months of retrospective data; \*Anemia not very severe/symptomatic = NT with documented rationale of "Anemia not very severe" and/or "Anemia not symptomatic"; only common terms reported in both the Peak Registry and NHS were included; ‡Liver biopsy for iron was performed in 1 patient in the NT 12M+ subgroup from the NHS registry; §Data available from Peak Registry only; †Data available from NHS registry only; ECG, electrocardiogram; MRI, magnetic resonance imaging; MUGA, multigated acquisition; NHS, PK deficiency Natural History Study; NT, never transfused; PK, pyruvate kinase

Table 4. Disease monitoring among NT patients with PK deficiency (2/2)

Disease monitoring* (documented during registry participation)	NT* (N=55)	NT 12M+ subgroup* (N=42)	Anemia not very severe/symptomatic subgroup* (N=34)
<b>Laboratory, n/N (%)</b>			
Hemoglobin	48/55 (87.3)	41/42 (97.6)	31/34 (91.2)
Ferritin	48/55 (87.3)	40/42 (95.2)	31/34 (91.2)
% reticulocyte and/or absolute reticulocyte count	41/55 (74.5)	36/42 (85.7)	29/34 (85.3)
Total, direct, and/or indirect bilirubin	39/55 (70.9)	34/42 (81.0)	26/34 (76.5)
Transferrin saturation†	22/45 (48.9)	20/32 (62.5)	21/34 (61.8)
<b>Among those with iron overload, n/N (%)</b>	<b>N=21</b>	<b>N=16</b>	<b>N=12</b>
<b>Endocrinopathy panel:</b>			
thyroid hormone, sex hormones‡	6/8 (75.0)	6/8 (75.0)	3/3 (100.0)
Fructosamine§	0/8	0/8	0/3
Endocrinopathy panel: sex hormones¶	3/17 (17.6)	3/12 (25.0)	3/12 (25.0)
<b>Among those with ongoing chelation, n/N (%)</b>	<b>N=7</b>	<b>N=5</b>	<b>N=4</b>
Ferritin	6/7 (85.7)	5/5 (100.0)	3/4 (75.0)
Creatinine**	3/3 (100.0)	3/3 (100.0)	1/1 (100.0)

N represents the number of patients with data available. \*Data only available from 1 registry for some monitoring procedures; †NT = subject has never been transfused up to data cutoff date; \*NT 12M+ = NT with ≥12 months of retrospective data; \*Anemia not very severe/symptomatic = NT with documented rationale of "Anemia not very severe" and/or "Anemia not symptomatic"; only common terms reported in both the Peak Registry and NHS were included; †Data available from Peak Registry only; ‡Data available from NHS registry only; §Fasting glucose, oral glucose tolerance testing, or fructosamine measurements are recommended as glycated hemoglobin A1C measurements are unreliable in hemolytic anemia. NHS, PK deficiency Natural History Study; NT, never transfused; PK, pyruvate kinase

## LIMITATIONS

- Over- or under-reporting of disease monitoring may have occurred in the registries
- Potential for information bias due to inaccurate documentation, or missing data (some outcomes were only collected by 1 of the 2 registries)
- Registry sites tend to be specialty and/or academic centers of excellence; their monitoring/treatment practices may not be representative of the management of patients in community/primary care settings

## CONCLUSIONS

- Our findings show that NT patients with PK deficiency are at risk for complications, such as iron overload, gallstones, osteoporosis, extramedullary hematopoiesis, and pulmonary hypertension, that require monitoring
  - The most common reason for not transfusing included "Anemia not very severe" followed by "Anemia not symptomatic", yet even this subgroup of patients experienced disease complications
- Although patients were NT, other types of disease management procedures, including cholecystectomy, splenectomy, and mitapivat treatment were observed
- Observed medical monitoring practices among NT patients fall short of evidence-based recommendations in recently published guidelines, such as annual ferritin monitoring, annual liver iron concentration by MRI among those on chelation or consistent serum ferritin concentrations >500 ng/mL, echocardiography and DEXA scan screening in all patients ≥18 years, and vitamin D monitoring at all ages<sup>2</sup>
- Findings emphasize the need for evidence-based disease monitoring to be consistently implemented for all patients with PK deficiency, enabling early detection and management of complications
- Given the significant rate of complications in patients with PK deficiency who have never been transfused, treatment to improve anemia and reduce hemolysis should be considered in these patients



This study was funded by Agios Pharmaceuticals, Inc. Acknowledgments: We would like to thank the patients and study investigators for taking part in these studies (a full list of study investigators can be found in Supplemental table 5 [QR code]). Medical writing assistance was provided by Julie Gray of Adelphi Group, Macclesfield, UK, funded by Agios Pharmaceuticals, Inc.

