

AGE OF ONSET OF COMPLICATIONS IN PARTICIPANTS WITH PYRUVATE KINASE (PK) DEFICIENCY

Analysis From The Peak Registry

Presented at the 64th American Society of Hematology (ASH) Annual Meeting and Exposition, December 10–13, 2022, New Orleans, LA, USA, and Virtual



The Peak Registry is a global longitudinal study of individuals diagnosed with PK deficiency sponsored by Agios Pharmaceuticals, Inc.

BACKGROUND

Pyruvate kinase (PK) deficiency is a rare, hereditary form of anemia¹

- Chronic anemia is the primary consequence of PK deficiency, which leads to a spectrum of complications¹⁻³
- Individuals may develop certain complications at an early age, due to the disease or side effects of supportive treatments, and they may have greater severity of complications at an earlier or later age than experienced by the general population¹⁻³

OBJECTIVE

To describe the age of onset and age distribution of select symptoms, severity, and complications in individuals with PK deficiency enrolled in the Peak Registry.

Instructions



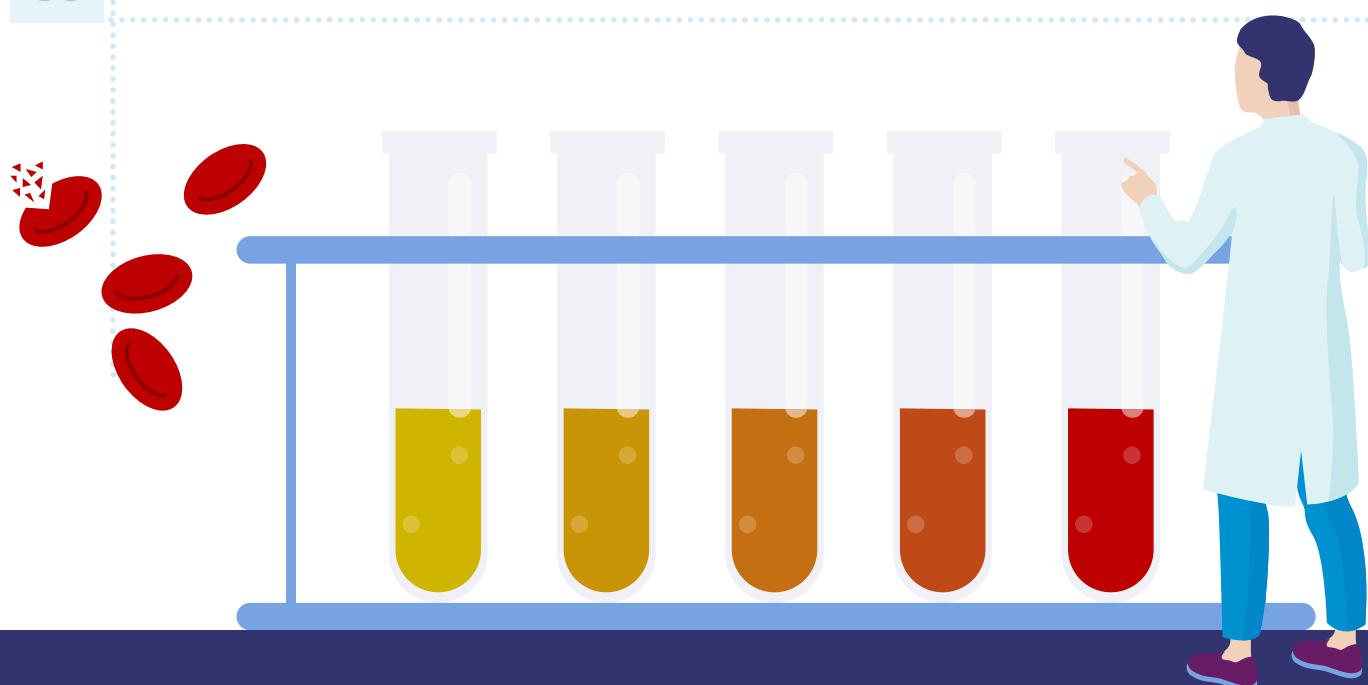
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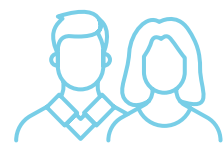


BASELINE CHARACTERISTICS

A total of 218 participants with available age data were included



101 pediatric participants
(younger than 18 years of age)

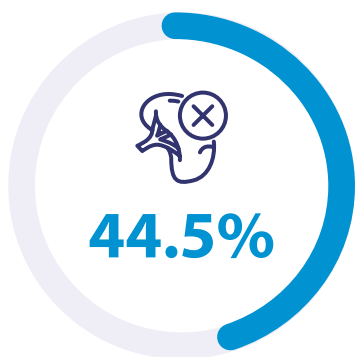


117 adult participants
(18 years of age or older)

The average age at enrollment was 19 years with an age range of birth to 77 years.

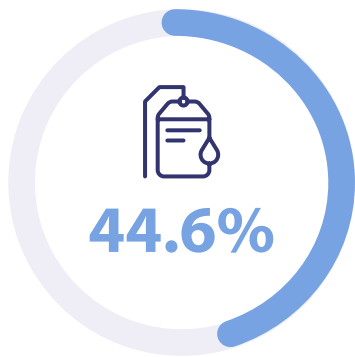


MEDICAL HISTORY OF THE PARTICIPANTS



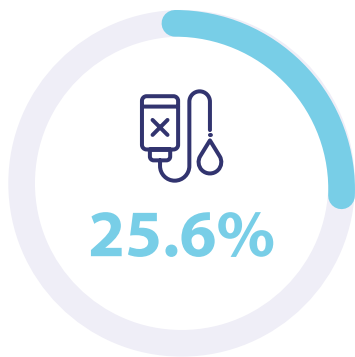
(participants who have had their spleen removed to improve anemia)

94 of 211 participants had a splenectomy prior to enrollment, at an average age of 6 years and a range of 1 to 27 years



(participants who had treatment to remove iron from the body)

90 of 202 participants had received chelation therapy prior to enrollment



Never received a transfusion
53 of 207 participants had never received a transfusion

* There are treatment benefits and risks. Consult with your physician.

HEMATOLOGIC AND IRON MARKERS



Overall Group



<18 years



≥18 years

average (range), g/dL

9.0 (5.8-18.3)



117 overall group

8.5 (5.8-14.4)



54 less than 18 years

9.5 (6.7-18.3)



63 18 years or older

average (range), µg/L

664 (17-6208)



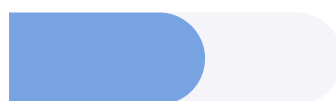
72 overall group

782 (51-3547)



27 less than 18 years

460 (17-6208)

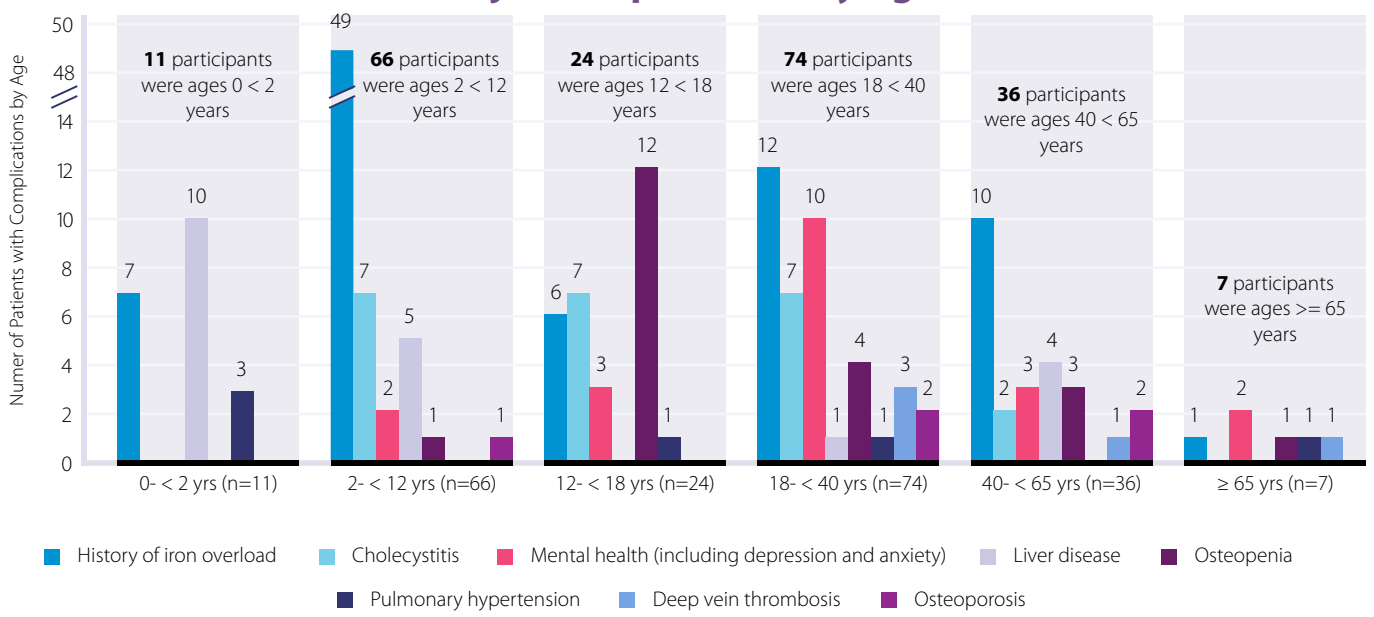


45 18 years or older

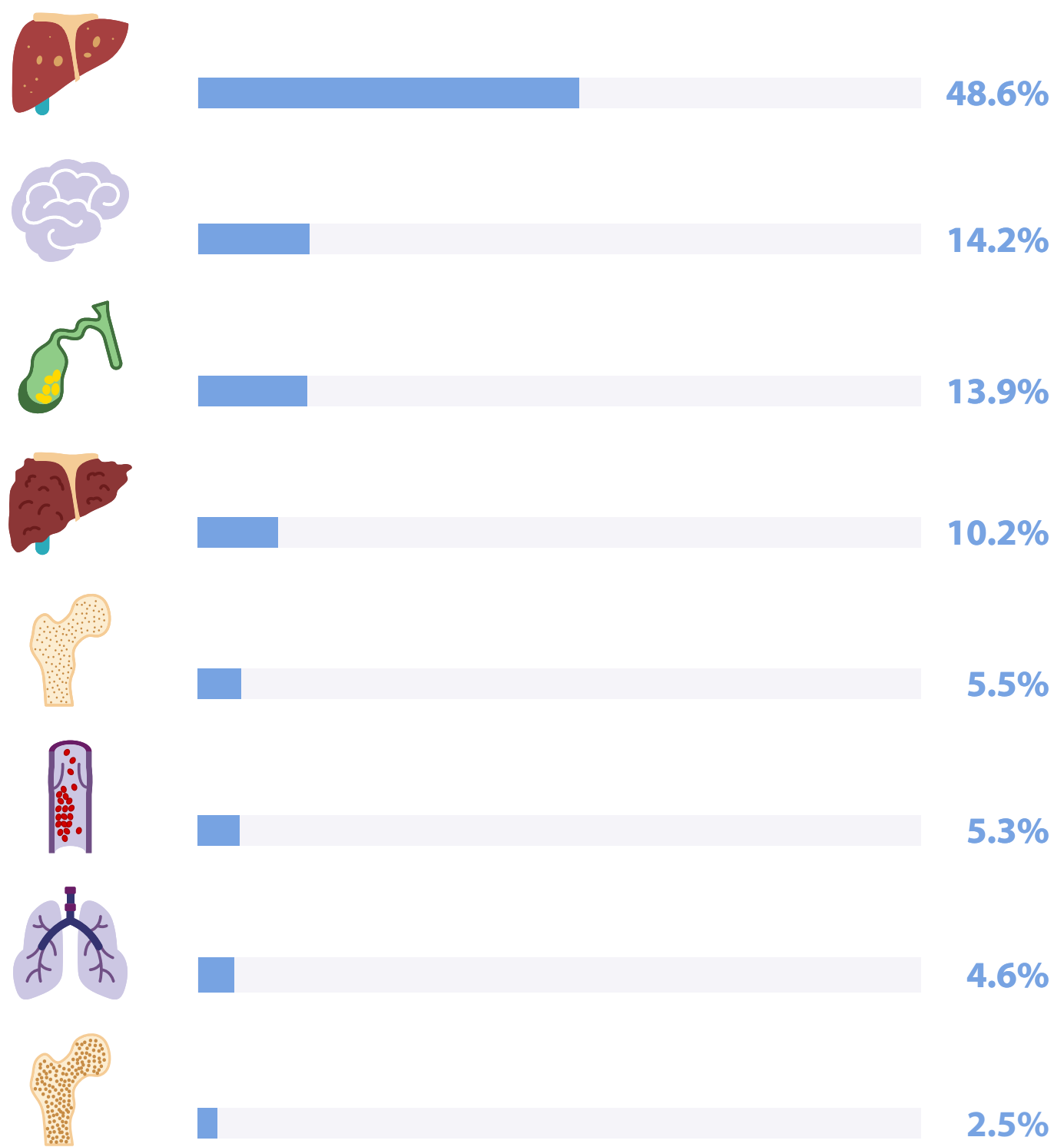
Ferritin levels tended to be higher in pediatric participants

AGE AT START OF COMPLICATIONS

Major Complications by Age



The most common diseases that occurred in the group included⁴⁻⁶:



When liver disease occurred early in individuals with PK deficiency, half these participants noticed disease onset at less than 2 years of age. The average age of onset was 1 year, with a range of 0 to 57 years.

Year of Birth: 1 year (average), 57 years (range)

Average age at start of complications was 35 years, with a range of 9 to 76 years.

9 years (range), 35 years (average), 76 years (range)

Average age at start of complications was 33 years, with a range of 9 to 64 years.

9 years (range), 33 years (average), 64 years (range)

HISTORY OF IRON OVERLOAD^{a,b}



72.9% of participants with history of iron overload had onset prior to 18 years of age



Among the remaining 27.1% of participants with iron overload, the complication began during adulthood (18 years or older)



Average age at start of complications was 5 years, with a range of 0 to 68 years



Iron overload occurred in 15.1% of participants who had never been transfused, with an average starting age of 50.5 years and a range of 47 to 68 years

^a Liver disease combines terms "cirrhosis", "nonalcoholic fatty liver disease," and "nonalcoholic steatohepatitis".
^b n=3 nonspecified mental health conditions.



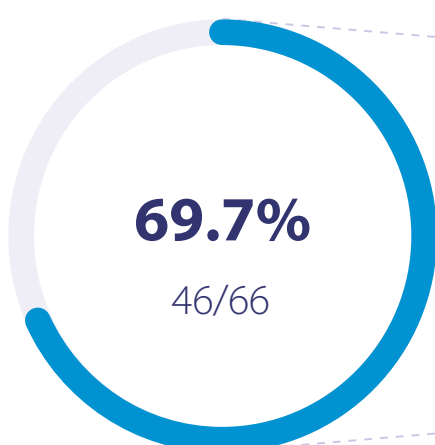
Of 67 participants with known onset age, the average age of the start of this complication was at birth, with a range of birth to 54 years.



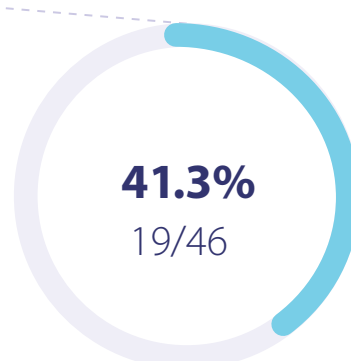
Participants With Ongoing Jaundice

Of 67 patients with jaundice and known onset age, average (range) age at onset was 0 years (0–54). Of these patients, 69.7% (46/66)* had ongoing jaundice at enrollment. **Ongoing jaundice occurred among pediatric and adult patients.**

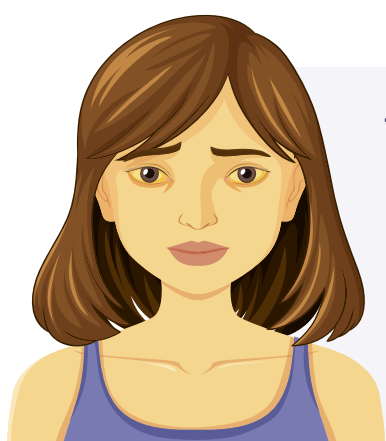
At enrollment, 46 out of 66 participants had active jaundice



Among those with active jaundice, 19 out of the 46 participants were 18 to less than 40 years of age



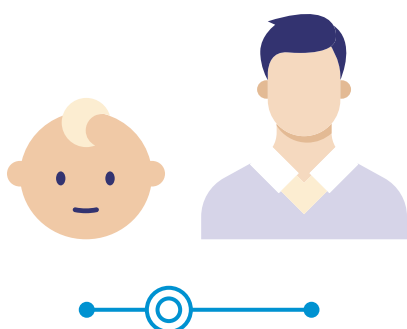
*n=1 missing



The overall average age of participants with ongoing jaundice was 16.5 years, with a range of at birth to 50 years of age.



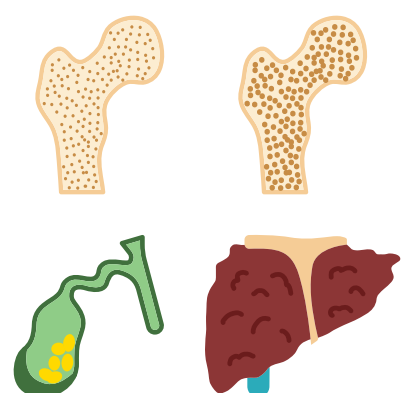
SUMMARY



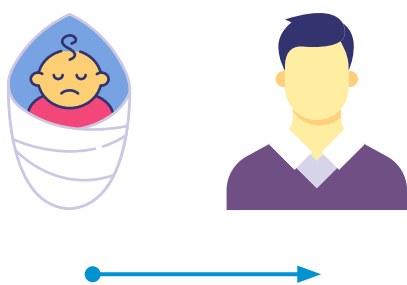
Individuals with PK deficiency have experienced a wide range of other diseases and complications throughout their lives, many of which occurred at an early age.



Participants 2 to less than 12 commonly experienced iron overload.



Osteopenia, osteoporosis, liver disease, and cholecystitis were observed at young ages, earlier than would be expected in the general population.⁵⁻⁷



Commonly observed very early in life, jaundice is a symptom that continues unresolved for many individuals with PK deficiency well into adulthood.

- Clinicians, including pediatric specialists, should be aware of the complications from PK deficiency.
- Early and regular monitoring can help prevent complications and improve overall outcomes for individuals living with PK deficiency.
- Early and regular monitoring of complications is strongly recommended for all individuals with PK deficiency.



References:

1. Grace RF et al. *Blood*. 2018;131:2183–92.
2. Boscoe AN et al. *Eur J Haematol*. 2021;106:484–92.
3. Chonat S et al. *Pediatr Blood Cancer*. 2021;68:e29148.
4. Grace RF et al. *Blood*. 2019;134:2223.
5. Lee J et al. *Endocrinol Metab*. (Seoul) 2013;28:180–91.
6. Sajja KC et al. *J Investig Med*. 2014;62:920–6.
7. NORD. Acute Cholecystitis. <https://rarediseases.org/rarediseases/cholecystitis/#:~:text=80%25%20of%20cases%20of%20acalculous,of%20age%2050%20and%20older>. Accessed July 9, 2023.



CHELATION THERAPY

- Chelation therapy reduces the amount of iron in your body. Iron overload is most common in people who receive blood transfusions.
- Some individuals with PK deficiency experience iron overload despite never receiving blood transfusions.
- Iron overload is a serious complication that can lead to organ damage over time.

8. Boscoe et al. Comorbidities and complications in adults with pyruvate kinase deficiency. *Eur J Haematol*. 2021 Apr;106(4):484-492.

CHOLECYSTITIS*

- Gallbladder inflammation

9. MedlinePlus.<https://medlineplus.gov/ency/article/000217.htm>. Accessed July 17, 2023.

DEEP VEIN THROMBOSIS*

- Deep vein thrombosis, or DVT, is a blood clot that forms in a vein deep in the body.
- There is a rare but potential risk of pulmonary embolism (lungs have an artery blocked by a blood clot) from DVT.

10. MedlinePlus.<https://medlineplus.gov/deepveinthrombosis.html>. Accessed July 17, 2023.

HEMOGLOBIN*

- Hemoglobin is a protein in your red blood cells that carries oxygen from your lungs to the rest of your body.
- Low hemoglobin is only one sign of anemia, a condition affecting how much oxygen your body is getting.
- The usual range of adult hemoglobin values:
Women: 11.9 - 14.8 g/dL
Men: 13.6 - 16.9 g/dL
- The usual range of hemoglobin values in children:
6 months to 2 years: 11 - 13.5 g/dL
2 to 6 years: 11 - 13.7 g/dL
6 to 12 years: 11.2 - 14.5 g/dL
12 to less than 18 years: Females: 11.4 - 14.7 g/dL; Males: 12.4 - 16.4 g/dL

11. UpToDate. <https://uptodate.com/contents/diagnostic-approach-to-anemia-in-adults>. Accessed March 7, 2023.

12. UpToDate. https://uptodate.com/contents/image/print?imageKey=PEDS%2F101544&topicKey=5927&search=complete%20blood%20count%20normal%20ranges&rank=1~150&source=see_link. Accessed March 7, 2023.

IRON OVERLOAD*

- History of iron overload defined at baseline as ever having received:
 1. chelation therapy
 2. phlebotomy for removal of iron
- or within 3 months of enrollment had any of the following:
 3. $\text{ferritin} > 1000 \text{ ng/mL}$
 4. liver MRI (an image obtained by magnetic resonance imaging) (including FerriScan®) $\text{greater than } 3 \text{ mg Fe/g (Iron/gram) dry weight}$;
 5. cardiac T2 MRI (identifies abnormal myocardial tissue iron levels) less than or equal to 20 ms (milli-second)

13. National Library of Medicine.<https://ncbi.nlm.nih.gov/books/NBK526131>. Accessed July 17, 2023

JAUNDICE*

- Jaundice is a yellow color of the skin, mucus membranes, or eyes. The yellow coloring comes from bilirubin, a byproduct of old red blood cells. Jaundice can be a symptom of several health problems.

14. MedlinePlus.<https://medlineplus.gov/jaundice.html>. Accessed July 17, 2023.

LIVER DISEASE*

- Nonalcoholic steatohepatitis (liver damage caused by a buildup of fat in the liver), nonalcoholic fatty liver (buildup of fat in the liver), Hepatic cirrhosis (chronic liver damage with scarring and liver failure), hepatomegaly (extra-large liver)

15. MedlinePlus.<https://medlineplus.gov/liverdiseases.html#summary>. Accessed July 17, 2023.

MENTAL HEALTH ISSUES*

- Anxiety, depression

16. MedlinePlus.<https://medlineplus.gov/mentalhealth.html>

OSTEOPENIA

- Low bone mass that is not low enough to be osteoporosis is sometimes called osteopenia.

17. MedlinePlus.<https://medlineplus.gov/bonedensity.html>. Accessed July 10, 2023.

OSTEOPOROSIS

- Osteoporosis is a disease of thin and weak bones.

18. MedlinePlus.<https://medlineplus.gov/osteoporosis.html>. Accessed July 10, 2023.

PULMONARY HYPERTENSION

- Pulmonary hypertension (PH) is high blood pressure in the arteries to your lungs.

19. MedlinePlus.gov/pulmonaryhypertension.html. Accessed July 10, 2023.

SERUM FERRITIN

- Serum ferritin is a protein that stores iron in the blood, muscle, and organ tissues.
- Iron is crucial for its ability to form healthy red blood cells.
- The usual range of ferritin in the blood depends on the age:

Adult females: 24 to 307 µg/L

Adult males: 24 to 336 µg/L

Newborns: 25 to 200 µg/L

1 month old: 200 to 600 µg/L

2 to 5 months old: 50 to 200 µg/L

6 months to 15 years: 7 to 140 µg/L

- Too much or too little iron can cause serious health problems.
- Ferritin levels greater than 1000 µg/L indicate iron overload, and levels greater than 500 µg/L require medical monitoring.

20. Urmc.rochester.edu. https://urmc.rochester.edu/encyclopedia/content.aspx?contenttypeid=167&contentid=ferritin_blood. Accessed February 23, 2023.

SPLENECTOMY

- Surgical removal of the spleen

21. Grace R. Pyruvate Kinase Deficiency: A Rare Genetic Disease That Affects Red Blood Cells. Basel, Switzerland: S. Karger Publishers Limited; 2019:1-40.

*Categories of symptoms, comorbidities, and complications (and consequences of PK deficiency, such as jaundice) with high clinical significance to either the adult or pediatric PK deficiency population were identified in collaboration with Peak Registry Steering Committee members and based on evidence previously reported in the literature and subsequently included in these analyses.

22. Secrest MH, Storm M, Carrington C, et al. *Eur J Haematol* 2020;105(2):173–184.

23. Boscoe AN, Yan Y, Hedgeman E, et al. *Eur J Haematol* 2021;106:484–492.

24. Chonat S, Eber SW, Holzhauser S, et al. *Pediatr Blood Cancer* 2021;68(9):e29148.

