Request for ICD-10-CM Code for Pyruvate Kinase (PK) Deficiency

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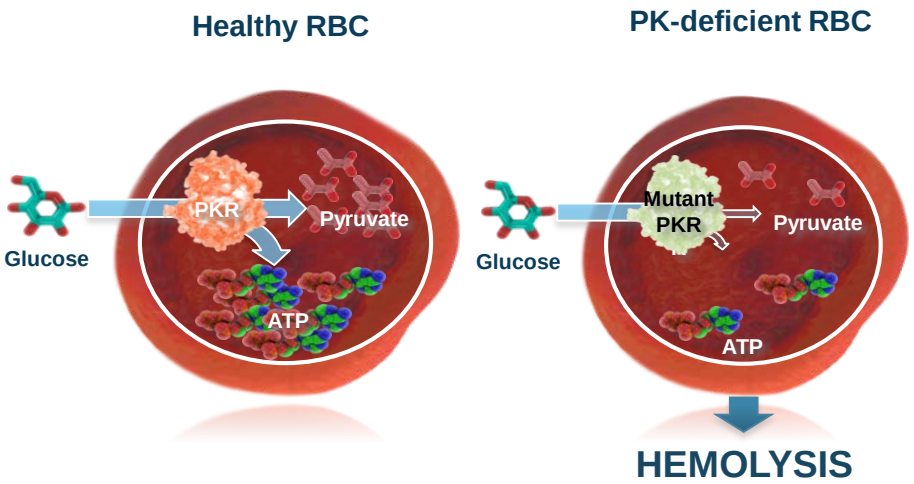
Pyruvate kinase (PK) deficiency is a rare and under-recognized congenital hemolytic anemia

Description

- PK deficiency is the most common red cell glycolytic enzyme defect[1]
- Caused by mutations in the *PKLR* gene, which result in reduced red-cell PK enzyme activity[2]
- Often presents in childhood[2,3]
- Characterized by a lifelong chronic hemolytic anemia associated with a serious disease burden and severe complications[3]
- Cases likely underestimated[4]
  - Diagnosed prevalence between 3.2 and 8.5 cases per million
  - Diagnosed and undiagnosed cases as high as 51 per million

1. van Beers EJ, et al. *Haematologica*. 2019;104(2):e51-e53 **2.** Grace RF, et al. *Am J Hematol.* 2015;90(9):825-830. **3.** Grace RF, et al. *Blood.* 2018;131(20):2183-2192. **4.** Secrest MH, et al. *Eur J Haematol*. 2020;105(2):173-184.

Pathophysiology of PK Deficiency



Mutation in *PKLR* gene

↓PK activity

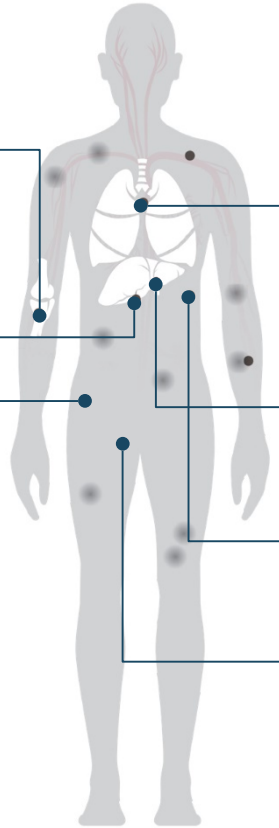
Inefficient glycolysis
↓ATP generation

↓RBC membrane integrity
↑RBC destruction[a]

Chronic hemolytic anemia

[a] In both spleen and liver, reticulocytes are particularly susceptible to destruction.

Patients with PK deficiency are at risk for serious long-term complications



Lifelong Hemolytic Anemia[1]

Iron Overload Independent of Transfusion History[2]

Jaundice[3]

Fatigue[3]

Extramedullary Hematopoiesis[3]

Gallstones[3]

Bone Deformities and Fractures[3]

Pulmonary Hypertension[3]

Liver Cirrhosis[3]

Splenomegaly[3]
Risk of thrombosis or infection post-splenectomy

Endocrine Abnormalities[3]

1. Grace RF, et al. *Am J Hematol*. 2015;90(9):825-830. **2.** van Beers EJ, et al. *Haematologica.* 2019;104(2):e51-e53 **3.** Grace RF, et al. *Blood*. 2018;131:2183-2192.

Once suspected, there is a well-defined diagnostic pathway for PK deficiency

When determining differential diagnosis, the following conditions may be considered and must be excluded[1,2]:

Acquired hemolytic anemia
- Autoimmune hemolytic anemia
- Paroxysmal nocturnal hemoglobinuria

Other hereditary hemolytic anemia
- Inherited disorders of RBC membranes; eg:
  Hereditary spherocytosis
  Hereditary elliptocytosis
- Inherited disorders in RBC enzymes; eg:
  Glucose-6-phosphate dehydrogenase deficiency
- Hemoglobinopathies; eg:
  Thalassemias, sickle cell disease

2 Tests Can Determine PK Deficiency:	Diagnostic Pathway	Diagnosis
Enzyme assay	• Measures PK enzyme activity	If either test is positive, the diagnosis is PK deficiency
Genetic testing	• Can be used to diagnose PK deficiency or to confirm a case based on decreased enzyme activity	

1. Posencheg MA, Dennery PA. Conn's Current 4. Therapy 2011: Expert Consult. 2010:424-427. **2.** Gallagher PG, Glader B. *Pediatr Blood Cancer*. 2016;63(5):771-772.

Current management of PK Deficiency[1,2]

	Selected clinical manifestations by patient group	Treatment
Newborns	▪ Hydrops ▪ Jaundice ▪ Marked anemia	▪ Phototherapy ▪ Exchange transfusion
Children/Adults	▪ Anemia ▪ Iron overload ▪ Gallstones ▪ Extramedullary hematopoiesis	▪ Transfusion ▪ Iron Chelation ▪ Splenectomy ▪ Cholecystectomy
Pregnant Women	▪ Exacerbation of anemia ▪ Preterm birth	▪ Transfusion

Limited case reports suggest that stem cell transplant is curative, but this approach is associated with significant documented risk, including death[3]

1. Grace RF, et al. *Br J Haematol.* doi:10.1111/bjh.15758. **2.** Grace RF, et al. *Am J Hematol.* 2015;90(9):825-830. **3.** van Straaten S, et al. *Haematologica.* 2017. doi: 10.3324/haematol.2017.177857.

Within the current code set, PK deficiency is classified under anemia due to disorders of glycolytic enzymes along with three other conditions[1]

Existing Nomenclature: Hemolytic anemias (D55)

- D55.2 Anemia due to disorders of glycolytic enzymes
  - Includes:

    Hemolytic nonspherocytic (hereditary) anemia, type II

    Hexokinase deficiency anemia

    Pyruvate kinase (PK) deficiency anemia

    Triose-phosphate isomerase deficiency anemia
  - Excludes 1: **Disorders of glycolysis not associated with anemia (E74.8)**

1. 2020 ICD-10-CM

PK deficiency is distinct from other anemias due to disorders of glycolytic enzymes

Other Anemias of Glycolytic Enzymes	Disease Features	PK deficiency Differentiating Factors[6,7,8]
Hemolytic nonspherocytic (hereditary) anemia type II	▪ There is currently no scientific literature available to contextualize this disease	▪ Most common of all these disorders (>500 cases reported) ▪ Well-defined disease caused by a different genetic mutation in the PKLR gene ▪ Affected enzyme is pyruvate kinase ▪ Complications vary among the different diseases ▪ There is currently a treatment in development to specifically target the defect in PK deficiency
Hexokinase deficiency anemia[1,2,3]	▪ Caused by mutations in the *HK1* gene ▪ Affected enzyme is hexokinase ▪ Approximately 30 cases reported ▪ Malformations, myelopathy and latent diabetes ▪ Treatment consists of transfusions and avoidance of environmental triggers of anemia	
Triose-phosphate isomerase deficiency anemia[4,5]	▪ Caused by mutations in the *TPI1* gene ▪ Affected enzyme is triose-phosphate isomerase ▪ Approximately 40 cases reported ▪ Cardiomyopathy, neurological degeneration and premature death ▪ Treatment may include transfusions or mechanical ventilation to support diaphragm paralysis	

1. GARD. https://rarediseases.info.nih.gov/diseases/3672/nonspherocytic-hemolytic-anemia-due-to-hexokinase-deficiency. Accessed September 1, 2020. **2.** Koralkova P, et al. *Blood Cells Mol Dis.* 2016;59:71-6. **3.** Rijksen G, et al. *Blood.* 1983;61(1):12-18. **4.** Genetics Home Reference. https://ghr.nlm.nih.gov/condition/triosephosphate-isomerase-deficiency#. Accessed September 1, 2020. **5.** Roland BP, et al. *J Cell Sci.* 2013;126(Pt14):3151-8. **6.** Grace RF, et al. *Am J Hematol*. 2015;90(9):825-830. **7.** Climent F, et al. *Cardiovasc Hematol Disor Drug Targets.* 2009;9(2):95-106 **8.** Grace RF, et al. *N Engl J Med.* 2019;381;10.

Summary

PK deficiency is a lifelong, chronic hemolytic anemia with serious complications

- Creating a unique code will aid in the following:
  - Improved accuracy of reporting PK deficiency to distinguish it from other less defined conditions that have different genetic, diagnostic, clinical and treatment characteristics
  - Improve diagnostic practices, treatment and follow-up of patients
    - More accurate tracking of patients after receipt of genetic testing
    - More accurate patient selection for targeted treatments
  - Facilitate further epidemiological research in the U.S. to continue to better understand this disease with the goal of improving management and longer-term outcomes for patients with this serious condition

The American Society of Hematology (ASH), which represents more than 18,000 clinicians and scientists committed to the study and treatment of blood disorders, has reviewed and supports this application

Thank you