Navigating pyruvate kinase deficiency today: How can the disease burden and unmet treatment needs be addressed?

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Agenda

What is our current understanding of the burden of disease and clinical presentation of pyruvate kinase deficiency?

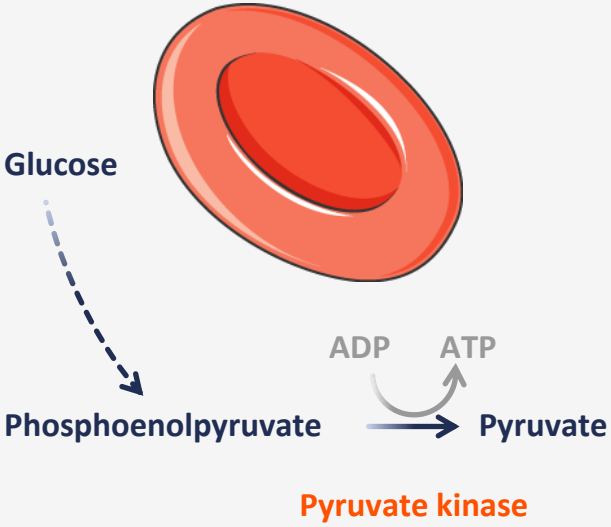
What therapies are currently available for pyruvate kinase deficiency and are there remaining unmet treatment needs?

What are the potential novel and emerging treatment approaches for patients with pyruvate kinase deficiency?

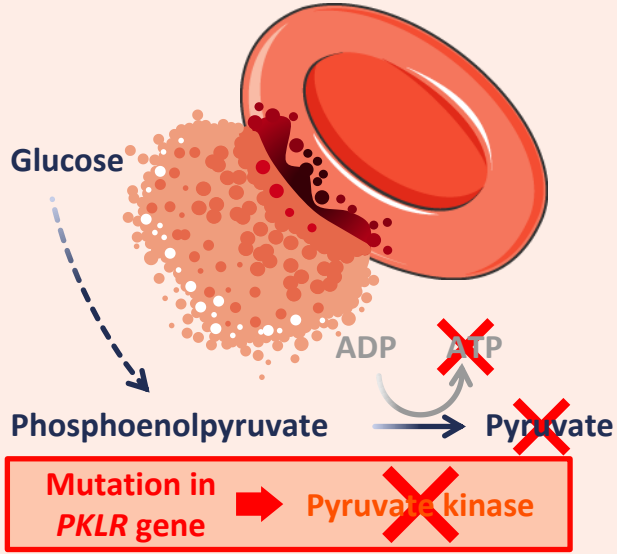
What is our current understanding of the burden of disease and clinical presentation of pyruvate kinase deficiency?

Pyruvate kinase deficiency leads to chronic haemolytic anaemia

Glycolysis in a healthy RBC



Glycolysis in an RBC in a patient with pyruvate kinase deficiency



- RBCs have reduced ATP production
- Normal membrane function compromised
- RBCs lose flexibility and are susceptible to premature haemolysis

Patients display signs and symptoms of haemolytic anaemia

Erythrocyte image: Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).
ADP, adenosine diphosphate; ATP, adenosine triphosphate; *PKLR*, pyruvate kinase, liver and RBC; RBC, red blood cell.
Alayash AI. *Haematologica.* 2021;106:9–11.

Pyruvate kinase deficiency is a rare genetic disorder that negatively impacts patient quality of life

Estimated prevalence 3.2–8.5 per million* although likely underdiagnosed[1]

- Affects males and females[2]
- Age at diagnosis varies based on symptoms and access to testing[3]

Over 400 pathogenic *PKLR* variants are known[4]

- Autosomal recessive, most compound heterozygous[5]
- Diagnosis made through a combination of low PK enzyme activity and genetic testing[6]

PK deficiency can negatively impact patient quality of life[7]

Physical limitations
Need for additional rest, difficulty with exercise

Daily activities
General negative impact on various activities, lack of motivation

Social and emotional impacts
Negative impact on social activities and relationships, concerns about the future

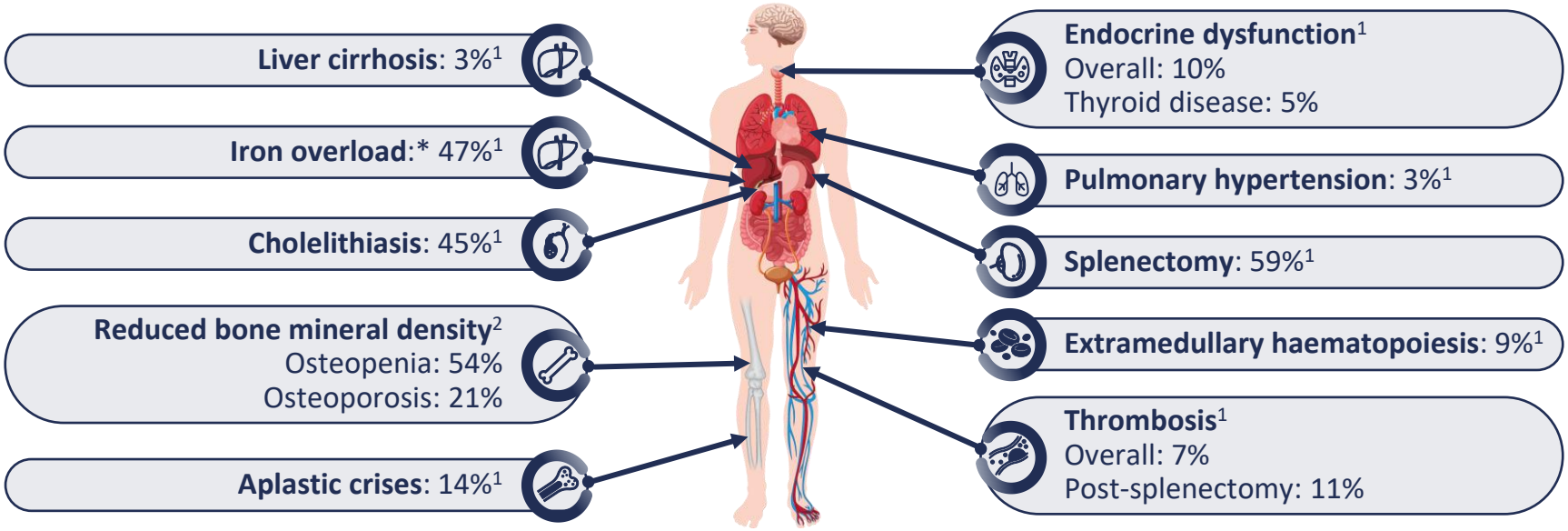
Negative impact on appearance
Looking pale, jaundiced, tired or generally unwell

*Western population.[1]

PK, pyruvate kinase; *PKLR*, pyruvate kinase, liver and red blood cell.

1. Secrest MH, et al. *Eur J Haematol.* 2020;105:173–84; 2. Grace RF, et al. *Br J Haematol.* 2019;184:721–34; 3. Grace RF, et al. *Am J Hematol.* 2015;90:825–30; 4. Leiden Open Variation Database. Available at: www.lovd.nl/PKLR (accessed 15 February 2023); 5. Bianchi P, et al. *Am J Hematol.* 2020;95:472–82; 6. Bianchi P, et al. *Am J Hematol.* 2019;94:149–61; 7. Grace RF, et al. *Eur J Haematol.* 2018;101:758–65.

PK deficiency is associated with comorbidities and long-term complications



Comorbidities and complications vary by age[3]

Data from different studies. All data from patients aged 0.1–69.9 years,[1] except for reduced bone mineral density data, which is from patients aged 18–78 years.[2]
*Ferritin level >1,000 ng/mL or had received chelation therapy in the 12 months prior to enrolment in the Pyruvate Kinase Deficiency Natural History Study.[1]
PK, pyruvate kinase. 1. Grace RF, et al. *Blood.* 2018;131:2183–92; 2. Al-Samkari H, et al. *Blood.* 2020;136(Suppl. 1):30–2; 3. Grace RF, Barcellini W. *Blood.* 2020;136:1241–9.

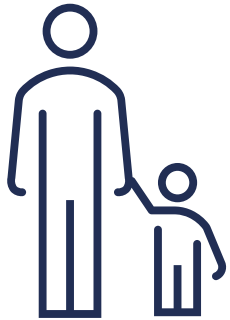
What therapies are currently available for pyruvate kinase deficiency and are there remaining unmet treatment needs?

Most current treatment options for pyruvate kinase deficiency are supportive

Treating the symptoms and complications of PK deficiency

- Blood transfusion[1,2]
- Splenectomy[1,2]
- Iron chelation[1,2]
- Cholecystectomy[1,2]
- Folic acid supplementation[2]

Given the wide variability of symptoms associated with PK deficiency, treatment is highly individualized[1]



Disease-modifying therapy for PK deficiency

- PK activator[1,3]

Curative treatment for PK deficiency

- Stem cell transplantation[2]

PK, pyruvate kinase.

1. Grace RF, Barcellini W. *Blood.* 2020;136:1241–9; 2. Morado M, et al. *Med Clin (Barc).* 2021;157:253.e1–253.e8;
3. FDA. Mitapivat PI. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2022/216196s000lbl.pdf (accessed 15 February 2023).

What are the potential novel and emerging treatment approaches for patients with pyruvate kinase deficiency?

Gene therapy aims to normalize red blood cell function and lifespan in patients with pyruvate kinase deficiency[1]

Patient with severe and/or transfusion-dependent anaemia due to **PK deficiency**[1]

HSPCs harvested from patient's peripheral blood[1,2]

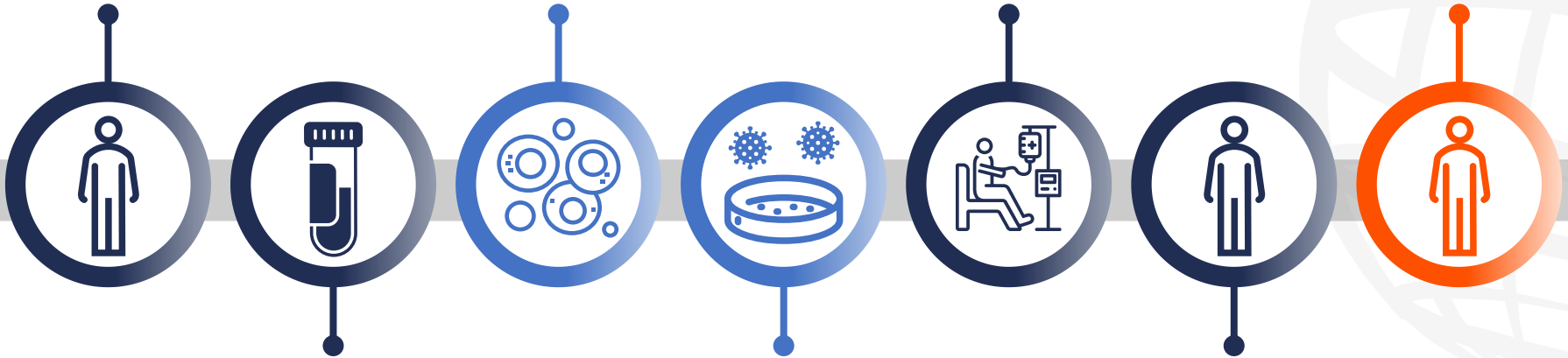
CD34⁺ HSPCs selected for genetic modification[1,2]

Genetic modification of HSPCs[1,2]

Myeloablative conditioning to create space in the patient's bone marrow for genetically modified cells[1,2]

Engraftment: Genetically modified cells are infused back into the patient[1,2]

PK production in RBCs, normal RBC function and lifespan[1]



HSPC, haematopoietic stem and progenitor cell; PK, pyruvate kinase; RBC, red blood cell.

1. Shah AJ, et al. Presented at: 64th ASH Annual Meeting, New Orleans, LA. 10–13 December 2022. Abstract 2138; 2. Germino-Watnick P, et al. *Cells.* 2022;11:1843.