



# Diagnosis and management of pyruvate kinase deficiency: international expert guidelines

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*Lancet Haematol* 2024;  
11: e228–39

Published Online  
February 5, 2024

[https://doi.org/10.1016/S2352-3026\(23\)00377-0](https://doi.org/10.1016/S2352-3026(23)00377-0)

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Pyruvate kinase (PK) deficiency is the most common cause of chronic congenital non-spherocytic haemolytic anaemia worldwide, with an estimated prevalence of one in 100 000 to one in 300 000 people. PK deficiency results in chronic haemolytic anaemia, with wide ranging and serious consequences affecting health, quality of life, and mortality. The goal of the International Guidelines for the Diagnosis and Management of Pyruvate Kinase Deficiency was to develop evidence-based guidelines for the clinical care of patients with PK deficiency. These clinical guidelines were developed by use of GRADE methodology and the AGREE II framework. Experts were invited after consideration of area of expertise, scholarly contributions in PK deficiency, and country of practice for global representation. The expert panel included 29 expert physicians (including adult and paediatric haematologists and other subspecialists), geneticists, laboratory specialists, nurses, a guidelines methodologist, patients with PK deficiency, and caregivers from ten countries. Five key topic areas were identified, the panel prioritised key questions, and a systematic literature search was done to generate evidence summaries that were used in the development of draft recommendations. The expert panel then met in person to finalise and vote on recommendations according to a structured consensus procedure. Agreement of greater than or equal to 67% among the expert panel was required for inclusion of a recommendation in the final guideline. The expert panel agreed on 31 total recommendations across five key topics: diagnosis and genetics, monitoring and management of chronic complications, standard management of anaemia, targeted and advanced therapies, and special populations. These new guidelines should facilitate best practices and evidence-based PK deficiency care into clinical practice.

## Introduction

Pyruvate kinase deficiency (PK deficiency) is the most common cause of chronic congenital non-spherocytic haemolytic anaemia worldwide, affecting at least one in 100 000 to one in 300 000 individuals.<sup>1–3</sup> An autosomal recessive disorder, PK deficiency results from mutations in the *PKLR* gene that encodes erythrocyte PK, an enzyme crucial for erythrocyte energy production and therefore normal erythrocyte function and lifespan.<sup>4</sup> PK deficiency is characterised by chronic haemolytic anaemia of variable severity, ranging from a mild asymptomatic anaemia to a life-threatening transfusion-dependent anaemia, as well as many chronic complications of haemolysis, including iron overload, reduced bone density, and cardiopulmonary complications.<sup>3,5,6</sup> PK deficiency is associated with increased overall mortality,<sup>7,8</sup> underscoring the significance of this diagnosis and its proper management. The clinical manifestations of PK deficiency also result in impairment of health-related quality of life (HRQoL),<sup>9–11</sup> which can be improved with effective disease management.<sup>12–14</sup> Accurate and timely diagnosis of PK deficiency is crucial for the administration of proper treatments, diagnosis, monitoring, prevention of disease complications, family planning and pregnancy care, and appropriate general medical care.<sup>3,15</sup>

The goal of the International Guidelines for the Diagnosis and Management of Pyruvate Kinase Deficiency (the International PKD Guidelines) was to develop comprehensive clinical guidelines informed by the best available evidence to improve the care of patients with PK

deficiency worldwide. As it is a rare disorder, the existence of such guidelines is crucial for universal access to expert and evidence-based diagnostic and care recommendations. In consideration of health-care resource limitations in low-income and middle-income countries, these guidelines include potential alternative management strategies if the recommended strategy is not possible.

## Methods

Recommendations for the International PKD Guidelines were developed with a guideline methodologist (NS) by use of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology<sup>16</sup> and conformed with the Appraisal of Guidelines for Research and Evaluation II (AGREE II) framework.<sup>17</sup> Five key topic areas were defined on the basis of input from PK deficiency experts and the PK deficiency patient community. To maximise quality, generalisability, and applicability, the process was systematic and evidence-based, with incorporation of expert opinion if evidence was insufficient by use of a transparent and structured consensus procedure.

The Guidelines Working Group (GWG) expert panel, led by co-chairs (HA-S and RFG), included clinical and genetic experts in PK deficiency from ten countries, including multiple medical specialties and subspecialties, a guidelines methodologist, laboratory specialists, health-care workers, patient advocacy representatives, caregivers of children with PK deficiency, and adults with PK deficiency (appendix p 3). Patient representatives and

Expert panel recommendations	COE	SOR	Agreement
A1 The expert panel recommends testing for PK deficiency in all patients with non-immune haemolytic anaemia after exclusion of haemoglobin disorders and erythrocyte membrane disorders	Moderate	Strong	91%
A2 The expert panel recommends initial testing for PK deficiency with either <i>PKLR</i> gene molecular analysis or PK enzyme activity (when done following established testing guidance) as both methods currently have similar performances in the diagnosis of PK deficiency	Moderate	Strong	95%
A3 The expert panel recommends confirmation of a diagnosis of PK deficiency initially made with PK enzyme activity measurements with <i>PKLR</i> gene molecular analysis	Moderate	Strong	91%
A4 The expert panel recommends confirmation of a diagnosis of PK deficiency initially made with <i>PKLR</i> gene molecular analysis with PK enzyme activity measurement in patients without two known pathogenic mutations in <i>PKLR</i>	Moderate	Strong	100%
A5 The expert panel recommends against the use of PK enzyme activity predicting disease severity or disease course	Moderate	Strong	96%

COE=certainty of evidence. International PKD Guidelines=International Guidelines for the Diagnosis and Management of PK Deficiency. PK=pyruvate kinase. SOR=strength of recommendation.

**Table 1: Clinical recommendations for the diagnosis and genetics of PK deficiency (A1–5) from the International PKD Guidelines**

caregivers of children with PK deficiency were included at every step of the guideline development process (CL, AW, RE, DP, and TS). GWG members were assigned to one key topic group—according to their experience and expertise—and developed key questions and prioritised outcomes to guide a formal literature review and ultimate development of the recommendations. The formal systematic literature search and development of evidence summaries, led by a medical librarian (KL-R) with input from the GWG co-chairs, was completed between April and June of 2023. Through a prespecified literature review process (appendix pp 4–14), including a review of each citation in duplicate, 368 articles were retrieved in full text formats for further review, and those meeting inclusion criteria were summarised in evidence summaries. Before the consensus conference, the key topic groups developed draft recommendations by use of GRADE.<sup>16</sup> Recommendation strength was categorised as strong or conditional and further defined in the appendix (p 15). Draft recommendations were distributed to all GWG members before the consensus meeting (which took place in July, 2023, in Boston, MA, USA) and all GWG members completed disclosures that were reviewed by the co-chairs and also distributed to the GWG before the conference.

At the conference, a structured consensus procedure was strictly followed (appendix p 15) following presentation of evidence summaries and recommendations. Anonymous voting was done with a prespecified agreement of greater than or equal to 67% for inclusion in the final guidelines. GWG members abstained from voting in the setting of substantial conflicts of interest (eg, first or senior authorship on clinical trial publications considered key evidence in the drafting of the recommendation). Recommendations failing to reach this agreement threshold on initial vote underwent review to identify areas of disagreement, followed by revision and a second vote, also requiring greater than or equal to 67% agreement for inclusion in the revised recommendation.

The draft manuscript and recommendations underwent comprehensive external review by 22 topic experts, general haematologists, and guidelines experts who were not involved with the guideline creation, and their comments were collected and addressed (appendix pp 41–42).

## Recommendations

Comprehensive clinical considerations, a detailed discussion, and references that formed the basis for each recommendation are included in full in the appendix (pp 16–38). Draft recommendations not achieving the agreement threshold are also included in the appendix (p 43).

### (A) Diagnosis and genetics of PK deficiency

The clinical presentation of PK deficiency includes the usual hallmarks of chronic haemolysis—anaemia, jaundice, and abnormalities in laboratory haemolysis markers—that are also seen in other forms of hereditary haemolytic anaemia.<sup>3,5,6</sup> The diagnosis can be made from the newborn period to adulthood due to variability in the degree of haemolysis and disease manifestations. The rarity of the disease and wide clinical spectrum can result in diagnostic challenges, including misdiagnosis and underdiagnosis.<sup>18</sup> Laboratory diagnosis of PK deficiency ultimately depends on the demonstration of decreased enzyme activity and the identification of causative mutations in the *PKLR* gene.<sup>18</sup> Table 1 summarises the diagnostic and genetic testing guideline recommendations with the certainty of the evidence, the strength of the recommendation, and the level of agreement reached for each.

#### Recommendation A1

The expert panel recommends testing for PK deficiency in all patients with non-immune haemolytic anaemia after exclusion of haemoglobin disorders and erythrocyte membrane disorders.

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See Online for appendix

Given the high phenotypic variability, misdiagnosis of patients with PK deficiency is possible.<sup>18,19</sup> PK deficiency should be considered in all patients after haemoglobinopathies and membranopathies have been excluded, particularly in those with evidence of dyserythropoiesis (including those originally diagnosed with a congenital dyserythropoietic anaemia that is not confirmed at the molecular level),<sup>20</sup> all patients with unexplained compensated or transfusion-dependent anaemia, and neonates with unexplained indirect hyperbilirubinemia. Because inherited red blood cell (RBC) abnormalities are common, co-inheritance with other erythrocyte defects should be considered.

#### Recommendation A2

The expert panel recommends initial testing for PK deficiency with either *PKLR* gene molecular analysis or PK enzyme activity (when done following established testing guidance) as both methods currently have similar performances in the diagnosis of PK deficiency.

If possible, the diagnostic evaluation should be done in an expert reference centre. The sensitivity of PK enzyme testing (approximately 80–90%) can be improved (>95%) when evaluated against another age-dependent RBC enzyme (PK:hexokinase ratio).<sup>21,22</sup> The choice to use molecular testing or enzyme assay as the first step in diagnosis is directed by clinical circumstances (for example, PK enzyme assays are unreliable if an RBC transfusion has been administered in the preceding 90 days),<sup>18</sup> by test availability, and payor or national health system recommendations and coverage. More than 300 known pathogenic mutations in *PKLR* have been identified.<sup>4</sup> Single-gene *PKLR* exon sequencing and multigene next-generation sequencing haemolytic anaemia panels are both reliable methods for PK deficiency diagnosis,<sup>23,24</sup> but can result in false-negative results due to pathogenic intronic variants, mutations in regulatory regions, non-canonical splice site mutations, or large deletions.<sup>19,24</sup>

#### Recommendation A3

The expert panel recommends confirmation of a diagnosis of PK deficiency initially made with PK enzyme activity measurements with *PKLR* gene molecular analysis.

Upon identification of decreased PK enzyme activity, *PKLR* genotyping should be done where possible as enzyme activity alone cannot reliably discriminate between the homozygote or compound heterozygote (disease) state and the heterozygote (carrier) state, cannot distinguish primary (congenital) from secondary (acquired) PK deficiency, and can be reduced due to mutations in genes other than *PKLR* (eg, *KLF1* or *GATA1*).<sup>18,25,26</sup>

#### Recommendation A4

The expert panel recommends confirmation of a diagnosis of PK deficiency initially made with *PKLR* gene molecular analysis with PK enzyme activity

measurement in patients without two known pathogenic mutations in *PKLR*.

Confirmatory reduced PK enzyme activity should be obtained where possible to confirm pathogenicity of novel *PKLR* variants or variants of unknown significance detected by molecular testing.<sup>18,19</sup>

#### Recommendation A5

The expert panel recommends against the use of PK enzyme activity predicting disease severity or disease course.

No relationship exists between PK enzyme activity and either genotype or clinical phenotype.<sup>18,19</sup> Therefore, the use of PK enzyme testing is limited to initial diagnostic testing only.

### (B) Monitoring and management of chronic complications of PK deficiency

PK deficiency can result in a range of chronic complications, including iron overload, bone mineral density disorder, cardiopulmonary disease, and others.<sup>3,5,6</sup> Comprehensive longitudinal data related to iron overload are not available for PK deficiency. However, the PK Deficiency Natural History Study provided evidence that iron overload develops even in the absence of RBC transfusions,<sup>6,27</sup> as observed in other chronic haemolytic anaemias, such as thalassemia. Data also suggest that individuals with PK deficiency have ineffective erythropoiesis on the basis of hepcidin, erythroferrone, and other markers.<sup>20</sup> Therefore, as in thalassemia, dysregulated iron metabolism and increased iron absorption from the intestine is believed to account for the development of iron overload in the absence of transfusions. The expert panel took available data for PK deficiency and extrapolated from the extensive data available for thalassemia to inform development of these recommendations. Tissue iron and serum ferritin thresholds were derived from the thalassemia literature and used to establish optimal goals for monitoring and treatment of PK deficiency. Table 2 summarises the monitoring and management guideline recommendations with the certainty of the evidence, the strength of the recommendation, and the level of agreement reached for each.

#### Recommendation B1

The expert panel recommends screening for iron overload with serum ferritin in children and adults with PK deficiency to detect and avoid complications of iron overload—irrespective of transfusion status—beginning aged 3 years or after 12 transfusion episodes, whichever occurs first.

Although evidence highlighting the risk, consequences, and management of iron overload in PK deficiency is scarce,<sup>6,27</sup> existing data are concordant with more exhaustive studies done in patients with both non-transfusion dependent thalassemia and transfusion-dependent

Expert panel recommendations	COE	SOR	Agreement
B1 The expert panel recommends screening for iron overload with serum ferritin in children and adults with PK deficiency to detect and avoid complications of iron overload—irrespective of transfusion status—beginning aged 3 years or after 12 transfusion episodes, whichever occurs first	Low	Strong	100%
B2 The expert panel recommends measurement of LIC by use of MRI in children and adults with PK deficiency with consistent serum ferritin concentrations >500 ng/mL to detect and avoid complications of hepatic iron overload, irrespective of transfusion status	Low	Strong	100%
B3 The expert panel recommends cardiac iron measurement by use of MRI in all patients with PK deficiency with LIC >7 mg/g dry weight to detect and avoid complications of cardiac iron overload, irrespective of transfusion status	Low	Strong	92%
B4 The expert panel recommends iron chelation therapy in patients with PK deficiency aged 2 years or older who have an LIC >5 mg/g dry weight, irrespective of transfusion status, to reduce the risk of complications from iron overload	Low	Strong	100%
B5 The expert panel recommends iron chelation therapy in patients with PK deficiency 2 years or older who have received >12 transfusions or have serum ferritin concentrations >1000 ng/mL, to reduce the risk of complications from iron overload	Low	Strong	100%
B6 The expert panel suggests echocardiography in all patients 18 years or older with PK deficiency to screen for pulmonary hypertension	Very Low	Conditional	100%
B7 The expert panel recommends annual 25-hydroxy vitamin D measurement beginning aged 1 year in all patients with PK deficiency not on regular vitamin D supplementation to detect and treat vitamin D deficiency and reduce the risk of bone density loss	Low	Strong	100%
B8 The expert panel recommends screening for reduced bone mineral density by use of dual-energy x-ray absorptiometry scanning in all patients with PK deficiency beginning aged 18 years to diagnose and manage low bone mineral density, osteopenia, and osteoporosis	Low	Strong	92%
B9 The expert panel recommends age-appropriate laboratory endocrine monitoring in patients with PK deficiency receiving regular transfusions and in patients not receiving regular transfusions who have iron overload, defined as serum ferritin concentrations >1000 ng/mL or LIC >5 mg/g dry weight, to identify and treat endocrinological complications of iron overload	Low	Strong	100%
B10 The expert panel suggests monitoring of renal function in children and adults with PK deficiency, irrespective of transfusion status for early detection of renal dysfunction	Low	Conditional	68%

COE=certainty of evidence. International PKD Guidelines=International Guidelines for the Diagnosis and Management of PK Deficiency. LIC=liver iron concentration. PK=pyruvate kinase. SOR=strength of recommendation.

**Table 2: Clinical recommendations for the monitoring and management of chronic complications of PK deficiency (B1–10) from the International PKD Guidelines**

thalassaemia.<sup>28,29</sup> Iron overload results in complications that can all potentially be avoided with effective iron chelation therapy.<sup>28,29</sup> Hence early assessment and initiation of chelation when appropriate could prevent complications. Ferritin-based monitoring frequency should be customised to each patient, although it must be done at least once a year. For patients receiving regular RBC transfusions, ferritin concentrations should be assessed every 1–3 months. Because ferritin is an acute phase reactant, if there are elevated concentrations in the context of inflammation, a repeat assessment is advised before proceeding with MRI. For example, it is unlikely that a child who has not had transfusions would develop iron overload by age 3 years, regardless of their ferritin level.

#### Recommendation B2

The expert panel recommends measurement of liver iron concentration (LIC) by use of MRI in children and adults with PK deficiency with consistent serum ferritin concentrations greater than 500 ng/mL to detect and avoid complications of hepatic iron overload, irrespective of transfusion status.

Liver iron overload can result in complications, including cirrhosis and hepatocellular carcinoma, with

substantial morbidity and mortality.<sup>30</sup> Where possible, MRI assessment of LIC is strongly recommended. For patients receiving regular RBC transfusions or iron chelation therapy, annual liver T2, T2\*, R2,<sup>31</sup> or R2\* MRI<sup>32</sup> should be done. Patients who do not receive regular transfusions might have LIC measurements done less frequently, based on trends in serum ferritin concentrations, but at least once every 5 years. For young children who do not receive regular transfusions, the initial liver MRI can be deferred until they are older than 5 years to balance the risks of sedation with the usefulness of the information to be gained from the MRI. It is unlikely that a child not receiving transfusions would develop iron overload by age 3–5 years. If serum ferritin concentrations are consistently elevated at a young age, other causes (ie, infection or inflammation) should be considered before an MRI is done under sedation.

#### Recommendation B3

The expert panel recommends cardiac iron measurements by use of MRI in all patients with PK deficiency with LICs greater than 7 mg/g dry weight to detect and avoid complications of cardiac iron overload, irrespective of transfusion status.



Cardiac iron overload can result in complications, including heart failure and arrhythmias, with substantial morbidity and mortality.<sup>33</sup> If available, cardiac T2\* MRI assessment of myocardial iron quantity could identify patients at risk for these complications and guide chelation therapy. Generally, experts agree that the risk of cardiac iron overload increases if the LIC exceeds 7 mg/g dry weight. In all patients with an LIC greater than 7 mg/g dry weight and in patients with a lower LIC, but who probably had periods with an LIC greater than 7 mg/g dry weight in the past, cardiac iron should be assessed by use of MRI. The cardiac T2\* should be maintained above 20 ms, which correlates with minimal or no iron deposition.<sup>34</sup> Cardiac T2\* and LIC do not correlate well since cardiac loading and unloading are both slower than in the liver.<sup>30</sup> Children should have their first cardiac T2\* at age 10 years if they are not receiving regular transfusions or are receiving transfusions but are well chelated. For patients receiving regular transfusions, monitoring is recommended every year (if they have a high LIC or ineffective chelation) or every 2 years (if LIC is in target range and they are effectively chelated). For patients not receiving regular transfusions, cardiac T2\* can be done less frequently, depending on their LIC.

#### *Recommendation B4*

The expert panel recommends iron chelation therapy in patients with PK deficiency aged 2 years or older who have an LIC exceeding 5 mg/g dry weight, irrespective of transfusion status, to reduce the risk of complications from iron overload.

Chelator agent selection, dosing, and monitoring is described in detail elsewhere.<sup>35</sup> If available, continued MRI LIC monitoring is important to establish the effectiveness of chelation and tailoring of the regimen. In individuals not receiving regular transfusions who have slower iron loading (than individuals receiving regular transfusions), LIC monitoring is important to establish if discontinuation of chelation is appropriate to avoid overchelation or chelator toxicity (possible when LIC is <2 mg/g dry weight).<sup>35</sup> In individuals receiving regular transfusions, annual LIC assessment will guide tailoring of the chelation regimen.

#### *Recommendation B5*

The expert panel recommends iron chelation therapy in patients with PK deficiency aged 2 years or older who have received greater than or equal to 12 transfusions, or have serum ferritin concentrations greater than 1000 ng/mL, to reduce the risk of complications from iron overload.

If LIC measurements are not available, serum ferritin or RBC transfusion thresholds can be used to trigger initiation of iron chelation.<sup>27</sup> Continued serum ferritin monitoring is important in these patients to establish chelation effectiveness and tailor the regimen.

#### *Recommendation B6*

The expert panel suggests echocardiography in all patients aged 18 years or older with PK deficiency to screen for pulmonary hypertension.

Pulmonary hypertension is an uncommon complication in PK deficiency<sup>6</sup> associated with substantial morbidity with severe effects on HRQoL.<sup>9</sup> Screening with echocardiography with the tricuspid regurgitation jet method can promote early detection of pulmonary hypertension and thus timely intervention,<sup>36</sup> potentially improving patient outcomes. The frequency of screenings should range between 1 and 5 years and should be tailored on the basis of individual risk factors, such as relevant symptoms, previous echocardiograph measurements, and history of splenectomy.

#### *Recommendation B7*

The expert panel recommends annual 25-hydroxy vitamin D measurement beginning aged 1 year in all patients with PK deficiency not on regular vitamin D supplementation to detect and treat vitamin D deficiency and reduce the risk of bone density loss.

Early-onset reduced bone mineral density, resulting in heightened fracture risk, is common in patients with PK deficiency irrespective of their transfusion status,<sup>6,37</sup> underscoring the importance of screening and treating all patients for vitamin D deficiency.

#### *Recommendation B8*

The expert panel recommends screening for reduced bone mineral density by use of dual-energy x-ray absorptiometry (DEXA) scanning in all patients with PK deficiency beginning aged 18 years to diagnose and manage low bone mineral density, osteopenia, and osteoporosis.

The frequency of monitoring should be tailored according to the results of previous DEXA scans and individual risk factors, such as fracture history, vitamin D status, and frequency of physical activity. Antiresorptive and osteoanabolic therapies can be initiated when appropriate to maintain and improve bone density. Younger patients diagnosed with low bone density (Z-score  $\leq -2.0$  in women in their reproductive phase and men <50 years) and older patients diagnosed with osteoporosis (T-score  $\leq -2.5$  in women who are post-menopause and men  $\geq 50$  years) should be referred to an endocrinologist if possible to manage treatment and oversee further DEXA monitoring.

#### *Recommendation B9*

The expert panel recommends age-appropriate laboratory endocrine monitoring in patients with PK deficiency receiving regular transfusions and in patients not receiving regular transfusions who have iron overload, defined as serum ferritin concentrations greater than 1000 ng/mL or LIC greater than 5 mg/g dry weight, to identify and treat endocrinological complications of iron overload.

Expert panel recommendations	COE	SOR	Agreement
C1 The expert panel recommends discussion of the individualised risks and benefits of splenectomy to treat anaemia in children older than 5 years and adults who require regular or frequent RBC transfusions, or who have symptomatic anaemia, to reduce transfusion burden and alleviate symptoms	Moderate	Strong	96%
C2 The expert panel recommends initiation of regular RBC transfusions in children younger than 5 years with PK deficiency who have symptomatic anaemia or anaemia that has an effect on growth and development, to improve symptoms and growth	Low	Strong	91%
C3 The expert panel recommends treatment with regular RBC transfusions in children 5 years and older and adults with PK deficiency who have symptomatic anaemia despite splenectomy or are unsuitable for or unwilling to undergo splenectomy to improve symptoms of anaemia	Low	Strong	92%
C4 The expert panel recommends that RBC transfusions be administered to children and adults with PK deficiency on the basis of anaemia symptoms and complications rather than a universal haemoglobin transfusion threshold	Low	Strong	87%
C5 The expert panel suggests that if a splenectomy is planned in a patient with PK deficiency, cholecystectomy is also considered and discussed with the patient, family, or caregiver	Low	Conditional	96%
C6 The expert panel recommends that appropriate psychological support be offered to children and adults with PK deficiency and their families or caregivers	Low	Strong	100%

COE=certainty of evidence. International PKD Guidelines=International Guidelines for the Diagnosis and Management of PK Deficiency. PK=pyruvate kinase. RBC=red blood cell. SOR=strength of recommendation.

**Table 3: Clinical recommendations for standard management of anaemia in PK deficiency (C1–6) from the International PKD Guidelines**

The heightened risk of thyroid, pancreatic, or pituitary dysfunction in patients with PK deficiency primarily pertains to those with iron overload.<sup>6,27,30</sup> Therefore, enhanced screening can be restricted to these individuals and directed by an endocrinologist. Because glycated haemoglobin A1c measurements are unreliable in haemolytic anaemia,<sup>38</sup> annual diabetes screenings with alternative measures (eg, fasting glucose, oral glucose tolerance testing, or fructosamine measurements) are recommended.

#### Recommendation B10

The expert panel suggests monitoring of renal function in children and adults with PK deficiency, irrespective of transfusion status for early detection of renal dysfunction.

Kidney disease, including hyperfiltration, hypercalciuria, and albuminuria in haemolytic anaemias is believed to occur from chronic anaemia, ongoing haemolysis, and free haem-mediated renal damage, as well as iron-mediated glomerular injury. Haemolysis-related renal injury can result from the production of reactive oxygen species and activation of inflammatory pathways.<sup>39</sup> Iron chelators, such as deferasirox, can additionally lead to renal tubular abnormalities, including renal tubular acidosis.<sup>40</sup> On the basis of the available data for other congenital haemolytic anaemias, the expert panel suggests monitoring renal parameters, including creatinine, phosphorus, and magnesium concentrations, albuminuria, and urine protein:creatinine ratios on the basis of individual risk factors (ie, underlying kidney dysfunction and chelation drugs).

#### (C) Standard management of anaemia in PK deficiency

Splenectomy and RBC transfusion are the two standard supportive treatment approaches to managing anaemia and associated symptoms in PK deficiency. As for most

rare diseases, there are no randomised controlled trials (RCTs) defining how or when these interventions should be used, and the following recommendations are based on observational and registry studies. A brief discussion of folic acid use in PK deficiency is in the appendix (pp 26–27).

Because of insufficient evidence, it was not possible to make recommendations regarding some important aspects of treatment, particularly whether regular transfusions or splenectomy should be used as the first-line treatment for patients with chronic symptoms of anaemia. This management decision-making has become complicated in adults with the emergence of PK activators in clinical treatment and will become increasingly complex as additional effective drugs emerge and trials are completed in children. Table 3 summarises the standard management guideline recommendations with the certainty of the evidence, the strength of the recommendation, and the level of agreement reached.

#### Recommendation C1

The expert panel recommends discussion of the individualised risks and benefits of splenectomy to treat anaemia in children older than 5 years and in adults who require regular or frequent RBC transfusions or who have symptomatic anaemia, to reduce transfusion burden and alleviate symptoms.

In a large observational study that included 150 patients with PK deficiency who underwent splenectomy, the transfusion burden was reduced in 90% of patients and haemoglobin concentrations increased by a mean of 1.6 g/dL, although 20% of patients had no response to splenectomy.<sup>6</sup> Patients with higher pre-splenectomy haemoglobin concentrations, lower bilirubin concentrations, and missense *PKLR* variants were more

likely to respond. Splenectomy is not curative and potential benefits must be balanced against the risks, including life-threatening infection,<sup>41,42</sup> thromboembolic disease, and late cardiovascular complications, including pulmonary hypertension and ischemic heart disease.<sup>43</sup> Therefore, the expert panel recommends that risks and benefits are discussed with the patients and their families, and decisions made based on individual preferences, availability of safe transfusions and iron chelation, and access to newer therapies. Additional recommendations regarding vaccination and post-splenectomy antibiotic prophylaxis are in the appendix (pp 25–26).

#### *Recommendation C2*

The expert panel recommends initiation of regular RBC transfusions in children younger than 5 years with PK deficiency who have symptomatic anaemia or anaemia that has an effect on growth and development, to improve symptoms and growth.

Due to insufficient evidence on the effect of severe anaemia on growth and development in children with PK deficiency, evidence is inferred from studies and guidelines on the management of other transfusion-dependent conditions, such as thalassemia. Regular transfusions are typically every 3–12 weeks to optimise childhood growth and development and treat symptoms of anaemia.

#### *Recommendation C3*

The expert panel recommends treatment with regular RBC transfusions in children aged 5 years and older and adults with PK deficiency who have symptomatic anaemia despite splenectomy or are unsuitable for or unwilling to undergo splenectomy to improve symptoms of anaemia.

Compared with splenectomy, regular transfusion offers a more predictable increase in haemoglobin concentration and can be modified or discontinued as circumstances change, but they require more time in hospitals and long-term iron chelation. Additional risks of regular transfusion include blood-borne infections, RBC alloimmunisation, and the need for regular intravenous access. Optimisation of childhood growth and development is crucial; in adults, regular transfusion is administered primarily to alleviate anaemia symptoms and improve HRQoL and the decision to initiate them is individualised between provider and patient.

#### *Recommendation C4*

The expert panel recommends that RBC transfusions be administered to children and adults with PK deficiency varies widely on the basis of anaemia symptoms and complications rather than a universal haemoglobin transfusion threshold.

Tolerance of anaemias vary between individuals and within the same individual at different points in the lifespan due to various factors. The decision to administer

unplanned or episodic transfusions should be on the basis of a combination of symptoms, laboratory results, circumstances, and patient and family preference, not on falling below or remaining above an arbitrary haemoglobin threshold.

#### *Recommendation C5*

The expert panel suggests that if a splenectomy is planned in a patient with PK deficiency, cholecystectomy is also considered and discussed with the patient, family, or caregiver.

Gallstone disease is common in PK deficiency as a complication of chronic haemolysis.<sup>6</sup> Given this risk, cholecystectomy at the time of a splenectomy might be beneficial and reduce the risk of future biliary complications, especially in patients with known gallstones or biliary sludge.

#### *Recommendation C6*

The expert panel recommends that appropriate psychological support be offered to children and adults with PK deficiency and their families or caregivers.

As with many chronic medical conditions, comorbid psychiatric complications, including anxiety and depression, are common in patients with PK deficiency and their caregivers.<sup>44</sup> Therefore, mental health should be discussed with patients and caregivers and services should be made available where appropriate.

### **(D) Targeted and advanced therapies**

The advent of a targeted activator of PK, mitapivat, has ushered in a new era of advanced therapy.<sup>14</sup> The only placebo-controlled RCT, ACTIVATE,<sup>12</sup> was done in adult patients not receiving regular transfusions, and a prospective single-arm trial, ACTIVATE-T,<sup>13</sup> was conducted in adults receiving regular transfusions.

Clinical trials of mitapivat in paediatric patients both receiving<sup>45</sup> and not receiving<sup>46</sup> regular transfusions are ongoing. Allogeneic transplantation is considered by members of the expert panel to be of potential use in carefully selected patients, but the published outcomes in case series have not been promising,<sup>47</sup> and few conclusions can be reached. Novel approaches, including gene therapy, are currently under study and are premature for recommendations from the expert panel at this time. Table 4 summarises the targeted and advanced therapy recommendations with the certainty of the evidence, the strength of the recommendation, and the level of agreement reached for each.

#### *Recommendation D1*

The expert panel recommends initiation of mitapivat therapy in adult patients with PK deficiency who are anaemic, who do not receive regular transfusions, and who do not have two non-missense mutations, irrespective of splenectomy status, to improve haemoglobin and HRQoL.

Expert panel recommendations	COE	SOR	Agreement
D1 The expert panel recommends initiation of mitapivat therapy in adult patients with PK deficiency who are anaemic, who do not receive regular transfusions, and who do not have two non-missense mutations, irrespective of splenectomy status, to improve haemoglobin and HRQoL.	High	Strong	100%
D2 The expert panel recommends patients with PK deficiency who do not receive regular transfusions and who do not respond to mitapivat should be declared as non-responsive to mitapivat only after at least 3 months of treatment with mitapivat at an optimal or maximum dose	High	Strong	100%
D3 The expert panel recommends initiation of mitapivat therapy in adult patients with PK deficiency who receive regular transfusions and who do not have two non-missense mutations, irrespective of splenectomy status, to reduce transfusion burden	Moderate	Strong	92%
D4 The expert panel recommends discontinuation of mitapivat therapy and return to best supportive care in patients with PK deficiency who do not respond to mitapivat, irrespective of transfusion status	Moderate	Strong	92%
D5 The expert panel recommends consideration of alternative approaches, including clinical trials, in patients with PK deficiency who do not respond to mitapivat, irrespective of transfusion status	Very Low	Strong	100%
D6 The expert panel recommends discontinuation of mitapivat therapy in patients with PK deficiency receiving regular transfusions who do not have at least a 33% reduction in transfusion requirement, with the exception of patients who have marked improvement in iron status, patient-reported health outcomes, jaundice, or other key disease parameters	Low	Strong	88%
D7 The expert panel recommends that adults with PK deficiency who receive regular transfusions and have not undergone splenectomy receive a trial of mitapivat therapy before consideration of splenectomy	Low	Strong	100%
D8 The expert panel suggests that PK deficiency-specific measures of HRQoL (patient-reported outcomes) can be a determining factor of success in individual trials of mitapivat in patients whose reduction in transfusion burden or increase in haemoglobin concentration does not reach an arbitrary numerical cutoff	Moderate	Conditional	82%

COE=certainty of evidence. HRQoL=health-related quality of life. International PKD Guidelines=International Guidelines for the Diagnosis and Management of PK Deficiency. PK=pyruvate kinase. SOR=strength of recommendation.

**Table 4: Clinical recommendations for targeted and advanced therapies in PK deficiency (D1–8) from the International PKD Guidelines**

This recommendation is based on the ACTIVATE phase 3 RCT for mitapivat.<sup>12</sup> The qualifications for age, transfusion status, and mutation status in the recommendation were eligibility criteria for enrolment on the ACTIVATE trial. The observation that mitapivat could be effective, regardless of splenectomy status, was made in both the phase 2 and 3 studies. Because mitapivat is an allosteric activator of the PK enzyme, it has no activity if the protein is absent (eg, in the presence of two null mutations; appendix p 31).<sup>48</sup> In addition to improvement of anaemia manifestations and HRQoL, data are emerging suggesting that mitapivat might ameliorate chronic complications of haemolysis, notably iron overload.<sup>49</sup> Along with monitoring for potential adverse effects of treatment, standard monitoring for complications of PK deficiency should be continued in patients receiving mitapivat.

#### Recommendation D2

The expert panel recommends that patients with PK deficiency who do not receive regular transfusions and who do not respond to mitapivat should be declared as non-responsive to mitapivat only after at least 3 months of treatment with mitapivat at an optimal or maximum dose.

The expert panel recommends dose optimisation of mitapivat according to the drug prescribing information. For many patients in the mitapivat group of the ACTIVATE trial,<sup>12</sup> haemoglobin improvement occurred less than 1 month after initiation at an optimal dose (appendix p 32). However, as a potential delay in observing a benefit might arise (for example, due to an

intercurrent illness), 3 months should be sufficient to assess haemoglobin response in most patients.

#### Recommendation D3

The expert panel recommends initiation of mitapivat therapy in adult patients with PK deficiency who receive regular transfusions and who do not have two non-missense mutations, irrespective of splenectomy status, to reduce transfusion burden.

This recommendation is based directly on results of the prospective, single-arm phase 3 ACTIVATE-T trial of adults with PK deficiency receiving regular transfusions.<sup>13</sup> This trial showed a greater than or equal to 33% reduction in transfusion burden in 37% of patients, including 22% who had complete transfusion independence.

#### Recommendation D4

The expert panel recommends discontinuation of mitapivat therapy and return to best supportive care in patients with PK deficiency who do not respond to mitapivat, irrespective of transfusion status.

Neither the ACTIVATE nor ACTIVATE-T trials directly address management strategies in patients who do not respond to mitapivat as a trial outcome, but all the alternative treatment strategies discussed are available for these patients. The expert panel acknowledges that both splenectomy status and transfusion status are related to patient–physician decision making, not necessarily to underlying biology. Therefore, in a patient who does not respond to mitapivat, splenectomy could be an option and if the patient did not previously receive



	Expert panel recommendations (good practice statements)	Agreement
E1	The expert panel recommends regular monitoring of children and adults with PK deficiency by a haematologist, irrespective of transfusion status	96%
E2	The expert panel recommends that women with PK deficiency—irrespective of transfusion status—who are pregnant or are planning pregnancy be referred to a multidisciplinary fetomaternal team (including a haematologist, obstetrician, neonatologist, and other specialists as appropriate) to reduce maternal and fetal complications.	100%

International PKD Guidelines=International Guidelines for the Diagnosis and Management of PK Deficiency.  
PK=pyruvate kinase.

**Table 5: Clinical recommendations for special populations in PK deficiency (E1–2) from the International PKD Guidelines**

transfusions, a strategy of chronic transfusions plus iron chelation could also be initiated.

#### Recommendation D5

The expert panel recommends consideration of alternative approaches, including clinical trials, in patients with PK deficiency who do not respond to mitapivat, irrespective of transfusion status.

Despite a paucity of high-quality evidence, this recommendation is included by the panel to acknowledge the importance of novel therapeutic approaches as trials of alternative approaches become available in the future. For example, a case series of 16 patients with PK deficiency receiving allogeneic haematopoietic stem cell transplants has been published.<sup>47</sup> Lentiviral-mediated gene therapy has been studied in a phase 1 trial,<sup>50</sup> but the data are too preliminary for an expert panel recommendation at this time.

#### Recommendation D6

The expert panel recommends discontinuation of mitapivat therapy in patients with PK deficiency receiving regular transfusions who do not have at least a 33% reduction in transfusion requirement, with the exception of patients who have marked improvement in iron status, patient-reported health outcomes, jaundice, or other key disease parameters.

In the ACTIVATE-T trial, the proportion of patients with a transfusion reduction of greater than or equal to 33% was 37% over a duration of 24 weeks.<sup>13</sup> The review panel found it plausible that outcomes other than transfusion reduction success might be clinically meaningful and merit continued mitapivat treatment. These outcomes includes the ability to be more effectively chelated,<sup>49</sup> improved patient-reported outcome (PRO) measures, or substantially improved jaundice. The trial was not designed for these outcomes to be declared as successes, but they might be reasonable cause to continue the medication in selected patients receiving transfusions, with the caveat that mitapivat should not be considered as only an adjunctive iron chelator without other evidence of improvement.

#### Recommendation D7

The expert panel recommends that adults with PK deficiency who receive regular transfusions and have not undergone splenectomy receive a trial of mitapivat therapy before consideration of splenectomy.

Although a splenectomy is permanent and comes with potential irreversible harms and heightened lifelong risks,<sup>6,51</sup> mitapivat can be easily discontinued and has shown a favourable safety profile in clinical trials.<sup>12,13,48</sup>

#### Recommendation D8

The expert panel suggests that PK deficiency-specific measures of HRQoL (PRO) can be a determining factor of success in individual trials of mitapivat in patients whose reduction in transfusion burden or increase in haemoglobin concentration does not reach an arbitrary numerical cutoff.

In the ACTIVATE and ACTIVATE-T trials, responders had improvement in disease-specific PRO measures as secondary endpoints.<sup>12,13</sup> The expert panel recognises that PRO measures are therefore important in judging the success or failure of treatments.<sup>11,52</sup> Considering PRO measures could be an ideal demonstration of value to health authorities and payors when therapeutic responses fall short of a particular haemoglobin increment or transfusion reduction target.

#### (E) Special populations in PK deficiency

Distinct clinical monitoring and treatment needs have been identified at different ages and during pregnancy and are therefore crucial to address with specific testing and management recommendations. Table 5 summarises the guideline recommendations for special populations with the level of agreement reached for each.

#### Recommendation E1

The expert panel recommends regular monitoring of children and adults with PK deficiency by a haematologist, irrespective of transfusion status.

For infants diagnosed at birth, if possible, the expert panel recommends haematologist monitoring in close partnership with the general paediatrician to manage hyperbilirubinemia and growth aged 2, 4, and 12 weeks, followed by a transition to monitoring visits every 3 months (with interval primary care visits aged 2 and 4 months). Children younger than 5 years should be monitored by a haematologist every 3 months and children aged 5 years and older not receiving regular transfusions should be monitored by a haematologist every 6–12 months to evaluate growth, physical and pubertal development, hypersplenism, and signs of extramedullary haematopoiesis.<sup>53</sup> Although they are not a special population, adults with PK deficiency should be monitored at least annually, and usually more frequently, by a haematologist.

### Search strategy and selection criteria

Evidence for this guideline was systematically identified and evaluated with five search strategies in Ovid MEDLINE and Ovid Embase, described in the appendix (pp 4–14). The main searches were conducted on May 8, 2023. Two reviewers for each search (from KL-R, ET, CD, HN, and JR) reviewed the titles and abstracts of each record and independently applied the inclusion criteria to all search results to identify full text articles to be retrieved for further review. Both reviewers then independently reviewed the full text and indicated whether each study met the inclusion criteria. If both reviewers agreed, the study was included and progressed to the data extraction stage. Any disagreements were reviewed and resolved by discussion until concordance was fully satisfied. Included references were then compiled into evidence summaries that were used by the Guidelines Working Group throughout the development of guideline recommendations.

### Recommendation E2

The expert panel recommends that women with PK deficiency—irrespective of transfusion status—who are pregnant or are planning pregnancy be referred to a multidisciplinary fetomaternal team (including a haematologist, obstetrician, neonatologist, and other specialists as appropriate) to reduce maternal and fetal complications.

Given the potential benefits to pregnancy outcomes by avoiding severe anaemia, the expert panel recommends routine monitoring during pregnancy with a primary focus on anaemia and its associated complications. Pregnancy is a potential trigger for an increased rate of haemolysis and increased physiological stress and could trigger the initiation of an intrapartum regular transfusion regimen in patients not previously receiving regular transfusions. International guidelines for thalassemia recommend maintaining maternal haemoglobin concentrations greater than 10 g/dL to reduce maternal complications, prematurity, and fetal growth restrictions.<sup>54</sup> In a large population-based study, anaemia defined as haemoglobin concentrations less than 10.0 g/dL was associated with an increased risk of preterm delivery, low birthweight, the need for a Cesarean delivery, and placental complications.<sup>55</sup> This risk was further increased when haemoglobin concentrations were less than 8.0 g/dL.

### Future directions and dissemination and implementation strategies

Future priorities for research and guideline development and comprehensive dissemination and implementation strategies for the current guidelines are in the appendix (pp 39–40). These evidence-based guidelines will be freely and globally available to patients and clinicians, including adult and paediatric haematologists, general practitioners, other specialists, patients, and caregivers. Dissemination in multiple

languages will occur via a dedicated website, patient brochures, online webinars, podcasts, and social media, and endorsements and presentations from professional societies, reference networks, and patient advocacy foundations.

#### Contributors

HA-S and RFG contributed to guideline initiative conception and design and provided administrative, technical, and logistic support. HA-S, RFG, KL-R, PB, AG, SS, EJN, DCR, and SC contributed to data collection and writing the first draft of the manuscript. All authors contributed to data analysis and interpretation, critical revision of the intellectual content, and final approval of the manuscript.

#### Declaration of interests

HA-S reports grants or contracts in research funding to their institution from Agios, Sobi, Vadderis, Novartis, and Amgen and reports consulting fees from Agios, Sobi, Novartis, Argenx, Rigel, Moderna, Forma, and Pharmacosmos. SWE reports receiving support for attending meetings, travel, or both from Agios and is on data safety monitoring boards or advisory boards for Agios. JAR reports grants or contracts from Pfizer, Agios, Novartis, Sanofi, Sobi, and Dova, and is on data safety monitoring boards or advisory boards for Agios, Global Blood Therapeutics, and Novartis. SS reports grants or contracts from Bristol-Myers Squibb/Celgene, Forma, and Agios; reports consulting fees from Agios, Bluebird Bio, Fulcrum, Chiesi, Bristol-Myers Squibb/Celgene, and Vertex; reports honoraria from Plexus, Clinical Care Options, and Physicians' Education Resource; reports receiving support for attending meetings, travel, or both from Agios, Bristol-Myers Squibb/Celgene and Bluebird Bio; and is on data safety monitoring boards or advisory boards for CRISPR/Vertex. KL-R reports funding provided to the Centre for Effective Practice (an independent not for profit corporation) to conduct the systematic literature review in this work. DCR is on data safety monitoring boards or advisory boards for Agios. AW reports receiving support for attending meetings, travel, or both from Agios and reports being in leadership in an advocacy group (the Pyruvate Kinase Deficiency Foundation). CL reports receiving support for attending meetings, travel, or both from Agios and reports being in leadership in an advocacy group (Metabolic Support UK). EJN reports consulting fees from Saliogen, reports receiving support for attending meetings, travel, or both from Agios; reports stock or stock options in Saliogen; and is on data safety monitoring boards or advisory boards for Agios, Imara, Merck/Acceleron, Sobi, and Pfizer. PB reports grants or contracts from Agios; reports honoraria from Rocket; reports support for attending meetings, travel, or both from Agios; and is on data safety monitoring boards or advisory boards for Agios. RFG reports grants or contracts from Agios, Novartis, and Sobi; reports consulting fees from Agios; is on data safety monitoring boards or advisory boards (Sanofi); and reports being in leadership in other boards, societies, committees, or advocacy groups (PK Deficiency Advocacy Advisory Council, Thrive with PK Deficiency, and Rare Anemias International Network). DPe reports receiving support for attending meetings, travel, or both from Eurobloodnet; is on data safety monitoring boards or advisory boards for Eurobloodnet; and reports being in a leadership role in an advocacy group (Stichting Zeldzame Bloedziekten). WB reports consulting fees from Alexion, Agios, Novartis, Sobi, and Sanofi; reports honoraria from Agios, Novartis, and Sanofi; reports receiving support for attending meetings, travel, or both from Sanofi; and is on data safety monitoring boards or advisory boards for Novartis. AJS is on data safety monitoring boards or advisory boards for Vertex and Bluebird Bio. NS reports receiving support for attending meetings, travel, or both from Agios. OA reports grants or contracts from Agios; reports honoraria from Agios; reports receiving support for attending meetings, travel, or both from the German, Austrian, and Swiss Society for Pediatric Oncology and Hematology, the German Society for Neonatology and Pediatric Intensive Care, and Agios; and is on data safety monitoring boards or advisory boards for Agios. AG reports grants or contracts from Agios, Bristol-Myers Squibb, Novo Nordisk, Saniona, and Sanofi; reports consulting fees from Agios, Novo Nordisk, Pharmacosmos, and Vertex; and reports receiving support for attending meetings, travel, or both from AbbVie. MDMMP reports grants or contracts from Agios and is

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on data safety monitoring boards or advisory boards for Agios. SC reports grants or contracts in research funding to their institution from Agios; reports consulting fees from Agios; and is on data safety monitoring boards or advisory boards for Agios. EJV reports grants or contracts in research funding to their institution from Agios and Horizon Europe; reports consulting fees from Bristol-Myers Squibb and Agios; is on data safety monitoring boards or advisory boards for Imara Pharmaceuticals; and reports being in a leadership role in other boards (Sickle Cell Outcome Registry Research The Netherlands and Eurobloodnet). JLK reports consulting fees from Forma, Agios, and Chiesi and is on data safety monitoring boards or advisory boards for Agios. TAK reports grants to contracts in research funding to their institution from Agios, Forma, and Novo Nordisk; reports consulting fees from Forma and Novo Nordisk; and is on data safety monitoring boards or advisory boards for Agios, Forma, and Novo Nordisk). FG is on data safety monitoring boards or advisory boards for Addmedica, Vertex, Agios, Global Blood Therapeutics, and Novartis. KHM reports grants or contracts from Agios and Pfizer; reports consulting fees from Alexion, Agios, Bristol-Myers Squibb, Forma, Pfizer, Novo Nordisk, and Vertex; reports honoraria from Agios and Bristol-Myers Squibb; and is on data safety monitoring boards or advisory boards for Bioverativ, Sanofi, and Sangamo. All other authors report no competing interests.

#### Acknowledgements

We thank the patients with PK deficiency who have participated in the clinical studies, the data from which have made development of this evidence-based guideline possible. We thank Tamara Schryver, from Thrive with PK Deficiency, for her contributions to the GWG. We thank the Centre for Effective Practice in Toronto, Canada, for their assistance with the systematic literature review, including Ellen Tulchinsky, Christina DeLonghi, Hasmik Nazaryan, and John Robertson. We thank Miriam Johnson for her administrative assistance and Maher Al-Samkari for his assistance with creation of the guideline logo. Funding for this guideline was provided by an unrestricted grant from Agios Pharmaceuticals. The funding source played no role in the guidelines process, including no role in the conception of the guidelines, the guideline development process at any stage, the selection of the GWG, the design, reporting, or implementation of the guidelines, the manuscript and its review process, or the decision to submit the guidelines for publication. No representative from the funding source was invited or present at any guidelines planning meeting or the consensus conference.

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