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SUPPORTING INFORMATION

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Who should be eligible for gene therapy clinical trials in red blood cell pyruvate kinase deficiency (PKD)?: Toward an expanded definition of severe PKD

To the Editor:

Red blood cell pyruvate kinase deficiency (PKD) is an autosomal recessive disorder caused by *PKLR* gene mutations, resulting in nonspherocytic hemolytic anemia[1] (see S10–S12 in supplementary material). *PKLR* encodes the erythrocyte pyruvate kinase enzyme, a rate-limiting reaction in the glycolytic pathway essential for red-cell adenosine triphosphate (ATP) production. Homozygous or compound heterozygote *PKLR* variants range from those of unknown significance to missense mutations of variable severity to nonsense variants and massive deletions (see S3, S4 in supplementary material). Heterogenous clinical manifestations include severe transfusion-dependent anemia in early childhood, which may persist through adulthood or variably resolve; milder cases include incidentally discovered hemolysis with minimal or no transfusion requirements.[1]

PKD therapy consists of transfusions, iron chelation, and splenectomy, which is associated with modest hemoglobin increases and reduced transfusion requirements (see S5 in supplementary material). A small-molecule allosteric enzyme activator, mitapivat, is currently under FDA review, and is associated with increased hemoglobin and reduced hemolysis in subsets of non-transfusion-dependent and transfusion-dependent adult patients[2] (see S6, S7 in supplementary material). Allogeneic hematopoietic stem-cell transplant has been curative in some cases, although toxicity precludes its consideration as a standard-of-care (see S8 in supplementary material). Gene therapy utilizing lentiviral transduction of autologous hematopoietic stem and progenitor cells (HSPCs) has yielded results in two initial adult patients suggesting potential for extensive correction of anemia and

TABLE 1 Characterization of severe pyruvate kinase deficiency: proposed expansion of initial Zanella classification

Disease component	Zanella classification	Proposed expanded classification[a]
Pre-splenectomy		
Transfusion status	Transfusion-dependent	Transfusion-dependent[b] or
Hemoglobin	6.8 g/dL	<7.0 g/dL
Post-splenectomy		
Transfusion status	-	Transfusion-dependent[b] or
Hemoglobin	8.4 g/dL	<8.0 g/dL
Fatigue or energy symptom burden	-	Fatigue or energy-related symptoms limiting ADLs[c] (NCI CTCAE v5.0 grade 3) Fatigue or energy-related symptoms limiting instrumental ADLs[c] (NCI CTCAE v5.0 grade 2) not responsive to available medical therapy
Clinical manifestations	-	Extramedullary hematopoiesis/paravertebral masses despite appropriate anemia management Non-healing lower extremity ulcers despite appropriate anemia management Non-traumatic bone fractures Icterus limiting social interactions, educational or work activities and not responsive to available medical therapy and not resulting from concomitant genetic disorders
Iron overload	-	Liver iron concentration (LIC) ≥3 mg/g on T2* MRI despite appropriate iron chelation or in settings of intolerance to chelation therapy Cardiac iron T2* <20 ms on MRI despite chelation therapy or in settings of intolerance to chelation Other clinical manifestations of severe iron overload
Mutation	Stop codons, frameshift, splicing, large deletions	Homozygote or compound heterozygote stop codons, frameshift, splicing, large deletions (in the context of at least one of the above-mentioned disease manifestations)

[a]Symptoms and clinical findings must be ascribed to PKD and not to any additional medical condition.
[b]No single consensus definition of transfusion-dependence has been established. One set of criteria that has been endorsed by several experts and at least one publication (see S21 in supplementary material) is: ≥6 transfusion episodes per year, or ≥3 episodes per year for 2 consecutive years.
[c]Activities of daily living (ADLs) are eating (i.e., feeding oneself), bathing, dressing, toileting, mobility, and grooming. Instrumental ADLs include managing finances, handling transportation, shopping, preparing meals, using the telephone or other communications devices, managing medications, doing laundry, housework, and other basic home maintenance.

hemolysis[3] (see S9 in supplementary material). As gene therapy is evaluated in additional adult and pediatric patients, there is a need to more extensively categorize severe PKD. Categorization has been challenging because of disease heterogeneity, but is now facilitated by PKD Natural History Study (PKD NHS) results and patient-reported outcome research. We summarize recent literature, and propose a potential expanded categorization of severe PKD to facilitate identification of PKD patients most appropriate for ongoing gene- and cell-based evaluations.

PKD-associated molecular and clinical diversity is evident from over 350 reported pathogenic mutation variants, with increases anticipated from enhanced disease awareness and diagnostic methods enabling identification of cryptic splice site or intronic variants (see S4, S10, S11 in supplementary material). Aspects of phenotype–genotype correlation have been generalizable — for example, a more frequent severe phenotype arises from nonsense or missense mutations affecting active sites or protein stability; more robust response to splenectomy is observed in patients with bi-allelic or compound heterozygote missense mutations (see S3, S13, S14 in supplementary material). Nonetheless, more severely afflicted individuals may harbor diverse mutation profiles, and substantial phenotypic variability has been observed within cohorts harboring the same mutation[4] (see S3, S15 in supplementary material). The limited genotype–phenotype correlation (and discordant symptom severity and hemoglobin levels) might result from variably increased 2,3-diphosphoglycerate levels and additional metabolic or epigenetic polymorphisms, not yet extensively categorized. Genetic analysis — frequently vital for diagnosis and prognostic in specific instances — is not a consistently independent component of severity assessment[5] (see S3 in supplementary material). More precise RPK protein quantification may become more clinically accessible in coming years, and would facilitate severity assessment (see S16, S17 in supplementary material).

PKD severity definitions were historically fluid; the frequently cited Zanella classification (Table 1) is not a point-based, rigid staging system, but a spectrum on which definable elements may be characterized (see S3, S18 in supplementary material). This is understandable, since PKD frequently does not represent an immediate survival risk and available therapies have been supportive. Additional PKD classifications have been posited recently, predominantly based on

TABLE 2 Characterization of severe pyruvate kinase deficiency: major and additional criteria for gene therapy evaluation

Disease component	Major	Additional
Pre-splenectomy		
Transfusion status	Transfusion-dependent[a] or	
Hemoglobin	Hb <7.0 g/dL	
Post-splenectomy		
Transfusion status	Transfusion-dependent[a] or	
Hemoglobin	Hb <8.0 g/dL	
Fatigue or energy symptom burden		Fatigue or energy-related symptoms limiting ADLs[b] (NCI CTCAE v5.0 grade 3) Fatigue or energy-related symptoms limiting instrumental ADLs[b] (NCI CTCAE v5.0 grade 2) not responsive to available medical therapy
Clinical manifestations		Extramedullary hematopoiesis/paravertebral masses despite appropriate anemia management Non-healing lower extremity ulcers despite appropriate anemia mgt Non-traumatic bone fractures Icterus limiting social interactions, educational or work activities, and not responsive to available medical therapy, and not resulting from concomitant genetic disorders
Iron overload		Liver iron concentration (LIC) ≥3 mg/g on T2* MRI despite appropriate iron chelation or in settings of intolerance to chelation ther. Cardiac iron T2* <20 ms on MRI despite chelation therapy or in settings of intolerance to chelation Other clinical manifestations of severe iron overload
Mutation		Homozygote or compound heterozygote stop codons, frameshift, splicing, large deletions (in the context of at least one of the above-mentioned disease manifestations)

Note: Symptoms and clinical findings must be ascribed to PKD and not to any additional medical condition in order to qualify as valid criteria.

Criteria previously considered sufficient to enable eligibility for gene- or cell-therapy evaluations:

- The presence of 1 Major Criteria (either transfusion-dependence or hemoglobin below stipulated levels).

Additional Criteria for future consideration:

- The presence of at least 1 Additional Criteria in addition to the Major Criteria of hemoglobin below stipulated levels.
- The presence of 1 Fatigue/Energy Additional Criteria in the presence of at least 1 Additional Criteria within the Clinical Manifestation, Iron Overload or Mutation categories.
- The presence of any 3 Additional Criteria within the Clinical Manifestation, Iron Overload or Mutation categories.

[a]No single consensus definition of transfusion-dependence has been established. One set of criteria that has been endorsed by several experts and at least one publication (see S21 in supplementary material) is: ≥6 transfusion episodes per year, or ≥3 episodes per year for 2 consecutive years.

[b]Activities of daily living (ADLs) are eating (i.e., feeding oneself), bathing, dressing, toileting, mobility and grooming. Instrumental ADLs include managing finances, handling transportation, shopping, preparing meals, using the telephone or other communications devices, managing medications, doing laundry, housework, and other basic home maintenance.

transfusion requirements, which may not be consistently indicative of morbidity or disease burden.[4,6]

PKD severity classification is also complicated because there is frequently no strong correlation between potential severity parameters. Patients may have different tolerance to similar anemia levels, transfusion requirements differ because of practice patterns; iron overload may not correlate with transfusion requirements or hemoglobin.[1,4] Splenectomy — a standard of care for patients with childhood transfusion requirements — confers variable benefit with incomplete correlation between patients' pre- and post-splenectomy status.[4] The disease burden itself may alter over time, with some adults demonstrating increasing symptoms and decreased anemia tolerance with advancing age and diminished cardiopulmonary reserves.[1] A demarcated classification system has been less critical because no disease-targeted therapies were available until recently. Enhanced PKD severity categorization becomes more important with the development of allosteric enzyme activators, and particularly necessary with the introduction of gene therapy investigations.

The first-in-human multinational gene therapy trial enrolled 2 splenectomized adult patients who received gene-modified autologous CD34+ enriched HSPCs in 2020. Initial results demonstrate hemoglobin increases in both patients from baseline levels of 7.4 and 7.0 g/dL to 13.3 and 14.8 g/dL at 12 months following therapy, respectively, with concomitantly reduced hemolysis markers, including indirect bilirubin, erythropoietin, and reticulocytes. No severe adverse

events related to the investigational infusion were reported as of November 2021.[3] Pediatric evaluation is underway.

As of November 2021, over 315 patients have received infusion of lentiviral-modified autologous HSPCs for treatment of hematopoietic and related disorders; the short-term side effects to date have been manageable with frequent reversal of the clinical phenotype (see S19, S20 in supplementary material). Gene therapy nonetheless entails several coordinated interventions — including HSPC mobilization and apheresis collection, immunoselection, transduction and myeloablative conditioning with therapeutic drug-monitored busulfan — prior to infusion of gene-modified HSPCs. Long-term risks — including potential insertional mutagenesis — are not fully delineated, nor are shorter-term busulfan- or transplant-related risks potentially specific to PKD. Resource commitments are substantial. In PKD, investigational gene therapy is considered a viable option for patients with more severe disease and hence the importance of defining this subgroup. Recent research by the PKD NHS provides insights regarding the diversity of PKD-related manifestations, including those most indicative of severe morbidity.[4] Key findings include:

1. Hemoglobin levels may not consistently correlate with symptom burden; there exists heterogenous anemia tolerance across the patient population[1,4] (see S3 in supplementary material).
2. Although transfusion dependence is considered a severe disease hallmark, transfusion burdens may vary markedly from year to year, and absence of transfusion dependence may be associated with severe disease (see S21 in supplementary material). Many patients (especially adults and older adolescents) avoid frequent transfusions because of lifestyle choice or side effect concerns, and tolerate higher symptom burden.[1,7]
3. Even in the absence of low hemoglobin or frequent transfusions, the disease burden is substantial. Quality-of-life (QOL)/patient-reported outcome (PRO) evaluations indicate a high prevalence of energy-related symptoms, including tiredness, fatigue and low energy, each reported in more than 50% of 21 adult patients in an interview-based evaluation in North America and Europe[8] (see S22, S23 in supplementary material). Other frequent symptoms include dyspnea and tachycardia. Jaundice is frequent (>80%) and may substantially impair social, educational, and work activities, especially for adolescents and young-adults. Additional symptoms include poor concentration and memory loss (24% and 19%, respectively), and bone or joint pain (38% and 14%, respectively). The development of PKD-specific QOL/PRO instruments will enhance understanding of symptom burden and its impact on well-being (see S24, S25 in supplementary material).
4. Iron overload occurs frequently in PKD and is not limited to the most anemic or transfusion-dependent patients. Although more than 90% of transfusion-dependent splenectomized patients have evidence of iron overload, approximately 50% of non-transfusion-dependent splenectomized patients also have iron overload — evidenced by serum ferritin levels >1000 ng/mL or chelation-requirements.[7] Iron chelation is effective but not universally tolerated; chelation agents are associated with frequent side effects and limited compliance (see S26, S27 in supplementary material).
5. Significant additional PKD-related complications may develop, even in the absence of extensive anemia or transfusion requirements.[1] These include extramedullary hematopoiesis with paravertebral or mediastinal masses, non-healing leg ulcers, gallstones, cirrhosis, pulmonary hypertension, osteoporosis (including pathologic fractures), and endocrinopathies[4,9] (see S28 in supplementary material).
6. Despite advanced genetic sequencing and extensive characterization of common mutations, substantial limitations persist regarding genotype–phenotype correlation. PKD genotyping is an inconsistent predictor of prognosis or complications. Bi-allelic non-missense mutations are likely associated with lower hemoglobin, higher transfusion requirements and iron overload. However, most patients' disease results from compound heterozygous missense mutations generating red cells which may contain several tetramer combinations with distinct structure and function, such that similar mutations may confer varied clinical manifestations[5] (see S4 in supplementary material).

Recent findings re-emphasize that no single clinical or molecular parameter independently enables identification of severe PKD. Severe disease continues to be defined by polymorphic manifestations. Building on the initial Zanella classification, revised severe disease criteria are proposed and were developed by a screening of PubMed-indexed abstracts published between 2015 and 2021 reporting data from the PKD NHS and/or PKD-focused QOL. Additional search terms included those pertaining to severity and clinical complications. Two authors (JDS and JCS) screened all full manuscripts that addressed the clinical aspects of PKD with emphasis on severity assessment, as determined by hemoglobin levels pre- or post-splenectomy, transfusion requirements, or qualitative description of the clinical spectrum of PKD-related complications, either as assessed by clinicians or by patient-reported (QOL) instruments. Of 53 publications identified, 15 full-length manuscripts were included in the development of these proposed severe PKD definitions[1,4–10] (see S5, S18, S21–S25 in supplementary material).

In these revised definitions, anemia and fatigue related thresholds were based on NCI CTCAE 5.0 grades. Iron-overload thresholds were based on criteria utilized in recent publications (adapted from β-thalassemia guidelines) with additional corroboration via hematopoietic transplant iron overload guidelines[10] (see S29–S31 in supplementary material). Based on expert consensus including an advisory meeting, subsequent review and concordance involving all co-authors, the working criteria delineated in Table 1 are proposed as those indicative of severe PKD. These criteria are further categorized in Table 2 as Major (based on either transfusion-dependence or severe anemia in the presence of additional phenomena) or Additional, including those pertaining to fatigue or energy symptom burden, iron overload,

or additional manifestations. As indicated in Tables 1 and 2, severity classifications to date have been based on transfusion requirements and hemoglobin levels. The proposed Additional Criteria may enhance identification of severely-afflicted patients, and may be considered for implementation in forthcoming investigations as the benefit/risk of gene therapy is further delineated.

Allosteric enzyme activators have been associated with improved hemolytic anemia in adult patients with transfusion-independent and transfusion-dependent PKD, specifically in those with at least one missense *PKLR* variant. In phase 2 and 3 clinical trials, mitapivat (AG-348), an oral small-molecule red-cell pyruvate kinase activator, conferred hemoglobin increases greater than 1.5 g/dL in 37% and 40% of adult non-transfusion-dependent PKD patients, respectively[2] (see S6 in supplementary material). In regularly transfused patients, a ≥33% reduction in transfusion burden was reported in 37% and transfusion independence was observed in 22% over 24-week follow-up (see S7 in supplementary material). Based on this agent's evolving role in adults (and potential pediatric investigation), severity definitions include the terminology "despite available medical therapy" in order to account for this agent's likely availability.

Definitions of severity in PKD are further conditioned by splenectomy status. Although the proposed classification incorporates aspects of clinical PKD in both pre- and post-splenectomy settings, the scenarios provided are most relevant to splenectomized children and adults. Splenectomy is currently a standard-of-care and is frequently performed during childhood (at age 4–5 years or older) for patients with significant anemia or transfusion requirements. Splenectomy is associated with an average 1.6 g/dL hemoglobin increase in PKD and with frequent decreased transfusion requirements.[4] Reductions in fatigue or other energy-related symptoms may be disproportionately higher than the relatively modest hemoglobin increases; this may result from diminished hemolysis and concomitant hematopoietic and metabolic requirements. Factors associated with persistent post-splenectomy hemoglobin less than 8 g/dL include pre-splenectomy levels less than 7 g/dL, higher pre-splenectomy bilirubin, and non-Amish ethnicity.[4] Splenectomy does not ameliorate the underlying disorder or concomitant iron overload, and is associated with a risk of significant infectious and thrombotic complications.

If the efficacy and safety demonstrated over 1-year in initial adult patients is replicated in the pediatric setting, evaluation of gene therapy in non-splenectomized patients may be warranted. This will require judicious determination of the pre-splenectomy population with the highest likelihood of ongoing severe PKD manifestations.

During recent years, the PKD NHS and additional research efforts have enabled improved understanding of the complex and varied PKD phenotypes. Although transfusion-dependence and anemia parameters factor substantively into severity assessment, no single parameter allows consistent identification of patients most extensively afflicted. Optimal investigation of PKD-focused therapies necessitates severity classification encompassing the entirety of the disorder, including the multiple components that impair patient well-being. We therefore developed this proposed severity classification to provide a broader potential definition of the most severely-afflicted PKD population. This is a narrative expert proposal and limitations include a methodology that did not incorporate formal development guidelines for expert-consensus recommendations (see S32 in supplementary material); we anticipate a subsequent and more exhaustive methodology involving a broader range of disease and therapeutic-area experts as additional adult and pediatric results become available. It is likely that the classification system presently proposed will undergo refinement guided by additional natural history and interventional study results.

CONFLICT OF INTEREST

Jonathan D. Schwartz is an employee and equity shareholder of Rocket Pharmaceuticals, Inc. Wilma Barcellini is a consultant for Agios Pharmaceuticals, Inc. Rachel F. Grace receives research funding from Agios Pharmaceuticals, Inc., Novartis Pharmaceuticals, Inc. and Dova Pharmaceuticals, Inc. She additionally serves on advisory committees for Principia Biopharma, Inc. and Dova Pharmaceuticals, Inc. Paola Bianchi is a consultant for Agios Pharmaceuticals, Inc. Alberto Zanella is a PKD IDMC member for Agios Pharmaceuticals, Inc. and Rocket Pharmaceuticals, Inc. José Luis López Lorenzo has no conflict of interest to disclose. Julián Sevilla receives honoraria and is a consultant and/or advisor for the following: Amgen, Inc., Novartis Pharmaceuticals, Inc., Miltenyi Biotech, Inc., Sobi, Inc., Rocket Pharmaceuticals, Inc.) and has licensed medicinal products from Rocket Pharmaceuticals, Inc. Ami J. Shah has no conflict of interest to disclose. Bertil Glader receives research funding from Agios Pharmaceuticals, Inc. Eileen Nicoletti is an employee and equity shareholder of Rocket Pharmaceuticals, Inc. Susana Navarro Ordoñez has licensed medicinal products and receives research funding and equity from Rocket Pharmaceuticals, Inc. José Carlos Segovia has no conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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SUPPORTING INFORMATION

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Voxelotor use in adults with sickle cell disease in a real-world setting

To the Editor:

In 2019, voxelotor was approved by the United States Food and Drug Administration for the treatment of sickle cell disease (SCD) in patients ≥16 years. The HOPE trial showed that treatment with voxelotor reduced hemolysis and improved anemia and rates of adverse and serious adverse events were no different between high dose, low dose, and placebo groups.[1] However, clinical trials do not provide all the information required for physicians to know how well the drug works in clinical practice. Postapproval real-world studies can identify barriers to use as well as risks and benefits not recognized in the initial clinical studies. We sought to examine voxelotor use in a real-world cohort of patients followed at a comprehensive urban sickle cell center. We hypothesized that economic and social barriers could prevent some patients from being able to obtain voxelotor, medication adherence may not be optimal, and that adverse events or side effects might result in fewer clinical and hematological benefits than those seen in the HOPE study.

Data were obtained retrospectively from electronic medical records (EMRs) at our center. Patients with SCD who had been prescribed voxelotor from November 25, 2019 to December 31, 2020 were included in this analysis. Use of hydroxyurea and erythropoiesis-stimulating agents (ESA) were defined by the presence of active prescription in the EMR. Demographics, clinical outcomes, and SCD-related morbidities were abstracted from the EMR.

Voxelotor therapy group included patients who verbally confirmed obtaining and starting the medication (VOX+), all others were defined as Vox−. Laboratory test results were obtained prior to ordering voxelotor, at steady state, defined as a visit with no acute complaints and at least 14 days from last episode of hospital or emergency room (ED) utilization. For VOX+ patients a second set of labs was obtained at least 14 days after starting voxelotor. Presence of voxelotor in patients' plasma was determined by changes in capillary zone electrophoresis based on methodology described in prior studies.[2–4] Episodes which resulted in a visit to the ED or admission to our hospital and number of packed red blood cell transfusions were noted for the 3 months prior to, and the 3 months post therapy initiation. Data on side effects, dose modifications, reasons for terminal discontinuation were collected.