The lifetime economic burden of pyruvate kinase deficiency in the United States

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BACKGROUND

- Pyruvate kinase (PK) deficiency is a rare inherited disorder caused by autosomal recessive mutations in the *PKLR* gene, whereby a glycolytic defect causes reduced adenosine triphosphate levels and leads to hemolytic anemia
- Patients with PK deficiency can experience serious complications associated with the disease and its treatment, including perinatal complications, iron overload, bone fractures, pulmonary hypertension, and liver cirrhosis
- The current standard of care for PK deficiency is supportive, including blood transfusions, splenectomy, cholecystectomy, iron chelation therapy, and/or interventions for other disease-related morbidity
- Although the clinical burden in patients with PK deficiency is well documented, the economic burden of long-term disease management, procedures, and disease complications has not been investigated and is unknown

OBJECTIVE

- To estimate the lifetime burden of patients with PK deficiency, from the perspective of the healthcare payer in the United States (US)

METHODS

Model overview

- A micro-costing model was developed to determine the lifetime direct costs of PK deficiency associated with diagnosis and monitoring, long-term disease management, relevant procedures, disease complications, and end-of-life care
- Patients with PK deficiency were stratified into early pediatrics (0–5 years old), adolescents (6–17 years old), and adults
- The adult patient population was further grouped by transfusion status: regularly transfused (RT, ≥ 6 transfusions in a year), not regularly transfused (NRT), and not transfused (NT)
- The model took the perspective of a US payer (direct healthcare costs only), with a time horizon of 100 years, and all costs were standardized to 2020 US dollars

Data extraction

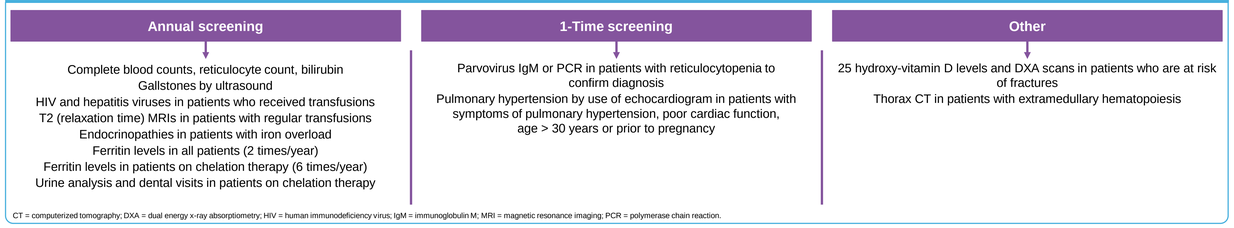
- The cost of diagnostics, monitoring, and 1-time procedures (eg, splenectomy and cholecystectomy) was derived from public databases, such as Healthcare Cost and Utilization Project (HCUP) and Medicare fee schedule[1–3]
- When appropriate, Medicare procedure fees were adjusted with a 2.15 multiplier to reflect higher commercial rates[4]
- The frequency of monitoring (eg, frequency of specialist visits) was based on clinical literature[5,6] and consensus from key opinion leaders[7]
- The probabilities of complications and procedures were based on PK deficiency Natural History Study (NHS)[8,9]
- The direct medical costs of complications were extracted from literature
- The inputs from similar hemolytic anemia conditions (eg, beta-thalassemia) were utilized[10] when data gaps specific to PK deficiency existed
- The mortality was estimated using the life table of the general US population[11] and a calculated hazard ratio of mortality (1.658) for PK deficiency patients from real-world data[12]

Diagnostics and monitoring

Diagnostics			
	• Genetic testing • Assay of PK • Red cell enzyme panel • Direct antiglobulin test • Indirect antiglobulin test	• Hemoglobin electrophoresis • Peripheral blood smear • Eosin-5'-maleimide (EMA) test • Lactate dehydrogenase • Haptoglobin	• Urine hemoglobin • Complete blood count • Complete metabolic panel (including liver function test) • Carbon monoxide breath test

- The PK deficiency monitoring schedule is described in **Figure 1**

Figure 1. Monitoring schedule of PK deficiency in patients

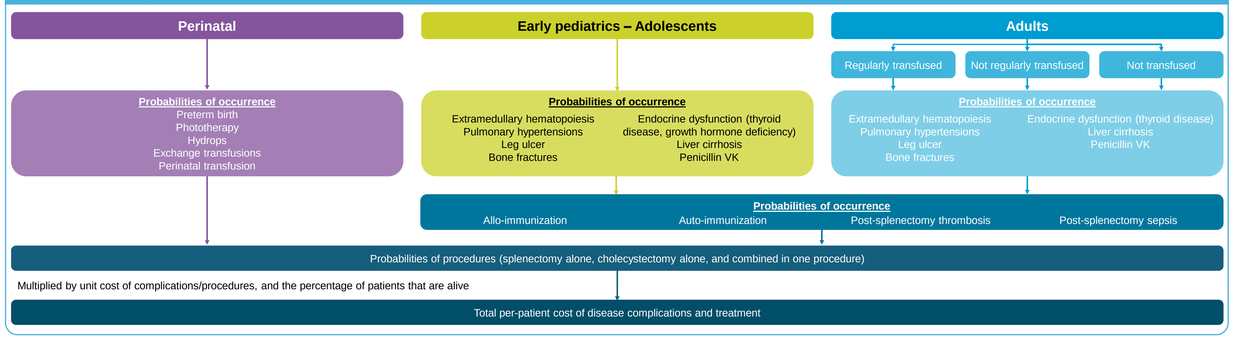


CT = computerized tomography; DXA = dual energy x-ray absorptiometry; HIV = human immunodeficiency virus; IgM = immunoglobulin M; MRI = magnetic resonance imaging; PCR = polymerase chain reaction.

Disease complications

- The occurrences of disease complications were derived from the PK deficiency NHS and converted to annual probabilities using constant-hazard survival models (**Figure 2**)

Figure 2. Estimating the cost of disease complications



METHODS (CONTINUED)

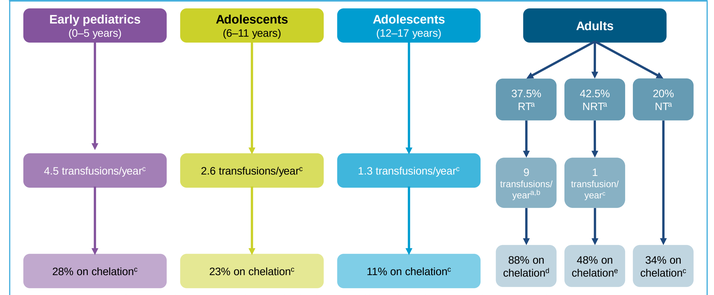
Transfusion and chelation

- Transfusion frequency (including regular and on demand transfusions) was derived from clinical trial and analysis of individual PK deficiency in the NHS data (**Figure 3**).[13] For RT and NRT patients, the need for transfusion was reduced, but not eliminated, after splenectomy. The estimated cost per transfusion is $1981[10]
- The utilization rate of chelation therapy (modeled for patients aged 2 years or older) was informed by trial data and claims analysis of patients with beta-thalassemia. There is still need for chelation for NT patients (**Figure 3**)
- The average cost of chelation therapy to treat iron overload was estimated based on published acquisition[14] and administration (Medicare Physician Fee Schedule 2020) cost and stratified by chelator types[10]

Other inputs

- The number of specialist visits per year for early pediatrics (0–5 years), adolescents (6–17 years), adults who were RT, NRT, and NT was 12, 3 ,12, 2, and 1, respectively. Cost per specialist visit was $358[15]
- The end-of-life cost was assumed to be the same as that of hematological cancers at $227,477[16]
- The simultaneous splenectomy and cholecystectomy procedure was assumed to have the same cost as splenectomy alone due to similar operation and patient recovery time

Figure 3. Frequency of transfusion and chelation by patient subgroups



[a]Key opinion leader consensus; [b]ACTIVATE-T baseline characteristics; [c]Analysis of individual pyruvate kinase deficiency in the NHS data (Agios Pharmaceuticals, data on file, 2021); [d]Based on regularly transfused patients with beta-thalassemia (Weiss, 2019) ; [e]Grace 2019b.
NHS = Natural History Study; NRT = not regularly transfused; NT = not transfused; RT = regularly transfused.

RESULTS

- The mean lifetime direct cost of a patient with PK deficiency is $3.3 million, with the majority of the costs occurring during the adult phase ($3.0 million). The cost of early pediatric and adolescent phases was $144,791 and $173,357, respectively
- The mean lifetime cost varied by adult transfusion status, with lifetime costs of $4.4 million, $2.8 million, and $2.4 million for RT, NRT, and NT patients, respectively (**Table**)
- The main cost-drivers overall were:
  - The utilization rate and cost of chelation therapies
  - Cost and frequency of transfusions
  - Cost associated with disease-related complications
- Although transfusion and chelation costs were higher in those with a greater transfusion burden, the costs of complications, particularly from iron overload, were higher in the NRT and NT populations. This is consistent with reported complication rates in the data source (PK deficiency NHS).[13] The lower rates of complications in RT patients are potentially related to the therapeutic effect of transfusion or iron chelation
- The monitoring cost for RT patients is significantly higher due to increased monitoring for ferritin levels, endocrinopathies, and chelation therapies
- The estimated total lifetime cost of PK deficiency is comparable to other rare genetic diseases[17,18]

Table. Total lifetime direct cost of PK deficiency by transfusion status

	RT	NRT	NT
Diagnosis	$10,689	$10,689	$10,689
Monitoring	$432,242	$129,470	$97,437
Transfusion	$1,076,923	$203,786	$94,644*
Chelation therapy	$1,849,451	$1,030,223	$750,685
Procedures	$44,640	$42,263	$37,833
Disease complications	$752,676	$1,187,667	$1,186,958
End-of-life care	$227,243	$227,243	$227,243
Total	**$4,393,864**	**$2,831,341**	**$2,405,489**

*Cost of transfusion before adulthood.
NRT = not regularly transfused; NT = not transfused; PK = pyruvate kinase; RT = regularly transfused.

Limitations

- Due to the rare nature of PK deficiency and the paucity of mortality data, the relative risk of death due to PK deficiency was derived from a patient population with limited sample size[12] and applied to background mortality rate from US life tables
- The model used a constant hazard survival model when deriving the occurrence of various complications and assumed the annual incidence rate of that complication remained the same among age subgroups
- The model took a conservative approach in estimating total cost. Only direct medical and pharmacy costs that are supported by clinical evidence to be caused by PK deficiency are included. Conditions that are comorbid with PK deficiency, hospitalizations that are unrelated to PK deficiency, and indirect costs (eg, absenteeism, presenteeism, caregiver burden) were not included in this model and are considered topics for future research
- There is no standard procedure in diagnosing and monitoring PK deficiency. The diagnostic workup included in this model represents consensus among treating physicians

CONCLUSIONS

- **The results of this study suggest that the lifetime economic burden of PK deficiency, from the perspective of the healthcare payer, is substantial**
- **A large proportion of the direct cost of PK deficiency comes from transfusion and chelation therapies**
- **Although the model provides a foundation for further economic evaluations, additional research regarding real-world healthcare resource utilization and indirect costs would further improve our understanding of the economic burden**

Disclosures

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References

1. Centers for Medicare and Medicaid Services. Clinical Laboratory Fee Schedule: Q2. 2020a. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched. Accessed May 25, 2021. **2.** Centers for Medicare and Medicaid Services. Facility Fee Addendum B. January 2020b. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/HospitalOutpatientPPS/Addendum-A-and-Addendum-B-Updates. Accessed May 25, 2021. **3.** Centers for Medicare and Medicaid Services. Physician Fee Schedule Look-up. 2020c. https://www.cms.gov/medicare/physician-fee-schedule/search/overview. Accessed May 25, 2021. **4.** Chernew ME et al. *Health Aff (Millwood)* 2020;39:791–99. **5.** Grace RF et al. *Br J Haematol* 2019a;184:721–34. **6.** Grace RF et al. *N Engl J Med* 2019b;381:933–44. **7.** KOL consensus [in-depth interviews conducted in May - November 2020 with 4 KOLs]. **8.** Grace RF et al. *Blood* 2018;131:2183–92. **9.** Boscoe AN et al. *61st American Society of Hematology (ASH) Annual Meeting* 2019: Poster 2175. **10.** Weiss M et al. *Am J Hematol* 2019;94:E129–32. **11.** Social security administration (SSA). Actuarial life table. Period life table, 2016. https://www.ssa.gov/oact/HistEst/PerLifeTables/Home.html. Accessed May 25, 2021. **12.** Zagadailov E et al. *62nd American Society of Hematology (ASH) Annual Meeting* 2020: Poster 1627. **13.** Data on file; Agios Pharmaceuticals, 2021. **14.** Red Book. IBM Micromedex. Copyright IBM Corporation 2020. **15.** Agency for Healthcare Research and Quality (AHRQ). Medical Expenditure Survey (MEPS). Table 1. Total Utilization and Mean Expenses per Visit by Type of Ambulatory Health Care Service, 2014. https://meps.ahrq.gov/data_stats/summ_tables/hc/mean_expend/2014/table1.pdf. Accessed May 25, 2021. **16.** Chastek B et al. *J Oncol Pract* 2012;8:75s–80s. **17.** Angelis A et al. *Health Policy* 2015;119:964–79. **18.** Yang G et al. The National Economic Burden of Rare Disease Study. February 25, 2021. https://everylifefoundation.org/wp-content/uploads/2021/02/The_National_Economic_Burden_of_Rare_Disease_Study_Summary_Report_February_2021.pdf?eType=EmailBlastContent&eId=1d1fcfbd-10fc-4553-bf38-dfd73c7e7cd8. Accessed May 25, 2021.

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