Understanding the Physical and Psychosocial Impacts of Pyruvate Kinase Deficiency: Patient-Led Development of the Pyruvate Kinase Deficiency Life Phase Model

3691

Rachael F Grace, MD[1], Lily Cannon, MA, MSc[2], Maaike Eijgenraam[3], Carl Lander, RN[4], Laura Miller-D'Angelo[5], Susan Morris, PhD[6], Janie Davis, MBA[6], Parija Patel, PharmD, MBA[6], Tamara Schryver, PhD, RD[7], Alejandra Watson[5], and Wilma Barcellini, MD[8]

[1]Boston Children's Hospital, United States; [2]Thalassaemia International Federation, Cyprus; [3]Advisory role at Thrive with PK Deficiency, The Netherlands; [4]Thrive with PK Deficiency, United Kingdom; [5]PK Deficiency Foundation, United States; [6]Agios Pharmaceuticals, Inc., United States; [7]Thrive with PK Deficiency, United States; [8]Hematology Unit, Pathophysiology of Anemias Unit, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Italy

BACKGROUND

- Pyruvate kinase (PK) deficiency is a rare congenital hemolytic anemia caused by mutations in the *PKLR* gene, which encodes PK, the enzyme that catalyzes the final enzymatic step in glycolysis and is required for the generation of adenosine triphosphate (ATP); insufficient ATP leads to premature red blood cell destruction, resulting in anemia and other complications (e.g., iron overload, pulmonary hypertension, endocrinopathies, osteoporosis)[1]
- With an estimated prevalence of 3.2–8.5 cases per million in Western populations[2], PK deficiency can have wide-ranging signs and symptoms that negatively impact patients' health-related quality of life (HRQoL), including their physical, emotional, and functional well-being[3]
- Patients, caregivers, and families report that improved resources are needed to support the PK deficiency community[4], with a particular need for better understanding of how disease-related physical and psychosocial experiences change over the course of a patient's lifetime[5]
- To address this gap, a multi-disciplinary group of patients, caregivers, patient advocates, and healthcare providers (HCPs) collaborated to develop the PK Deficiency Life Phase Model, a descriptive tool that communicates the physical and psychosocial impacts of PK deficiency for patients and their caregivers across six life phases

OBJECTIVE

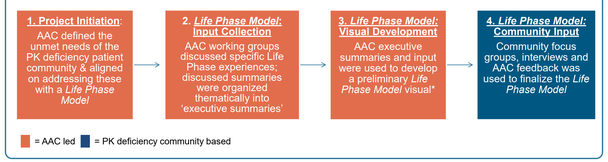
Provide HCPs, patients, and caregivers a guiding resource to further understand the potential physical and psychosocial impacts of PK deficiency through a *Life Phase Model* based on the lived experiences of patients and caregivers

METHODS

Project Initiation

- The PK Deficiency Advocacy Advisory council (AAC) is a multi-disciplinary advisory group consisting of 8 members: 2 HCPs, 5 patient advocates (4 living with PK deficiency), and 1 caregiver
- As a first step, the group assessed and defined unmet community needs, aligning on:
  - **Primary Need**: better understanding among patients and HCPs about the burden of the disease at different phases in a patient's life
  - **Secondary Need**: improve available resources for patients/caregivers to support them in communicating about their disease to those around them, including HCPs
- To address these, the AAC developed a *Life Phase Model* detailing the progression and potential impacts of the disease at different phases of life from their perspectives (**Figure 1**)

Figure 1. *Life Phase Model* development process



Life Phase Model: Input Collection

- Life phases were defined based on a review of existing literature and AAC input[6–10]
  - Infant (0–2), Child (3–12), Adolescent (13–18), Young Adult (19–33), Adult (34–64), and Older Adult (65+)
- Working groups (2–3 AAC members) were assigned to each life phase and tasked with describing the important physical and psychosocial experiences
- Discussion summaries from each group were reviewed by the full AAC to ensure broad input and alignment
- Finalized discussion summaries were organized thematically to 'group' AAC-reported experiences into core physical and psychosocial themes; these formed the AAC 'executive summaries'
- Executive summaries were further reviewed by the AAC HCPs to ensure medical and phasing accuracy
- The group sought to further support the summaries with published references provided by AAC members and Agios representatives where available[11–20]; for experiences not supported by these references, targeted searches were conducted in PubMed and Cochrane databases (search period = 5 years; inclusion criteria = search term stated within the abstract, title, or item tags)[20–28]
  - Where available, published literature was referenced in the executive summaries of physical experiences to ensure medical accuracy
  - Psychosocial experiences were supported by fewer references and therefore the corresponding executive summaries the AAC- and community-reported psychosocial experiences only
- See **Supplemental Figure 1** (available via QR code) for additional information on this step

Life Phase Model: Visual Development

- To show the potential impact of PK deficiency across life phases, a preliminary *Life Phase Model* was developed based on:
  - AAC opinion as reflected in the executive summaries (**Figure 2A**)
  - Visual representation of potential impact at defined life phases (**Figure 2B**)
    - The potential impact of physical and psychosocial experiences on individuals with PK deficiency, their families, and caregivers was assessed based on a research team member's review and synthesis of the AAC-reported experiences across each life phase, with lighter shading depicting lower potential impact and darker shading depicting higher potential impact
    - In life phases where further input was required to confidently assign a specific shade, additional AAC input was also considered
    - To complete the shading of the 'co-morbidities and complications' theme, literature-based information was also referred to[19,29]
  - The preliminary *Life Phase Model* was brought back to the AAC for further feedback and refinement

Life Phase Model: Community Input

- Given the lower volume of literature supporting the psychosocial executive summaries and themes in the preliminary *Life Phase Model* visual, additional community input was sought via community-based focus groups and 1-1 interviews:
  - Focus group participants were recruited (9 countries) across 3 categories: young adult patients aged 18–25 (n=9), adult patients aged >25 (n=14), and caregivers (n=7)
  - In-depth interviews were conducted with 2 young adult patients and 2 caregivers to gather further qualitative data
  - Focus groups and interviews were conducted in accordance with British Healthcare Business Intelligence Association Legal and Ethical Guidelines[30] and guidelines established by the UK Market Research Society[31]
- Feedback from the focus groups and interviews was reviewed by the AAC and the *Model* was further refined and finalized

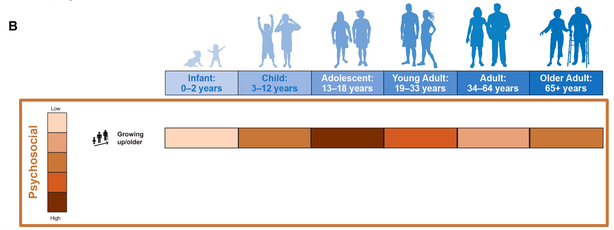
Figure 2. (A) AAC opinion as reflected in executive summaries (example using the 'Growing Up/Older' theme). (B) Visual representation of potential impact at defined life phases (example using the 'Growing Up/Older' theme)

A

Growing up/older	*Infant (0-2 years)*	*Child (3-12 years)*	*Adolescent (13-18 years)*	*Young adult (19-33 years)*	*Adult (34-64 years)*	*Older adult (65+ years)*
(Delayed) puberty and/or reaching sexual maturity[23]		●	●	●		
Impact on child development/childhood from overprotective/overbearing parents trying to protect their children		●	●			
Increased anxiety & concern as child's understanding of their disease increases		●	●			
Increased need for self-management of disease as one becomes more independent and transitions to adult care[12]		●	●	●		
Further understanding of their disease/treatment and increasing independence and autonomy over their body		●	●	●	●	●
Engaging in high-risk behaviors associated w/adolescence possibly due to low self-esteem[12]			●	●		
Transition of care from pediatric to adult medical care			●	●		
Concerns & misinformation around pregnancy/hereditary nature of the disease			●	●	●	

● Person with PK deficiency
● Caregiver
● Family

B

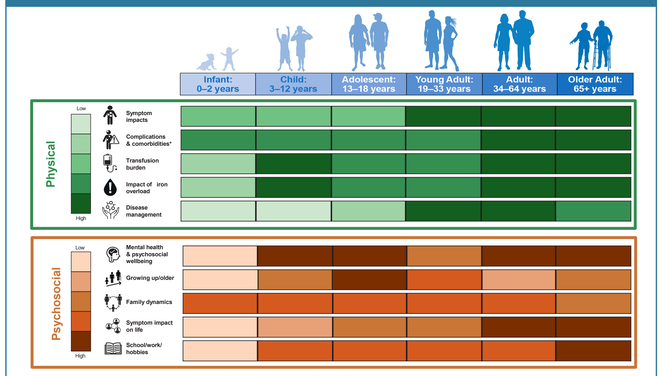


RESULTS

- Physical themes detailed in the executive summaries included Symptom Impacts, Complications and Comorbidities, Transfusion Burden, Impact of Iron Overload, and Disease Management
  - Complications and Comorbidities associated with PK deficiency occur in all life phases
  - Adolescents struggled with challenges associated with growing up with a chronic condition
- Psychosocial themes detailed in the executive summaries included Mental Health and Psychosocial Wellbeing, Growing Up/Older, The Future*, Family Dynamics, Symptom Impact on Life and School, Work and Hobbies
  - PK deficiency AAC members described the potential impact of medical trauma on their mental health; negative medical experiences in the past also impacted patients and caregivers throughout all life phases
  - The potential impact of PK deficiency on mental health and psychosocial wellbeing affects patients, families, and caregivers
  - Anxiety and depression-related themes were commonly observed with both patients and caregivers, and the potential economic impact of PK deficiency was commonly reported by families, as well as patients
  - Overall, the potential psychosocial impacts of PK deficiency appeared to increase with age
  - AAC discussions, as well as focus group and interview findings, showed that the potential impact of PK deficiency on school, work, and/or hobbies is observed in all life phases
- See **Supplemental Table 1** and **Supplemental Table 2** (available via QR code) for full executive summary tables
- The literature review process found more evidence supporting certain physical themes[12–13,15–23, 25–28] than psychosocial themes[11–14,18, 20–27] indicating a literature gap
- The PK Deficiency Life Phase Model (**Figure 3**) illustrates how the physical and psychosocial experiences identified through this project may vary between life phases

** Note that 'The Future' was combined with the 'Growing Up/Older' theme in the Model visual, given similarity in experiences explored between these two categories*

Figure 3. Conceptual Pyruvate Kinase Deficiency Life Phase Model



Shading reflects the potential symptom impact on lived experiences at different life phases, as described by the AAC, community input via focus groups, 1-1 interviews. Shading in the 'complications & comorbidities' theme of the Life Phase Model was also informed by literature-based information.
** Literature audit findings were also used to substantiate the Life Phase Model domains where possible.*

LIMITATIONS

- PK deficiency is an ultra-rare disease with a clinically heterogenous population, and the *Life Phase Model* visual was developed using subjective input from a small group; insights elucidated by this analysis may not be generalizable to the broader population of those living with PK deficiency or other rare diseases

CONCLUSIONS

- First-hand knowledge shared by patients, caregivers, and HCPs helped further understand the physical and psychosocial experiences that may impact individuals affected by PK deficiency at different phases of life
- This work led to the development of a descriptive *Life Phase Model* to help patients and their healthcare supporters better understand how the spectrum of disease burden potentially impacts patients and caregivers over time
- The model could further serve as a source of information for patients, caregivers, and HCPs in support of this rare disease community
- Future research could build upon our understanding of the impact of PK deficiency over the lifetime
- The process followed by the PK Deficiency AAC could potentially be adapted by other rare disease communities, allowing for the collection of relevant qualitative information and insights to inform discussions and decision-making surrounding their unique needs

Disclosures: This work was funded by Agios Pharmaceuticals, Inc.; The AAC was founded and funded by Agios Pharmaceuticals, Inc.
Editorial assistance was provided by Ingrid Koo, PhD, of FleishmanHillard, and funded by Agios
Conflict of Interests: Susan Morris, Parija Patel, and Janie Davis are all current Agios employees and stockholders; Alejandra Watson, Laura Miller-D'Angelo, Rachel F Grace, Lily Cannon, Maaike Eijgenraam, Carl Lander, Wilma Barcellini, and Tamara Schryver all receive honoraria from Agios Pharmaceuticals as members of the Pyruvate Kinase Deficiency Advocacy Advisory Council; Rachael F Grace: Research funding: Agios, Novartis, Sobi; Consultancy: Sanofi; Wilma Barcellini: Alexion, Novartis – honoraria; Agios – research funding; Bioverativ, Incyte – board membership or advisory committee
References: 1. Al-Samkari H et al. Haematologica 2020;105(9):2229–2239; **2.** Secrest MH et al. Eur J Haematol 2020;105(2):173–184; **3.** Grace RF et al. Eur J Haematol 2018;101(6):758–765; **4.** Barcellini W, Grace R. Pyruvate Kinase Deficiency Reflections on the Patient Experience to Support Treatment and Care. 2021 https://www.agios.com/wp-content/uploads/2021/12/PKD-ALL-0167-Agios-PK-Deficiency-Advocacy-Advisory-Council-White-Paper.pdf. Accessed Nov 24, 2023; **5.** Data on file; **6.** Geifman N et al. *Age (Dordr)* 2013;35(6):2357–66; **7.** Kastner M et al. *J Med Internet Res* 2006;8(4):e25; **8.** World Health Organization. The life-course approach: from theory to practice: case stories from two small countries in Europe. 2021. https://www.who.int/europe/publications/i/item/9789289053266. Accessed Nov 24, 2023; **9.** Centers for Disease Control and Prevention. National Center for Health Statistics - Life Stages and Populations. 2016. https://www.cdc.gov/nchs/fastats/life-stages-and-populations.htm; Accessed Nov 24, 2023; **10.** Centers for Disease Control and Prevention. Child Development - Positive Parenting Tips. 2021. https://www.cdc.gov/ncbddd/childdevelopment/positiveparenting/index.html. Accessed Nov 24, 2023; **11.** National Child Traumatic Stress Network. Pediatric Medical Traumatic Stress A Comprehensive Guide. 2014. https://www.nctsn.org/sites/default/files/resources/pediatric_toolkit_for_health_care_providers.pdf. Accessed Nov 24, 2023; **12.** National Organization for Rare Disorders. Voice of the Patient Report: Pyruvate Kinase Deficiency. 2020. https://rarediseases.org/wp-content/uploads/2020/04/NRD-2029-Voice-of-the-Patient-Report-PKD_FNL_SmallestFile-FINAL-1.pdf. Accessed Nov 24, 2023; **13.** Grace RF et al. *Eur J Haematol* 2018;101:758–765; **14.** Kaushik P et al. *Value in Health* 2022;25:12(Suppl):S422; **15.** Grace RF, Barcellini W. *Blood* 2020;136(11):1241–1249; **16.** Grace RF et al. *Blood* 2018;131(20):2183–2192; **17.** Zaninoni A et al. *Eur J Haematol* 2020;11:1309; **18.** Rachael Grace. Fast Facts for Patients and Supporters Pyruvate Kinase Deficiency: a rare genetic disease that affects red blood cells. 2018. https://www.knowpkdeficiency.com/pdf/hcp-refresh/Fast-Facts-PKD-Patient+Booklet.pdf. Accessed Nov 24, 2023; **19.** Glenthøj A et al. *Blood* 2022;140(Supplement 1):5323–5325; **20.** Al-Samkari H et al. *Blood Adv* 2022;6(6):1844–1853; **21.** Belzer LT et al. *Children (Basel)* 2022;9(7):933; **22.** Boscoe AN et al. *Eur J Haematol* 2021;106(4):484–492; **23.** Fattizzo B et al. *J Blood Med* 2022;13:461–471; **24.** Salek MS et al. *Qual Life Res* 2019;28(2):399–410; **25.** Al-Samkari H et al. *Haematologica* 2020;105(9):2229–2239; **26.** Grace RF et al. *Br J Haematol* 2019;184(5):721–734; **27.** van Straaten S et al. *Haematologica* 2018;103(2):e82–e86; **28.** Yang H et al. *Clin Pharmacol Drug Dev* 2019;8(2):246–259; **29.** Data on file; **30.** British Healthcare Business Intelligence Association. BHBIA Legal and Ethical Guidelines. 2023. https://www.bhbia.org.uk/guidelines-and-legislation/legal-and-ethical-guidelines. Accessed Nov 24, 2023; **31.** UK Market Research Society. MRS Guidance. 2023. https://www.mrs.org.uk/standards/mrs-guidance. Accessed Nov 24, 2023.

This study was funded by Agios Pharmaceuticals, Inc.
Presented at the 65th American Society of Hematology (ASH) Annual Meeting & Exposition, December 9–12, 2023, San Diego, CA, USA