

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

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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 populations², 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-being³
- Patients, caregivers, and families report that improved resources are needed to support the PK deficiency community⁴, with a particular need for better understanding of how disease-related physical and psychosocial experiences change over the course of a patient’s lifetime⁵
- 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

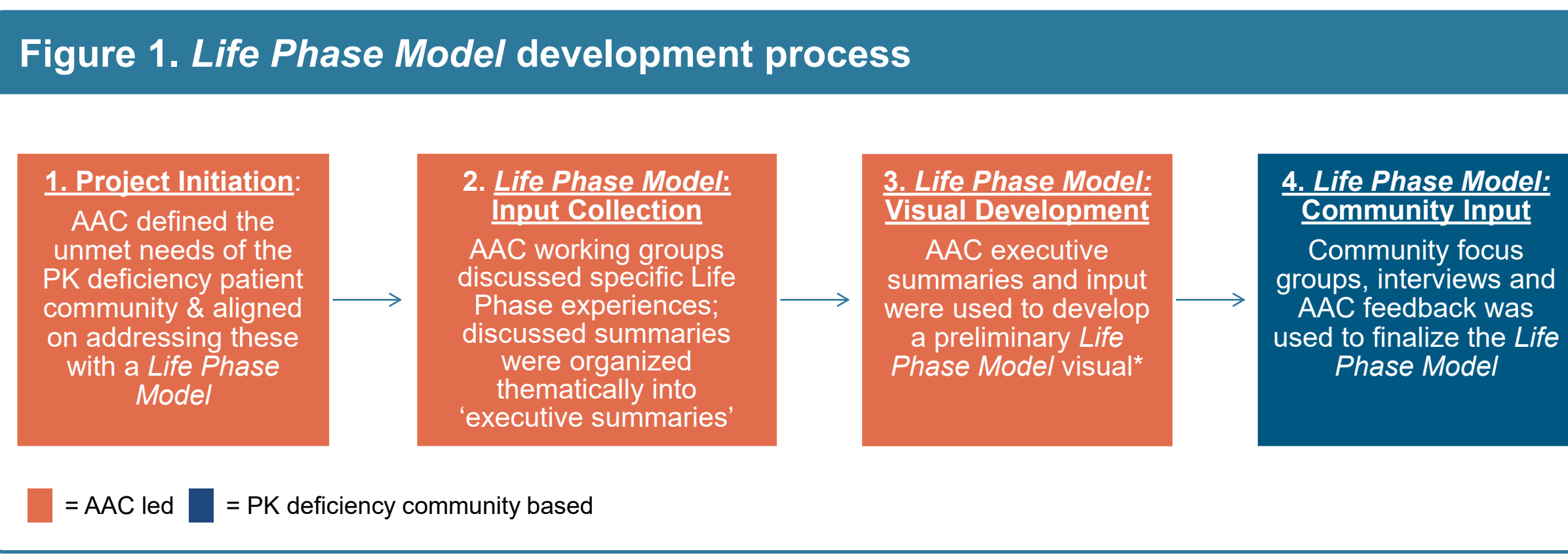
OBJECTIVE

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**)



Life Phase Model: Input Collection

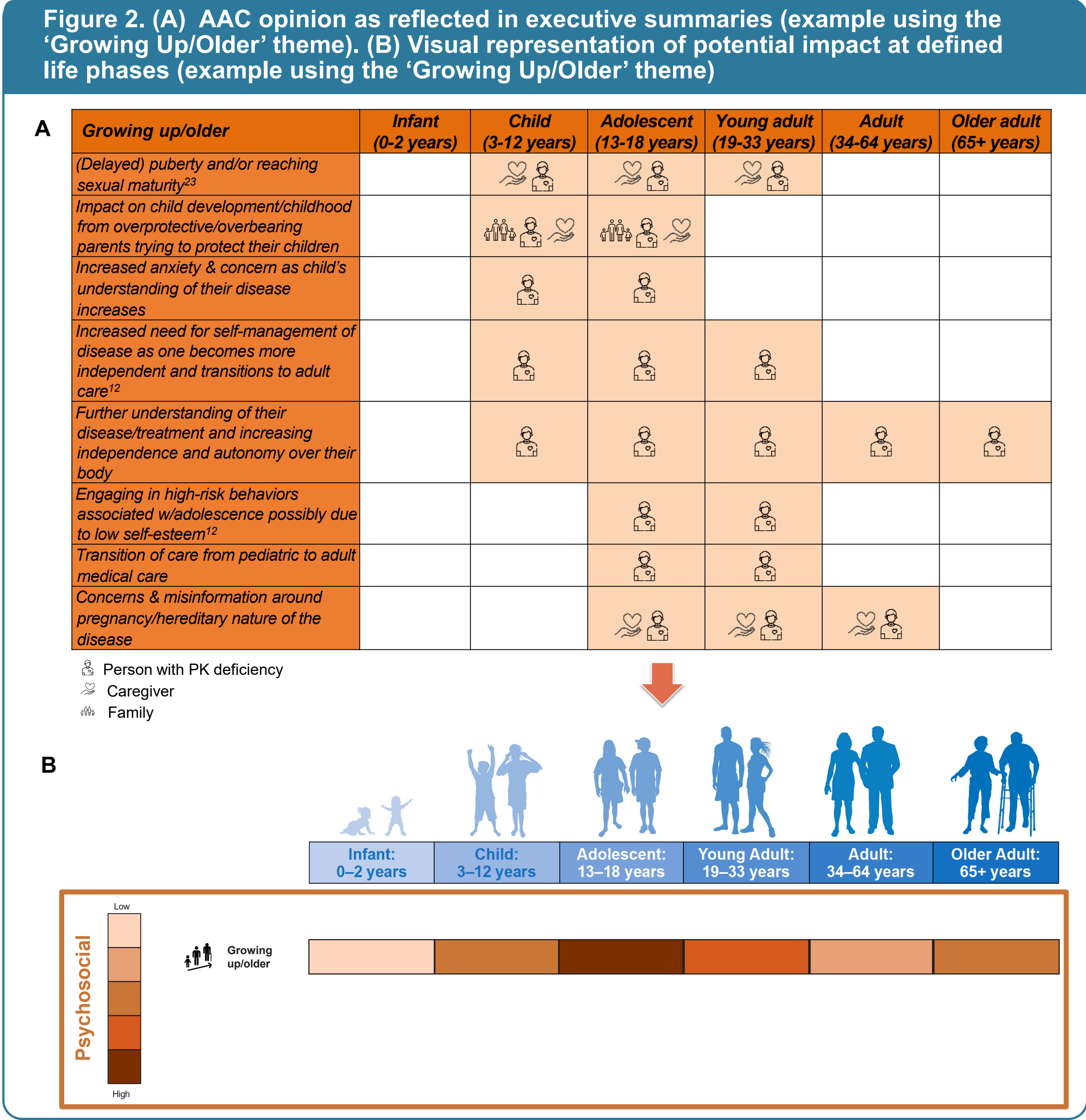
- Life phases were defined based on a review of existing literature and AAC input^{6–10}
 - Infant (0–2), Child (3–12), Adolescent (13–18), Young Adult (19–33), Adult (34–64), and Older Adult (65+)
- Working groups (2–3 AAC members) were assigned to each life phase and tasked with describing the important 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

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

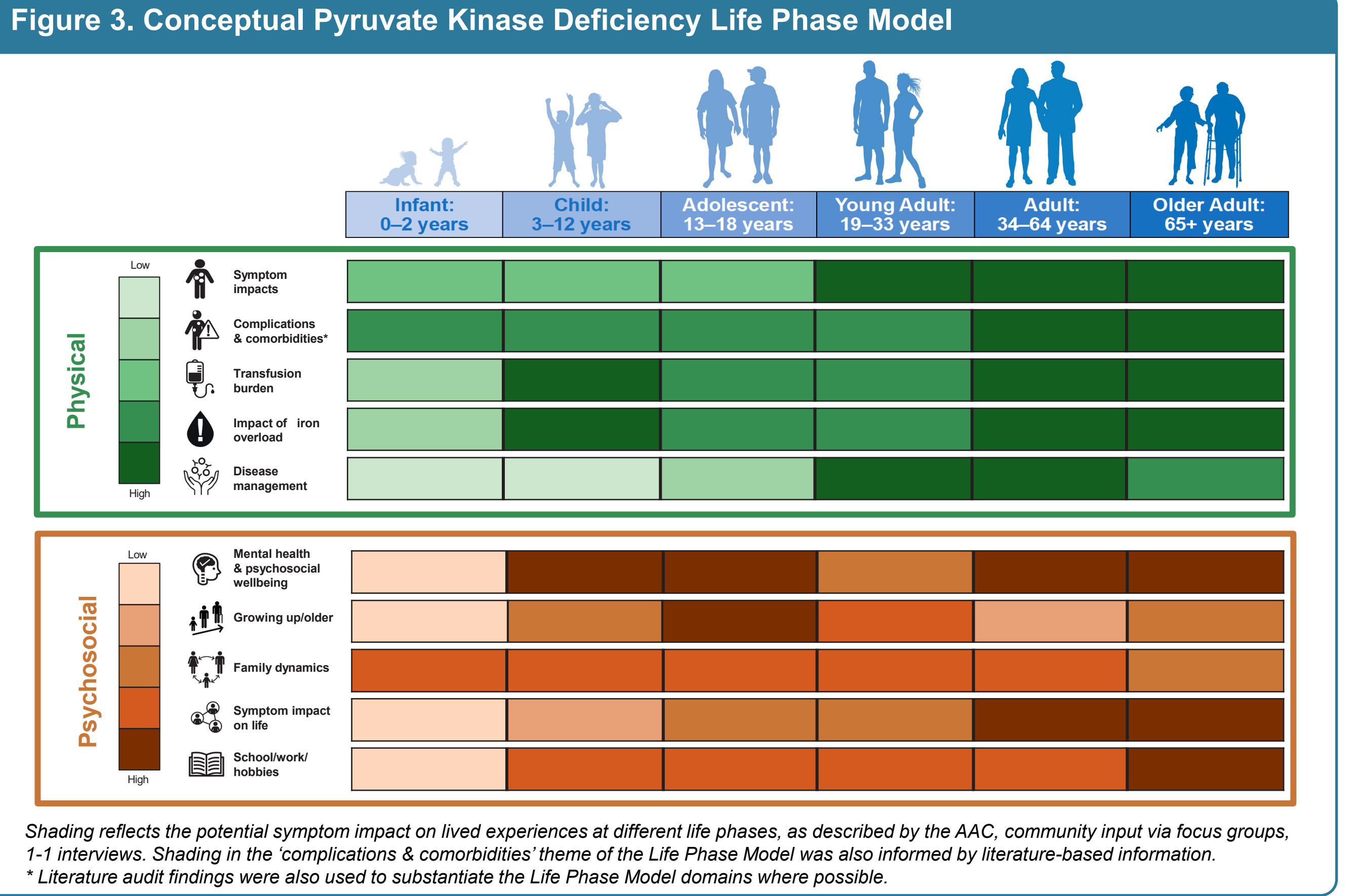
Life Phase Model: Community Input

- 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 Guidelines³⁰ and guidelines established by the UK Market Research Society³¹
- Feedback from the focus groups and interviews was reviewed by the AAC and the *Model* was further refined and finalized



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



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, Maaïke 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, Sobri; Consultancy: Sanofi; Wilma Barcellini: Alexion, Novartis – honoraria; Agios – research funding; Bioerativ, Incyte – board membership or advisory committee. **References:** 1. Al-Samkari H et al. *Haematologica* 2020;105(2):173–184; 2. Secreti 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. Geilman 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 studies from two small countries in Europe. 2021. <https://www.who.int/europe/publications/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/NORD-2020-Voice-of-the-Patient-Report-PKD-FNL_SmilesFile-FINAL_1.pdf. Accessed Nov 24, 2023; 13. Grace RF et al. *Eur J Haematol* 2018;101(6):758–765; 14. Koushik 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. Glenhøj A et al. *Blood* 2022;140(Supplement 1):5323–5325; 20. Al-Samkari H et al. *Blood Adv* 2022;6(6):1844–1853; 21. Selzer 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. BHIA Legal and Ethical Guidelines. 2023. <https://www.bhia.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.

* 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

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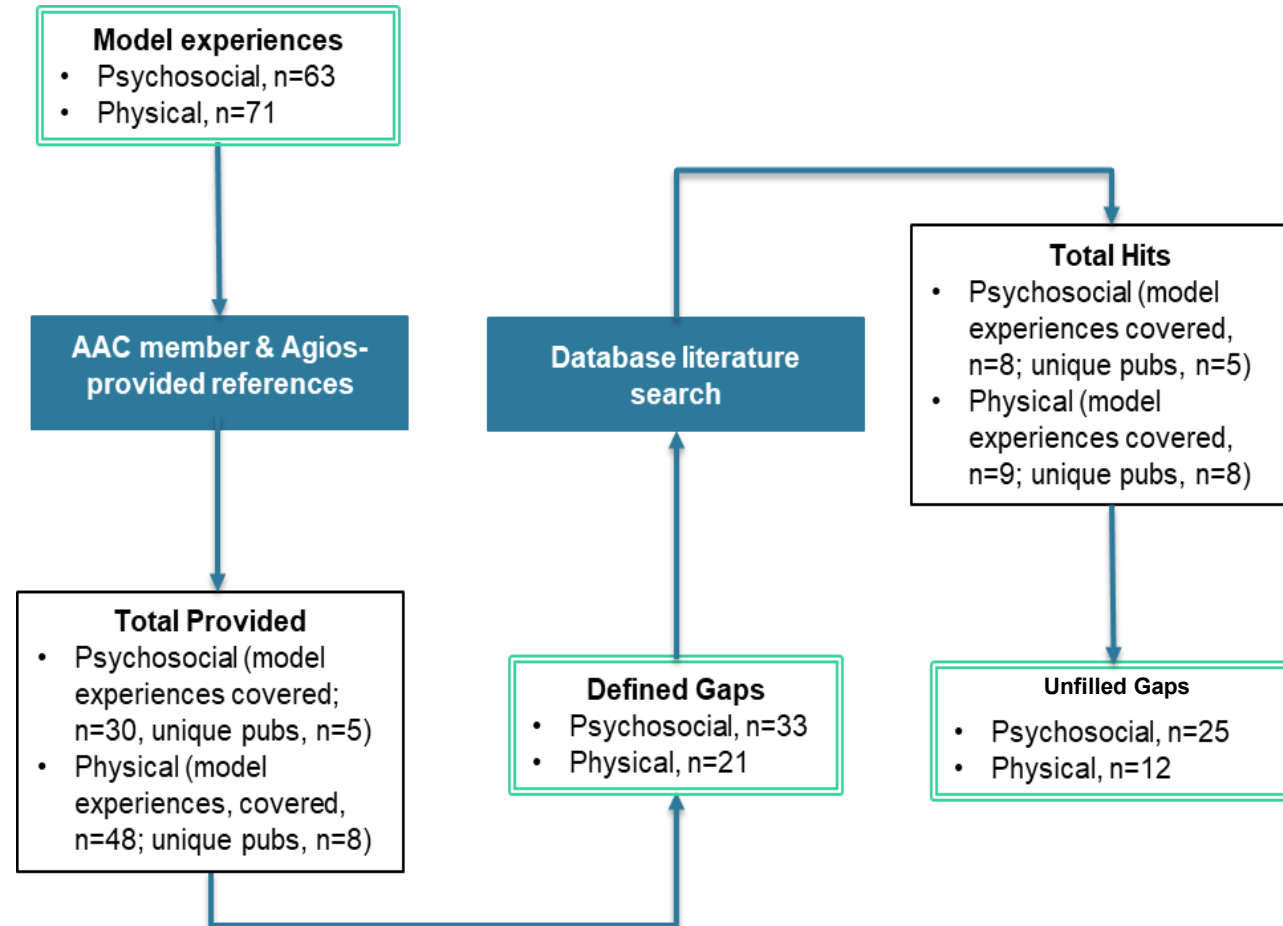
Supplementary Material

Rachael F Grace, MD¹, Lily Cannon, MA, MSc², Maaïke Eijgenraam³, Carl Lander, RN⁴, Laura Miller-D'Angelo⁵, Susan Morris, PhD⁶, Janie Davis, MBA⁶, Parija Patel, PharmD, MBA⁶, Tamara Schryver, PhD, RD⁷, Alejandra Watson⁵, and Wilma Barcellini, MD⁸

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Supplemental Figure 1: Literature Substantiation Process



Supplemental Table 1: Key psychosocial themes at different life stages of PK Deficiency

Note –shaded boxes depict how the psychosocial theme potentially impacts the individual with PK deficiency. Life phase groupings were chosen from review of existing literature.¹⁻⁵

Key:

In some instances, key themes have wider implications than just for the person with PK deficiency. Where this is the case, the below icons have been used to differentiate who the impacted person/group is Shaded boxes indicate that the theme/consideration relates to the person with PK deficiency.

	Parents/partners/carers
	Family
	Person with PK deficiency

	Infant (0–2 years)	3–12 years	13–18 years	19–33 years	34–64 years	65+ years
Mental health/psychological well being						
Stress/medical trauma ⁶						
Anxiety to do with catching contagious diseases and potential avoidance of situations						
Difficulties trusting medical professionals after negative experiences						
Difficulties trusting medical professionals after misdiagnosis ⁷						
Stress/anxiety about the future ⁷						
Coming to terms with the diagnosis of a child (especially due to lack of treatment)						
Coming to terms with your own diagnosis						
Impact of sleep irregularities ⁸						
Stress/anxiety from bullying ⁸						
Impact of fatigue ^{8,9}						
Concern about appearance and body image ⁸						
Possibility of accepting disease in later years ⁸						
Concerns around life expectancy						
Impact on child attachment/bonding with parents due to high stress and medical treatments ¹⁰						
Impact on child attunement with parents due to high stress and medical treatments ¹⁰						
Unstable environment/childhood trauma and the effects on health which may complicate effects on mental health later on ⁵						
Grieving missed opportunities due to burden of disease						
Impact of comorbidities associated with older/natural aging ¹¹						

Supplemental Table 1: Key psychosocial themes at different life stages of PK Deficiency

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	Infant (0–2 years)	3–12 years	13–18 years	19–33 years	34–64 years	65+ years
Family dynamics						
Financial/emotional burden of the disease and navigating medical system on family ⁷				 	 	 
Burden of juggling family life/work and managing the disease (own or child's) ⁷	 	 	 	 	 	 
Impact on family dynamics and untangling regular family dynamics from those related to PK deficiency ⁸				 	 	
Learning how to support the person with PK deficiency as an equal family member				 	 	
Balancing the need to work vs the desire to monitor and protect children from environments due to their PK deficiency ⁷				 	 	 
Caring for a newborn with PK deficiency						
Jealousy and guilt affecting both people with PK deficiency and their parents/caregivers/siblings	 	 	 	 	 	 
Impact of fatigue on behavior, coping with life and mental development	 	 	 	 	 	 
Economic impact of caring for parent(s) or partner with PK ¹²			 	 	 	 
Emotional impact of caring for parent(s) or partner with PK ⁸			 	 	 	 
Stress and emotional impact on decisions related to family planning ⁸			 	 	 	

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	Parents/partners/carers
	Family
	Person with PK deficiency

	Infant (0–2 years)	3–12 years	13–18 years	19–33 years	34–64 years	65+ years
Growing up/older						
<i>(Delayed) puberty and/or reaching sexual maturity¹³</i>						
<i>Impact on child development from overprotective/overbearing parents trying to protect their children</i>						
<i>Increased anxiety and concern as child's understanding of their disease increases</i>						
<i>Increased need for self-management of disease as one becomes more independent and transitions to adult care⁷</i>						
<i>Further understanding of their disease/treatment and increasing independence and autonomy over their body</i>						
<i>Engaging in high-risk behaviors associated with adolescence possibly due to low self-esteem⁷</i>						
<i>Transition of care from pediatric to adult medical care</i>						
<i>Concerns and misinformation around pregnancy/hereditary nature of the disease</i>						

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	Parents/partners/carers		Infant (0–2 years)	3–12 years	13–18 years	19–33 years	34–64 years	65+ years
	Family	School/work/extracurriculars/sports/other activities						
	Person with PK deficiency	Accommodations needed at school/work to ensure safety/best performance ⁷						
		Impact of disease symptoms, particular fatigue on ability to learn and keep up academically ⁷						
		Fears around going to school and growing up ¹⁴						
		Potential bullying ⁸						
		Demands of trying to keep up with peers						
		Impact on extracurricular activities/sports/hobbies ¹⁴						
		Financial burden and decisions around claiming financial support (impact on self-esteem and feelings of guilt) ¹²						
		Impact on professional development, earning potential ⁷						
		Impact on relationships with colleagues						
		Being treated differently and made to feel less than human by peers/colleagues/society ¹⁴						

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	Parents/partners/carers
	Family
	Person with PK deficiency

	Infant (0–2 years)	3–12 years	13–18 years	19–33 years	34–64 years	65+ years
Symptom impact						
Impact of culture/religious beliefs on symptom management						
Noticing and listening to your body's limits						
Isolation from friends due to lack of energy ⁸						
Learning to cope with missed opportunities due to the burden of disease						
Impact of PK deficiency (hormone imbalances and fatigue) on intimacy/libido ¹⁵						
Consequences due to earlier poor management of the condition and related feeling of anger, regret, and resentment						
Cognitive functioning, memory impairment and impact on self-esteem ⁸						
Decreasing ability to exercise (may impact on mental health) ⁸						

Supplemental Table 1: Key psychosocial themes at different life stages of PK Deficiency

Note –shaded boxes depict how the psychosocial theme potentially impacts the individual with PK deficiency. Life phase groupings were chosen from review of existing literature.¹⁻⁵

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	Parents/partners/carers					
	Family					
	Person with PK deficiency					
The future						
Hope for the future/questions about what the future looks like ⁸						
Planning for the future, setting realistic (but ambitious) goals, and the associated stress and anxiety associated						
Increasing concern about health problems and old age. How will normal aging be affected? ⁸						
Possibility of additional support needed with aging and ahead of aging peers						
Concerns about retirement ⁸						
Preparing and anticipating end of life						
Legacy planning						

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	Person with PK deficiency	Accommodations needed at school/work to ensure safety/best performance ⁷						
		Impact of disease symptoms, particular fatigue on ability to learn and keep up academically ⁷						
		Fears around going to school and growing up ¹⁴						
		Potential bullying ⁸						
		Demands of trying to keep up with peers						
		Impact on extracurricular activities/sports/hobbies ¹⁴						
		Financial burden and decisions around claiming financial support (impact on self-esteem and feelings of guilt) ¹²						
		Impact on professional development, earning potential ⁷						
		Impact on relationships with colleagues						
		Being treated differently and made to feel less than human by peers/colleagues/society ¹⁴						

Supplemental Table 2: Key physical themes at different life stages of PK Deficiency

Note – shaded boxes depict how the psychosocial theme potentially impacts the individual with PK deficiency. Life phase groupings were chosen from review of existing literature.¹⁻⁵

	Infant (0–2 years)	3–12 years	13–18 years	19–33	34–64 years	65+ years
Signs and Symptoms						
Jaundice ^{16,17}						
Pale skin ⁸						
Fatigue ^{8,9,16}						
Bone pains						
Poor appetite ¹⁶						
Liver enlargement/failure/disease ^{16,17}						
Shortness of breath ¹⁶						
Disease complications/comorbidities						
Osteopenia/Osteoporosis (low Bone density) ^{11,16,17,18}						
Increased hemolysis due to acute stressors incl viral infections ¹⁶						
Sleep irregularities						
Gallstones ¹⁶						
Anemia ^{16,17}						
Hematopoiesis ¹⁹						
Leg ulcers ¹⁹						
Pulmonary hypertension ^{16,17}						
Hemolysis/Hemolytic crisis ¹⁶						
Thrombosis (blood clots) ¹⁷						
Memory/concentration issues (Brain fog) ⁸						

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	Infant (0–2 years)	3–12 years	13–18 years	19–33	34–64 years	65+ years
Disease Management Options						
Treatment with blood transfusions ^{16,17}						
Monitoring iron levels/iron overload ^{16,17}						
Monitoring chelation side effects ¹⁶						
Regular diagnostics and monitoring of bone density, osteoporosis and VIT D/ Calcium treatment and exercise to strengthen bones ¹⁶						
Treatment with Hematopoietic stem cell transplant ²⁰						
Participation in clinical trials and the potential for future curative treatment options ⁷						
Gall stone monitoring (abd US) ¹⁹						
Echocardiograms						
Splenectomy ¹⁶						
Monitoring for transfused patients, including endocrine and infections ¹⁹						
Sleep hygiene						
Folic acid supplementation ¹⁹						
Gall bladder removal						
Risk of thrombosis and consideration of anticoagulation and antiplatelet medications (blood thinners) ^{11,16}						
Medication adherence and impact on disease						
Noticing and listening to your body's limits and the implications of overexertion						
Monitoring before/during pregnancy ¹⁹						
PK activators ¹⁸						

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	Infant (0–2 years)	3–12 years	13–18 years	19–33	34–64 years	65+ years
Treatment complications						
<i>Relating to treatment options including transfusions, chelation, splenectomy and PK activators.</i>						
Potential for loss of vision or hearing due to chelation therapy						
Lifelong risk of iron overload ¹⁶						
Problems with vein access						
Headaches as a symptom/side effect of anemia or treatment ^{8,21}						
Post-splenectomy thrombosis ¹⁹						
Post-splenectomy serious bacterial infection ¹⁹						
Loss of libido (male and female) due to lethargy and hormone changes (natural and iron overload related) ¹⁵						
Impacts of iron overload						
Endocrinopathies ^{16,22}						
Delayed puberty/sexual maturity ^{13,23}						
Cardiac dysfunction/failure ¹⁵						
Liver cirrhosis ^{11,16}						
Liver cancer ²³						
Other considerations						
Gender-specific considerations, such as PK deficiency's impact on pre-menopause or male hormone imbalances						
Sport and exercise considerations ¹⁶						
Mental health considerations ¹⁷						
Lack of information about disease progression in older people						
Lack of/finding HCPs with an expertise in PK deficiency						
Family support / medical psychology/ relaxation techniques / financial support / Patient groups ⁷						

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