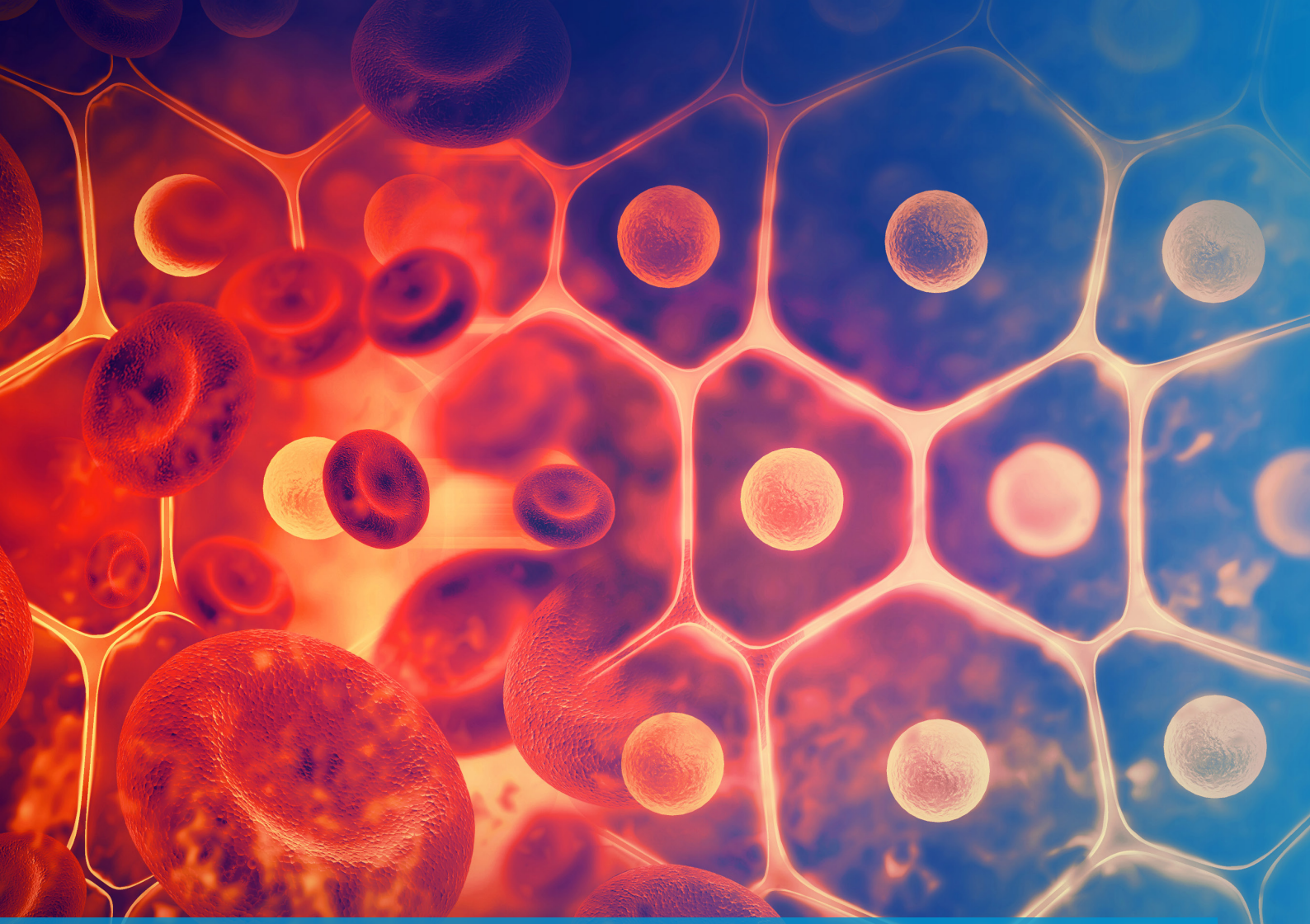

Pyruvate Kinase Deficiency

Reflections on the Patient Experience to Support Treatment and Care

A White Paper by the following contributors*:
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PKD-ALL-0167, September 2021

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Advocacy Groups:

THALASSAEMIA INTERNATIONAL FEDERATION

METABOLIC SUPPORT UK

hrive WITH PYRUVATE KINASE DEFICIENCY ORGANIZATION

PYRUVATE KINASE DEFICIENCY FOUNDATION

Contents

Hematologist View

Pyruvate kinase (PK) deficiency is a rare congenital hemolytic anemia, affecting approximately three people per million individuals worldwide[1, 2], with a wide spectrum of disease symptoms and complications.

DR. RACHAEL GRACE

DR. WILMA BARCELLINI

Due to the rarity of this anemia and the variability in clinical manifestations, clinicians can have difficulty recognizing and diagnosing PK deficiency. In addition, most hematologists will care for only one or two patients with PK deficiency during their career, which makes deep expertise for both monitoring and managing the symptoms and complications of PK deficiency challenging for practicing clinicians. In this report of the patient experience, several themes and key aspects for improvement of care for patients with PK deficiency are highlighted. The importance of this effort is underscored by the number of participants who took part in the survey which is presented in this White Paper, in spite of the rarity of this disease: namely, 200 patients and 75 caregivers representing a wide spectrum of age ranges and diversity of experiences from around the globe.

The survey results demonstrated that most patients and caregivers feel their hematologist manages their PK deficiency well; however, important areas were emphasized in which clinicians can improve in their approach to care. The results also underline the opinion that individual hematologists should develop a deeper understanding of PK deficiency or consult with a colleague with disease expertise. Educational materials and other resources about living with PK deficiency should be available to patients and caregivers. A multidisciplinary team should care for patients with PK deficiency. Hematologists should help identify patients who would benefit from psychological and other mental health resources or offer these resources routinely to all patients with PK deficiency.

At this time, only supportive management (transfusions, splenectomy) is available for treatment of PK deficiency. The survey demonstrates that patients who are not transfused have the greatest unmet needs in terms of communication with their hematologists. Patients who are not transfused may be less likely to have routine monitoring or regular visits to discuss the impact of PK deficiency on daily life. If patients are not being transfused, clinicians may not recognize what care is required including monitoring for complications, mental health issues, and changing transfusion needs over time. Decisions about transfusions should be regularly re-evaluated and based on symptoms rather than hemoglobin values. Clinicians should ask open-ended questions and consider transfusions in symptomatic patients.

As the therapeutic landscape evolves and disease-directed therapies enter clinical trials, it will be more important than ever for patients with chronic hemolytic anemias to have an accurate diagnosis and an informed clinical team. Disease support groups for PK deficiency are expanding and will become a robust added resource for patients and their families. Continued research into best practice for monitoring, supportive management and treatment of patients with PK deficiency will remain critical to optimize care and inform practicing hematologists as treatment options expand.

Patient and Caregiver View

Pyruvate kinase (PK) deficiency is a life-long condition that can be very serious for many patients. Clinical management guidelines, along with other related research have been developed by hematologists with expertise in the disease. However, the lived experience has been less well reported upon. We know this from the Voice of the Patient[3] report and regular commentary amongst the PK deficiency community. We advocate that the lived experience is as important as and should contribute to clinical treatment.

CARL LANDER, RN, PATIENT

TAMARA SCHRYVER, PHD, RD, PATIENT

We have known within our community that mental health issues are not properly supported and often not spoken about. The time has arrived to make a call to action across healthcare to consider the psychosocial needs of patients with PK deficiency. Our joint experience as patients and caregivers ranges hugely, however the one constant is the need for care that is truly holistic. We need to not only treat physical symptoms, but also help in dealing with the emotional impact. Western medicine is the only medical culture that deals with body and mind as two separate entities. It is time to consider both as one, within the care of those with long-term conditions such as PK deficiency.

This White Paper has been developed in partnership, not just with Agios representatives but with expert hematologists, patient advocacy groups and us as patients and caregivers. The value of this collaboration is immense as it enables the voice of the patient to be embedded within the hematology community in a way that has not happened before.

The patient and caregiver voice are very strong but work now needs to take place to turn this into meaningful action. Communication is a critical factor in the doctor-patient relationship; the ability of the hematologist to listen, research and provide solutions is critical in helping patients navigate their own concerns.

> “The most difficult part of being a mother (caregiver) was to accept that the world was not prepared for people with PK deficiency. Most of my fears, worries, and questions were always disregarded by others because my son looked “fine” or “at least he doesn’t have cancer”. Most people find it hard to believe how much he goes through on a day-to-day basis. I decided that my son was going to be heard by others unlike what was happening in the past. We have been teaching him to stand up for himself, and we are here to help him find a way to do that while helping others to do the same. He has learned that we live in a selfish world, but we can change it if we offer help and hope to those who need it.
>
> We are committed to informing health workers, physicians, mental health providers, and the world in general about PK deficiency, to make it clear that it is a real medical condition that requires a large amount of resources to treat. We need stakeholders to understand the burden of this disease and the impact it has on patients’ lives.
>
> PK deficiency is a long road patients and their families must traverse, with mountains and rivers to cross and beautiful dawns to appreciate, but it is not without its darkest of nights.”

ALEJANDRA WATSON, CAREGIVER

Executive Summary

Pyruvate Kinase (PK) deficiency is an underrecognized and misunderstood rare genetic disease. As with many other chronic diseases, over time patients and caregivers simply learn how to cope as best they can.

First discovered in 1961, PK deficiency is a rare inherited disorder of the blood resulting in lifelong anemia and serious complications, such as chronic iron overload in the liver and heart, low bone density, and pulmonary hypertension[3]. The disease has a profound and wide-ranging impact on quality of life: anemia results in exhaustion and fatigue, which can lead to difficulty concentrating at work or at school; jaundice can create an additional psychosocial burden; and many patients report social isolation and depression, among other challenges[3]. A complex and poorly understood disorder, PK deficiency often goes misdiagnosed or undiagnosed[3]. Its true prevalence is unclear[4, 5]. Treatment is supportive, rather than targeted at the underlying cause, with a focus on blood transfusions to control symptoms[3].

Until recently, PK deficiency patient advocacy was limited to private Facebook groups. In 2020, Agios brought together a group of leaders in PK deficiency to share their unified perspectives and voices. This is the aim of the Agios PK Deficiency Advocacy Advisory Council (AAC), a multi-disciplinary group of patients, caregivers, patient advocates and physicians.

By bringing together medical experts and leaders within the community – both patients and caregivers – the vision of the AAC is that people around the world affected by PK deficiency receive timely diagnosis and can easily access the education, support and care they individually need.

As a first step towards achieving this vision, the group identified priority unmet needs it could work to address. Within these discussions, AAC members acknowledged that in their experience, patients and caregivers often feel that hematologists have a low understanding of the condition and do not appreciate the burden of the disease. As a result, the group decided to explore communication between patients and caregivers and their hematologists, in order to better understand those interactions, determine best practices and develop a call to action for improved communication between these stakeholders. To this end, the AAC launched an international survey to collect further information.

The survey found that most patients and caregivers believe their hematologist manages their own or their loved one's PK deficiency "well", and that communication with the hematologist (Figure 2) is somewhat positive to very positive (Figure 3). However, contradictory

Executive Summary Continued

experiences emerge upon further exploration, pointing to unmet needs lying beneath the surface. One particular area for improvement relates to hematologist understanding of PK deficiency. Just half of respondents, or fewer, agree that their hematologist is able to answer their questions about how to manage PK deficiency; explain potential health complications in a clear way; or demonstrates extensive knowledge and understanding of PK deficiency (Figure 2).

Furthermore, the data make clear that interactions with hematologists have an emotional impact (Figure 3): for example, nearly one in three respondents (29%) report at least one negative emotion following interactions with their hematologist, such as “anxiety” or “worry” (Figure 4). Within verbatim survey responses and qualitative interviews, respondents refer to a lack of understanding, both from healthcare professionals and the general public, leading to feelings of isolation and judgement from others. The findings point to the mental toll of living with PK deficiency, as a chronic disease that lasts a lifetime, and a need for better understanding of the burden of living with PK deficiency – along with holistic disease management that addresses both physical and mental health.

Importantly, communication with the hematologist is reported to be negative most often among respondents who have zero transfusions annually. For example, just over half of respondents receiving zero transfusions per year report that their hematologist appreciates and understands the impact of PK deficiency on their quality of life and understands the disease well (Figure 7). Further, most report feeling neutral to negative following interactions with their hematologist. While the survey was not powered to establish whether there is a causal connection between receiving transfusions and positive communication with the hematologist, these findings nonetheless highlight the unique needs of non-transfused patients.

This paper outlines unmet needs in communication along with calls to action for hematologists, patients and caregivers, to help address those gaps. Ultimately, more research is needed to build on the survey insights and broaden understanding of the needs of those living with this serious and debilitating condition. This should be part of the wider evolution of a unified voice for the PK deficiency community. In the meantime, it is hoped that this resource can be used to promote best practices and foster dialogue among healthcare professionals, patients and caregivers alike, to help improve the lives and futures of people with PK deficiency.

ABOUT THE AGIOS PK DEFICIENCY ADVOCACY ADVISORY COUNCIL (AAC)

Established in April 2020, the AAC is an international, multi-disciplinary group of experts in PKD – patients, caregivers, patient advocates and physicians – fully supported and resourced by Agios. The vision of the AAC is that people around the world affected by PK deficiency receive timely diagnosis and can easily access the education, support and care they individually need.

PK Deficiency – A Rare and Under-Recognized Blood Disorder

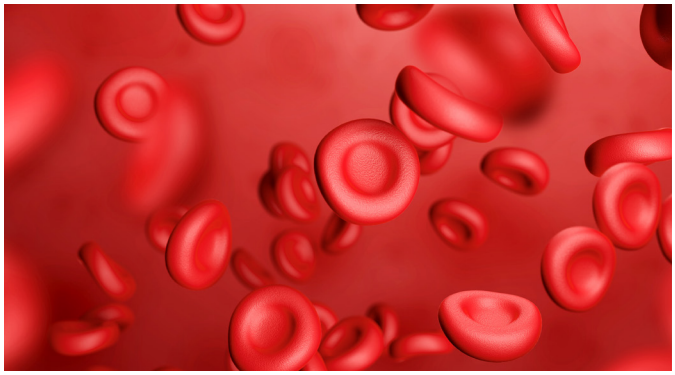
Pyruvate kinase (PK) deficiency is a rare inherited genetic blood disorder that is characterized by the premature destruction of red bloods cells[6,7]. It is caused by mutations in the *PKLR* gene that is expressed in liver and red blood cells, leading to a deficiency of the pyruvate kinase enzyme[6] – a crucial component of the glycolytic pathway that leads to the formation of adenosine triphosphate (ATP), a cell's energy source.

Reduced pyruvate kinase enzyme leads to a shortage of ATP and a shortened lifespan for red blood cells[6,8,9]. The abnormal red blood cells are collected by the spleen for destruction (hemolysis)[8]. The overall impact is a decrease in red blood cells carrying oxygen to the body's cells: in short, chronic hemolytic anemia[6].

PK deficiency affects approximately three people per million individuals worldwide[1, 2] and in Europe it is estimated that 1 in 20,000 people have PK deficiency[9]. However, it is thought that the condition may be under and/or misdiagnosed due to a lack of awareness of this rare disease among clinicians, as well as challenges in diagnosing the disorder[3,10].

The severity and clinical symptoms of PK deficiency vary considerably, but common symptoms include fatigue, dyspnea, jaundice, and splenomegaly[11-13].

The condition is chronic and lifelong, and in some cases, it can be life-threatening at birth. Complications associated with the premature destruction of red blood cells include the development of gall stones, blood iron overload, low bone density and pulmonary hypertension, which can be life-threatening if left untreated[3].



With no disease-modifying treatments currently available, management tends to be focused on supportive symptom control such as blood transfusions to increase hemoglobin levels. Nonetheless, significant unmet need and a severe disease burden remains, particularly among children, pregnant women, and aging adults[14].

Typically, patients will be managed and cared for by a hematologist. However, a patient may see a variety of healthcare experts as part of their care, including pediatricians, obstetricians, endocrinologists, pulmonologists, cardiologists, and nurses, with variations according to regions and country infrastructures. Collaboration between patient, caregiver and clinical communities is required to ensure that the best possible management plan is identified.

Current Advocacy Landscape

Until recently, there were few advocacy groups focused specifically on PK deficiency, and no existing cohesive patient and caregiver community for peer collaboration[3].

In 2019, the National Organization for Rare Disorders (NORD) represented the PK deficiency community in an externally-led Patient Focused Drug Development (EL-PFDD) meeting with the FDA, and since then has helped the community through its "Rare Launch" program – ultimately leading to the establishment of the US PK Deficiency Foundation in 2021 (see box to the right). In addition, further patient organizations focused on PK deficiency are in development in the UK and other countries. Since 2020, the Thalassaemia International Federation (TIF) and Metabolic Support UK (MSUK) have expanded their focus on PK deficiency with the development of educational and advocacy initiatives. Furthermore, there are now several PK deficiency-specific groups on social media, including the group People with PK Deficiency.

PYRUVATE KINASE DEFICIENCY FOUNDATION

ABOUT THE PK DEFICIENCY FOUNDATION

The PK Deficiency Foundation is a US-based national non-profit organization whose mission is to enhance the quality of life for patients and their families by providing awareness, expanding education, and promoting advocacy.

Key objectives include:

- Developing programs that meet the medical, financial, psychosocial, and education concerns/needs of those affected by PK Deficiency
- Offering educational and support materials through its website, provider database, newsletter, and brochures
- Providing a national database of specialists knowledgeable in PK deficiency
- Providing a resource list of physicians participating in clinical trials
- Sponsoring education to assist medical professionals in establishing appropriate standardized diagnostic and treatment guidelines
- Sponsoring national and regional meetings
- Supporting research into the causes and management of PK deficiency

Find out more at: www.pkdf.org

thrive WITH PYRUVATE KINASE DEFICIENCY ORGANIZATION

ABOUT THE THRIVE WITH PYRUVATE KINASE DEFICIENCY ORGANIZATION

The Thrive with Pyruvate Kinase Deficiency Organization brings together people and families affected by PK deficiency to address and advocate for their unique needs. By uniting our community, Thrive encourages the sharing of experiences to alleviate the isolation of living with a rare disease.

To improve PK deficiency care, we strive to:

- Build community connectivity and support social well being
- Support personalized and evidence-based treatment choice
- Educate and improve awareness among all stakeholders
- Optimize mental health and body autonomy

And with a board of patients and caretakers linked to PK deficiency, we seek to improve treatment accessibility for people of all walks of life. Rare but not alone, PK deficiency.

Find out more at: www.thrivewithpkd.org.

THREE PATIENT ORGANIZATIONS WITH AAC REPRESENTATION

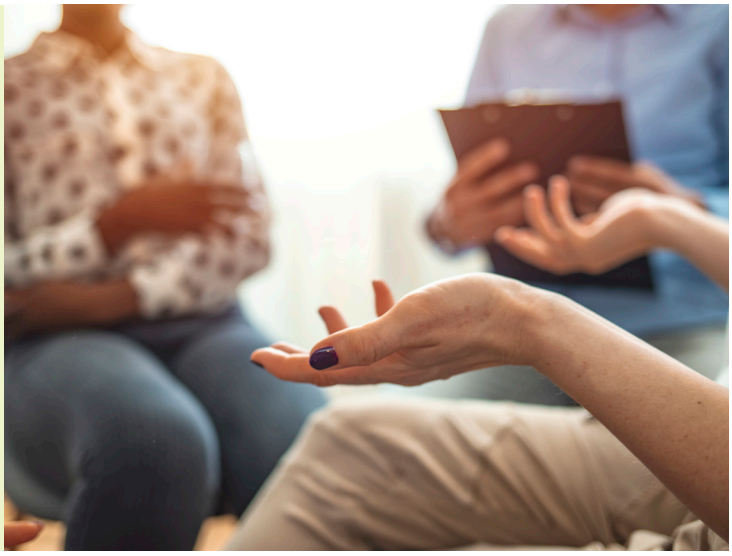
NATIONAL ORGANIZATION FOR RARE DISORDERS (NORD)
rarediseases.org

A US-based patient advocacy organization dedicated to individuals with rare diseases and the organizations that serve them. With 300 member organizations, NORD is committed to the identification, treatment and cure of rare disorders through programs of education, advocacy, research and patient services.

METABOLIC SUPPORT UK
metabolicsupportuk.org

An umbrella patient organization for Inherited Metabolic Disorders, supporting thousands of patients and families worldwide that have no other support. Focuses on individual support, building communities, patient empowerment and advocacy.

METABOLIC SUPPORT UK
Your rare condition. Our common fight.



THALASSAEMIA INTERNATIONAL FEDERATION (TIF)
thalassaemia.org.cy

An international patient-driven non-profit, non-governmental umbrella organization representing 232 National Thalassaemia Associations in 62 countries. TIF is based in Cyprus and its vision is to ensure equal access to quality health care for every patient with thalassemia and other hemoglobin disorders across the world.

THALASSAEMIA INTERNATIONAL FEDERATION

Survey Methodology

An internet-based quantitative and qualitative survey was developed to explore the role of communication between patients and caregivers and their hematologists in their experience of disease management.

The survey was open to adults diagnosed with PK deficiency, and to adult caregivers (e.g., parent, spouse, partner, child, relative) who provide unpaid care for someone diagnosed with the condition. Two versions of the survey were developed: the first for patients and the second for caregivers. Closed-ended, multiple choice, Likert scale and binary choice questions were included, with several questions offering the opportunity to respond via free text.

Survey questions covered topics including:

- Information, advice and support tools provided at or around the time of diagnosis;
- Knowledge and understanding of PK deficiency on the part of the hematologist providing care to a person with PK deficiency*, including its impact on quality of life;
- Levels of communication with the hematologist, including feelings following interactions;
- The patient or caregiver's relationship with the hematologist and (among caregivers) its impact on the care they provide to their loved one.

**Note, the survey asked respondents to provide experiences on the basis of interactions with one hematologist. Respondents were not asked whether their hematologist is or is not a PK deficiency 'expert'.*

Data collection and fieldwork was completed between January and February 2021 and was carried out according to British Healthcare Business Intelligence Association (BHBIA) Legal and Ethical Guidelines, as well as guidelines established by the UK's Market Research Society (MRS). The survey was fielded among participants recruited via online panels that met required BHBIA and MRS standards for data collection. Due to the small number of patients with PK deficiency worldwide, additional respondents were identified via AAC member channels, including PK deficiency Facebook groups.

The survey was open to patients and caregivers worldwide and made available in English as well as French, German, Spanish and Italian. Completion of the survey questionnaire took respondents approximately 20 minutes to complete. Demographic information including age, country of residence and gender was collected.

As part of the survey, patients and caregivers were asked if they would like to participate in a 45-minute follow-up telephone interview to discuss topics related to the survey, to complement the data obtained via the survey and provide further insights. These interviews were conducted in March 2021.

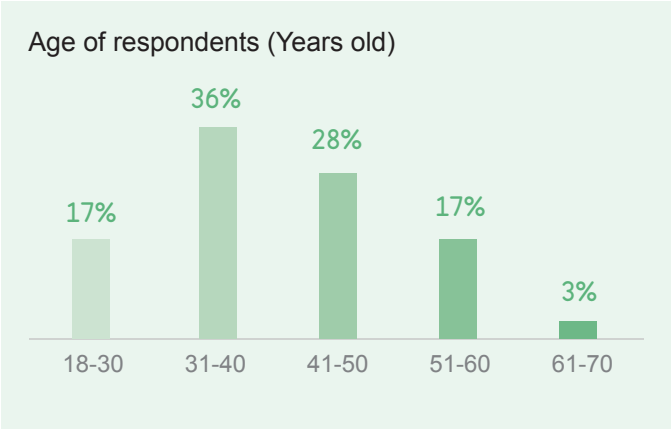
Survey and interview information was handled in accordance with Agios Data Privacy Notice, country-specific regulations, and the General Data Protection Regulation (GDPR) guidelines where appropriate.

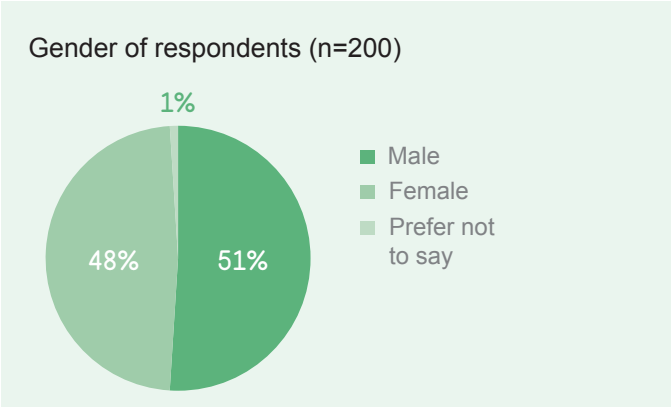
Survey Demographics

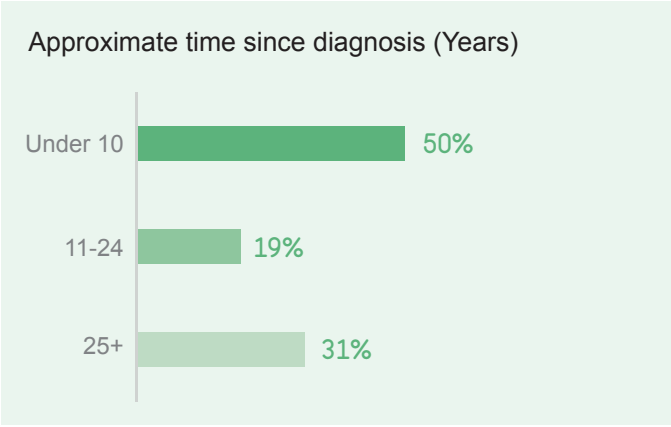
A total of 200 patients and 75 caregivers aged 18 and over completed the survey. Summary demographics for survey respondents are shown below.

FIGURE 1: RESPONDENT DEMOGRAPHICS

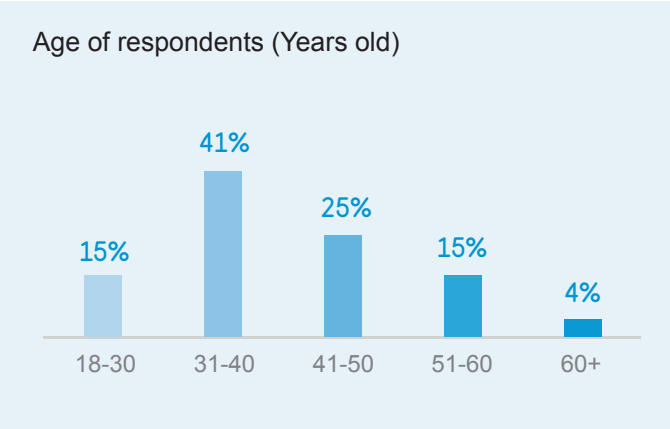
PATIENTS

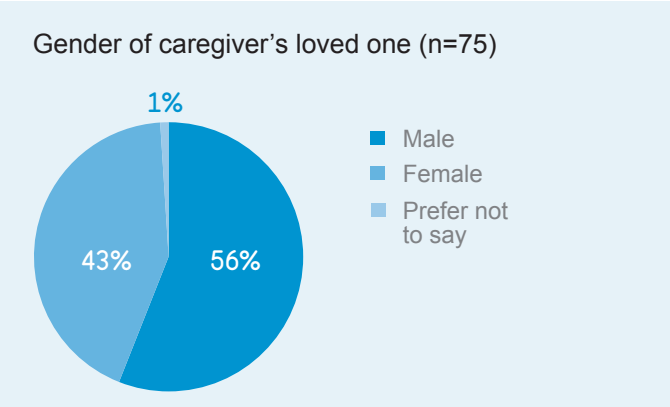


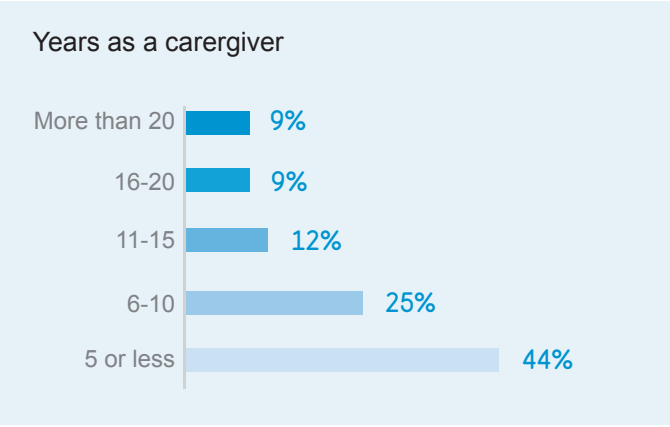




CAREGIVERS





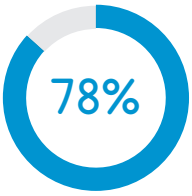


A small number of survey respondents opted-in to take part in a follow-up phone interview to discuss topics related to the survey.

Findings

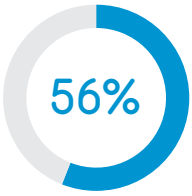
1 While most patients and caregivers report positive communication with their hematologist, the data reveal gaps in hematologist understanding and other unmet needs.

The majority of respondents surveyed say that their hematologist manages their own or their loved one's PK deficiency "well"...

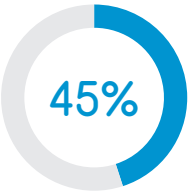


...and regards PK deficiency as a serious condition

However, when these respondents were probed regarding their hematologist's level of understanding of PK deficiency, a more complex picture emerges (Figure 2).



Just over half of respondents say their hematologist is able to answer their questions about how to manage PK deficiency...



...and less than half report that their hematologist demonstrates a deep knowledge and understanding of PK deficiency.

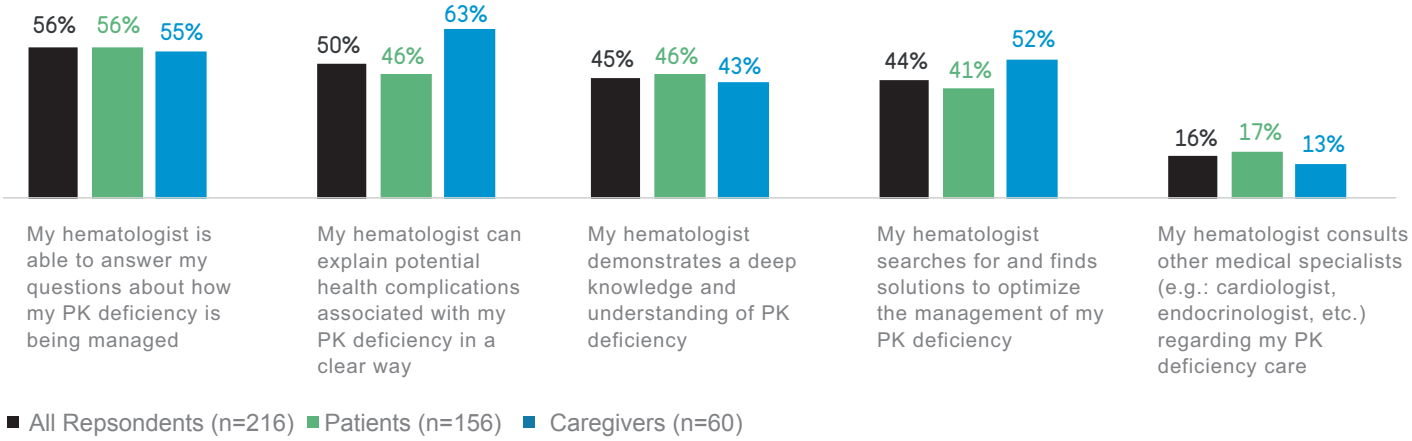
Overall, half of respondents (50%) say their hematologist explains potential health complications in a clear way, although the level of agreement with this statement among patients (46%) was notably lower than among caregivers (63%) (Figure 2), which may point to differing communication needs between patients and caregivers.

There is an apparent disconnect, in which respondents consider their PK deficiency to be managed "well" despite their hematologist not demonstrating an extensive knowledge of the condition or an ability to answer questions. A similar disconnect was observed within the follow-up phone interviews: participants described their PK deficiency as being managed "well" but acknowledged a lack of deep knowledge on the part of their hematologist. When asked about this disconnect, phone interviewees cited the nature of PK deficiency, as a chronic, rare disease that they have learned to cope with over time. They also acknowledged that treatment options for PK deficiency are limited.

Less than half of respondents (44%) agree that the hematologist searches for and finds solutions to optimize the management of their PK deficiency, despite reporting that their disease is managed "well" (Figure 2).

Responses in the qualitative interviews indicate patients would like their hematologist to be more proactive in searching for solutions – one patient commented that while their hematologist "might not immediately have the answer", they would like their hematologist "to think 'Okay, I'm not sure, I don't have the answer at the moment but I'm going to look into it". Another patient commented that they would like their hematologist to be "a little more progressive in researching treatments".

FIGURE 2: REASONS PK DEFICIENCY IS WELL MANAGED



A minority (16%) of those who consider their PK deficiency to be managed "well" say their hematologist consults other medical specialists regarding their PK deficiency (Figure 2). While the frequency with which the hematologist should consult other medical specialists may vary from case to case, the serious complications associated with the condition, such as splenomegaly, osteoporosis or pulmonary hypertension, mean it is advisable for hematologists to reach out to other specialists and seek advice when making decisions.

While the above findings reveal areas for improvement in hematologist understanding of PK deficiency and their ability to answer questions, encouragingly, patients and caregivers who believe their PK deficiency is managed "well" say their hematologist makes it easy to ask questions about the condition (88%) and to ask questions about the way their PK deficiency is managed (87%).

THE PATIENT AND CAREGIVER PERSPECTIVE

"I think most patients, especially younger patients, are so grateful for treatment they receive and don't like expressing their true feelings, and maybe even fear jeopardizing the situation. Patients learn to live with themselves and don't know any differently, or are embarrassed to express how they're truly feeling to the hematologist. This may explain the disconnect seen in the findings, where respondents say they consider their PK deficiency to be managed "well" despite then saying their needs aren't being met."

Linda McNeely, Caregiver

"I've seen many hematologists in my 20's and 30's at the referral of my doctors and I felt like they were using me as a project. At first I thought they were trying to help, but I wasn't getting a diagnosis or confirmation of PK deficiency. I got frustrated so I just stopped going."

Laura Miller-D'Angelo, Patient

Findings Continued

2 Interactions with hematologists have an emotional impact, and there is a particular unmet need regarding emotional and psychosocial support.

While most respondents report feeling somewhat positive or very positive after interacting with their hematologist (75%), a quarter (25%) state they feel neither positive nor negative, or somewhat negative (Figure 3). Furthermore, nearly one in three respondents (29%) report at least one negative emotion following interactions with their hematologist.

Among respondents who said they feel neither positive nor negative after interactions, a notable proportion report feeling "worried" (21%), "anxious" (17%), or "depressed" (17%) (Figure 4). Although in the survey respondents were not asked about their emotional wellbeing in general, outside of interactions with their hematologist, these findings point to the emotional toll of PK deficiency, even among those who say that interactions with their hematologist are positive. Importantly, only a minority of patients (11%) and caregivers (14%) report feeling "empowered" after interactions with their hematologists (Figure 4).

FIGURE 3: FEELINGS FOLLOWING HEMATOLOGIST INTERACTIONS

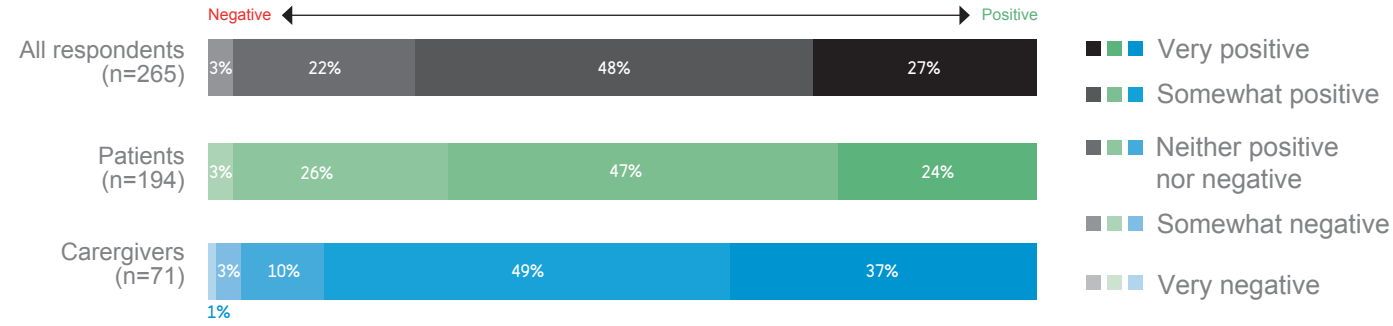
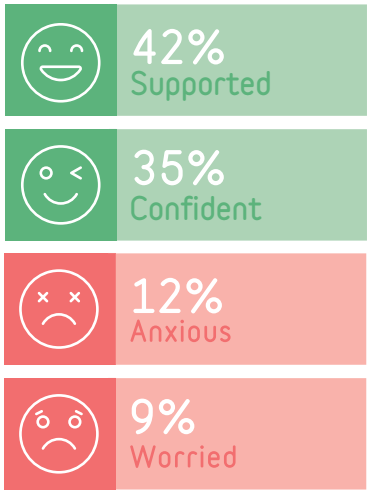


FIGURE 4: RESPONDENT EMOTIONS FOLLOWING HEMATOLOGIST INTERACTIONS

	All (n=265)	Neither + or - (n=58)
Supported	42%	9%
Confident	35%	19%
Optimistic	27%	5%
Encouraged	26%	7%
Understood	26%	10%
Content	20%	10%
Assured	19%	7%
Connected	18%	7%
At ease	18%	5%
Empowered	12%	3%
Happy	11%	-

	All (n=265)	Neither + or - (n=58)
Anxious	12%	17%
Worried	9%	21%
Frustrated	7%	10%
Depressed	6%	17%
Alone	5%	14%
Unempowered	5%	12%
Misunderstood	5%	10%
Dismissed	4%	7%
Disappointed	3%	10%
Insecure	3%	7%
Pessimistic	3%	7%



The neither positive or negative (neither + or -) respondent group in this graph refers to those who reported that overall, they felt neutral after interactions with their hematologist. However, when probed further, they reported feeling a wide range of emotions. Respondents could select multiple emotions when answering this question.

THE PATIENT PERSPECTIVE

Generally I try and live life without thinking about the ways in which PK deficiency impacts me. During consultations it does rather slap you on the face when you review how you feel, the meds you need and the scans and tests required – these take up the time we should be living and having fun."

Carl Lander, Patient

I felt well enough that I didn't see a hematologist on a regular basis until I got older. Then I started having symptoms like brain fog and extreme fatigue. Around the same time, I learned about the rare disease community and that I wasn't the only with these experiences, that's when I knew I had to teach my hematologist so that he could help me in a partnership."

Laura Miller-D'Angelo, Patient

The emotional toll of living with PK deficiency is reinforced by responses given during the qualitative interviews and open-text survey responses. Respondents linked the emotional burden of the disease with a perceived lack of understanding on the hematologist's part of what it is like to live with the condition. For example, one interviewee mentioned that their hematologist "doesn't understand how it feels to live on [a particular hemoglobin level] and how it impacts your life. They don't get the more qualitative parts of living". Another commented:

"The doctor can look at the numbers, but there is a psychology behind the numbers. There is me as a person. That's what I think gets missed."

Another respondent expressed how their hematologist "does not take seriously enough how this disease bothers me and the person I care for". A further respondent explained: "My PK deficiency isn't managed. I am often dismissed by the hematologist. I have major concerns that the disease will affect both my quality of life and my life itself".

These findings highlight a clear need to improve hematologists' understanding of the burden of PK deficiency, particularly as this perceived lack of understanding can lead patients to minimize their concerns:

"Even if my hemoglobin level looks good on paper, I struggle with fatigue. Sometimes I lack that courage to tell my doctor about my struggles. I don't want to complain."

Findings Continued

Another patient explained that they "try to hide [their symptoms] and try to be normal, but in reality, it is heavily impacting my life".

As well as improving hematologist understanding of what it's like to live with PK deficiency, the data also point to a need for increased referrals to support groups as a resource for emotional support. Among patients who were diagnosed as adults and caregivers present at the time of their loved one's diagnosis, just under a third (32%) were given information about rare disease support groups, and less than a third (26%) received referrals to local disease support groups or counselling services (Figure 5). This suggests that hematologists may not be fully aware of the number of groups focused on PK deficiency that have sprung up in the last 25 years with the advent of the Internet – indicating a need for greater awareness of such groups, both within the medical and patient communities. As well as improving awareness of existing groups, there is also a need for more support groups to be created, focused specifically on PK deficiency. This includes in-person options, as many PK deficiency support groups are Facebook-based, which may deter those who do not use Facebook or prefer not to speak about their experiences on social media.

THE PATIENT PERSPECTIVE

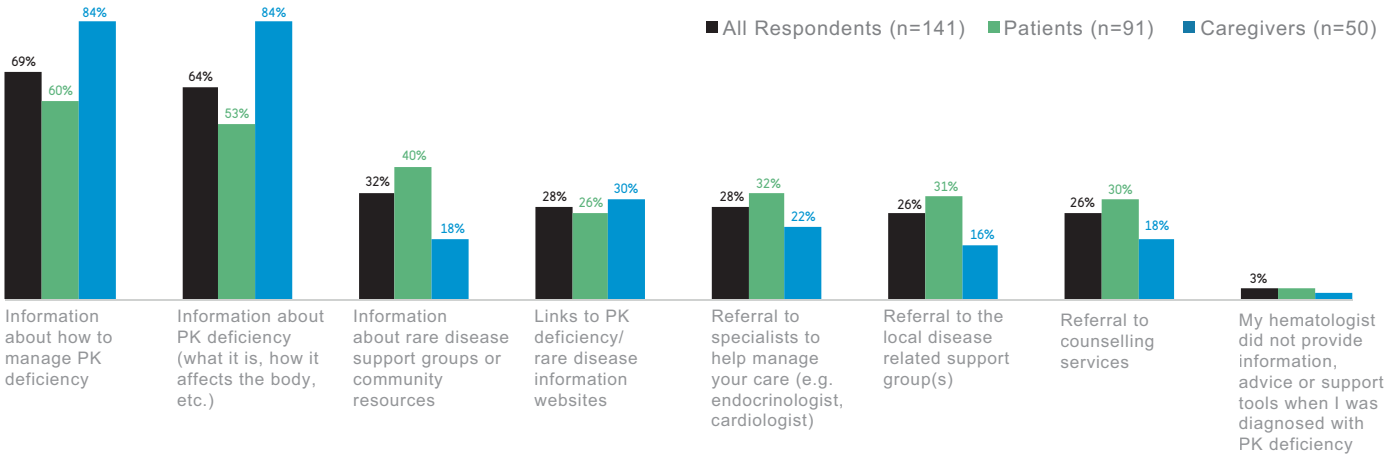
"After many years of coping with PK deficiency I think that people start to wonder about what the future holds. It is at that point that their past comes alive and they feel the need to talk to someone. Sadly, Rare Diseases don't have the funding that other diseases have (such as cancer) and these services are generally not available."

Carl Lander, Patient

"I'm not surprised to see an unmet need regarding emotional and psychosocial support emerging from the data. Twenty, thirty, fifty, sixty, seventy years of anxiety, depression, and fear chips away at a person's reserves and makes it difficult for them to continue seeking the best treatment, take care of themselves, and stay mentally healthy. Patients and caregivers of people with PK deficiency are dealing with a chronic disease that lasts a lifetime and hematologists need to address the mental toll this takes on the patient and their family."

Tamara Schryver, Patient

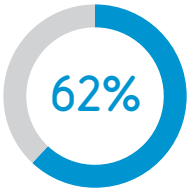
FIGURE 5: INFORMATION, ADVICE & SUPPORT TOOLS PROVIDED AT DIAGNOSIS



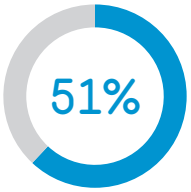
Findings

3 Communication with the hematologist is reported to be negative most often among respondents who have zero transfusions annually, highlighting the unique needs of this group.

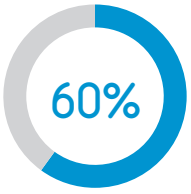
Those receiving zero transfusions each year are much less likely than those receiving one or more transfusions annually to report that their hematologist manages their condition "well" or listens to their concerns.



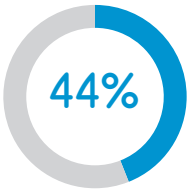
Within the non-transfused group, less than two thirds report that their hematologist manages their condition "well".



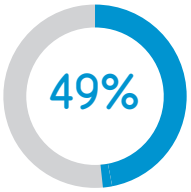
Just over half report that their hematologist appreciates and understands the impact of PK deficiency on their quality of life.



Less than two thirds say that the hematologist listens to their concerns about PK deficiency.



Less than half report that the hematologist takes their perspective and experiences into consideration for their PK deficiency management plan.



A similar proportion report that the hematologist listens to their perspective and experiences about how PK deficiency impacts quality of life.

These scores are all markedly lower than for those having one or more transfusions a year, and when compared to responses overall. A need for hematologists to listen to the perspectives of non-transfused patients was also reflected in the qualitative interviews, where one patient shared: "every time I bring up the subject of another iron scan...the doctor just says, the risk of iron overload is very low for you, so we won't do that. I do appreciate scans are expensive, but having a scan would give me reassurance, because iron levels can elevate quite quickly. I want to avoid any damage before it's too late".

Findings Continued

FIGURE 6: PATIENT PERSPECTIVE: HEMATOLOGIST'S MANAGEMENT OF PK DEFICIENCY

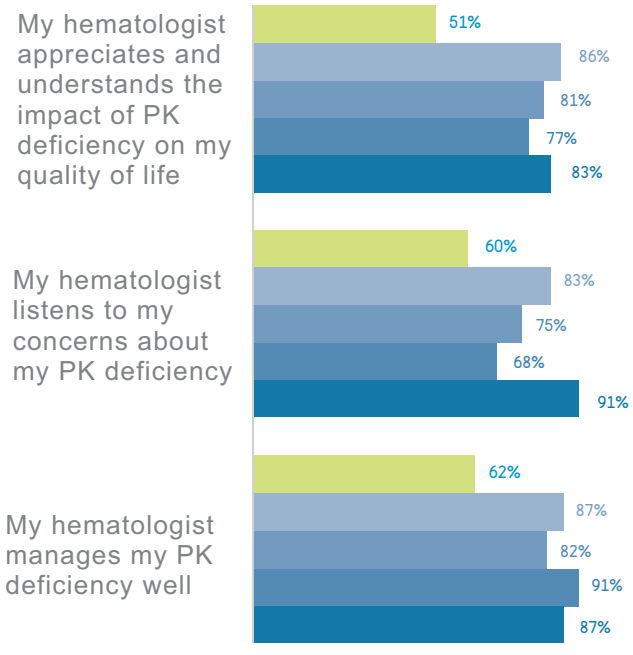
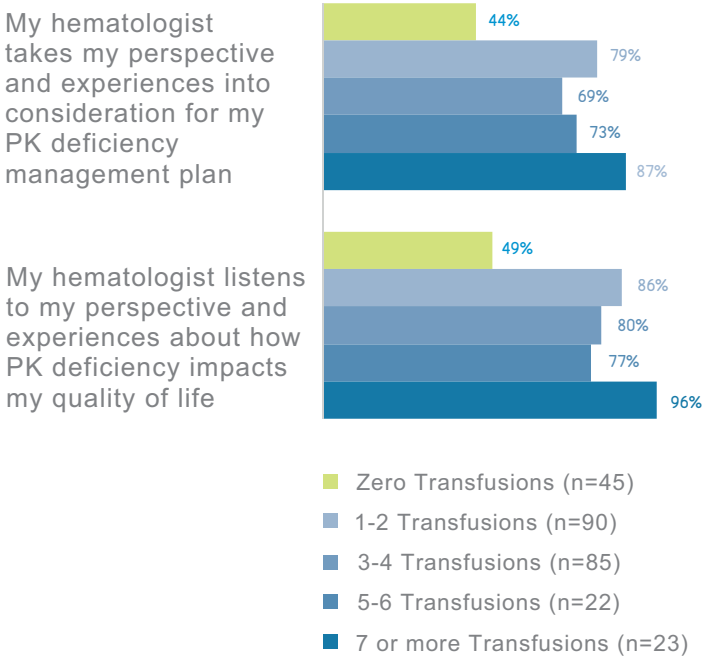


FIGURE 7: PATIENT PERSPECTIVE: HEMATOLOGIST'S CONSIDERATION OF PERSPECTIVES



Among non-transfused patients, less than half (47%) report feeling either “somewhat positive” or “very positive” following interactions with their hematologist.

The most common negative emotion non-transfused patients report following interactions is “frustration”, followed by feeling “alone, “anxious” and “unempowered” (Figure 8).

Just over a third (36%) report at least one negative emotion following interactions, which is higher than other transfusion frequency groups. The emotional toll and lack of support faced by non-transfused patients and their caregivers is further reinforced by responses given during the qualitative interviews and open-text survey responses, with one patient commenting that he felt that there was “no hope” for him, and that the ideal would simply be “to really have a two-way conversation”.

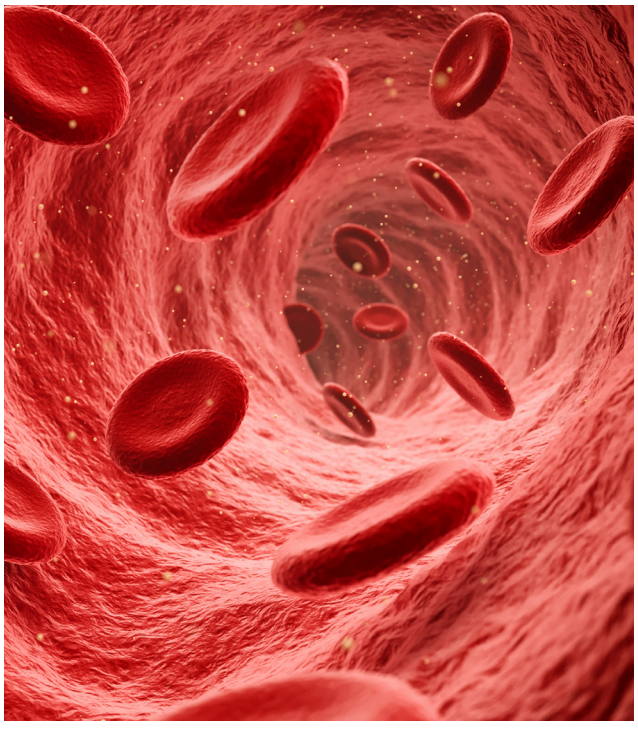


FIGURE 8: EMOTIONS FELT FOLLOWING HEMATOLOGIST INTERACTION AMONG NON-TRANSFUSED PATIENTS

POSITIVE EMOTIONS

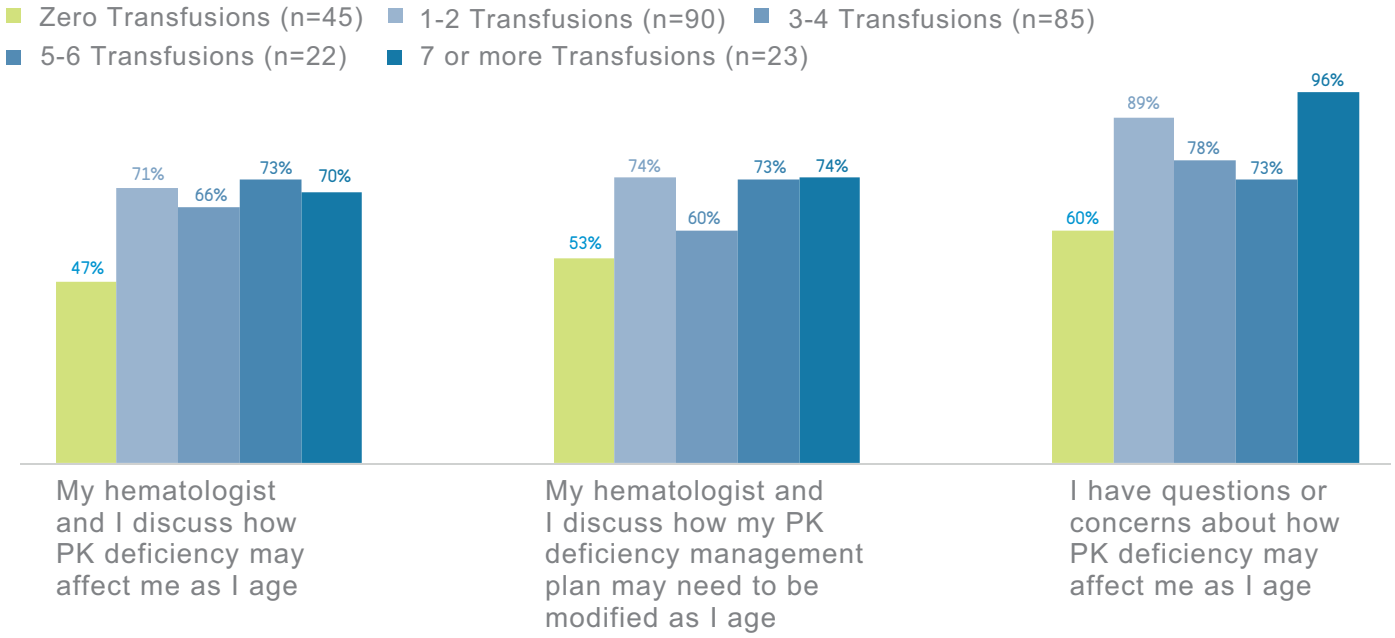
	All (n=265)	0 transfusions (n=45)
Supported	42%	31%
Confident	35%	31%
Optimistic	27%	7%
Encouraged	26%	16%
Understood	26%	18%
Content	20%	11%
Assured	19%	18%
Connected	18%	7%
At ease	18%	20%
Empowered	12%	13%
Happy	11%	2%

NEGATIVE EMOTIONS

	All (n=265)	0 transfusions (n=45)
Anxious	12%	7%
Worried	9%	4%
Frustrated	7%	11%
Depressed	6%	2%
Alone	5%	7%
Unempowered	5%	7%
Misunderstood	5%	4%
Dismissed	4%	-
Disappointed	3%	4%
Insecure	3%	2%
Pessimistic	3%	2%

Findings Continued

FIGURE 9: HEMATOLOGIST'S CONSIDERATION OF AGING IN DISEASE MANAGEMENT



The data also show that non-transfused patients and their caregivers are much less likely than those that receive transfusions to talk with their hematologist about how PK deficiency will impact them as they age and how their PK deficiency management plan may need to be modified as they age.

Although the majority of this group (60%) say they have questions about how their PK deficiency will affect them as they age, less than half (47%) report that their hematologist discusses this topic with them, and just over half (53%) report that their hematologist discusses how their PK deficiency management plan may need to be modified as they age (Figure 9). These findings indicate specific unmet needs among non-transfused patients and their caregivers and a need for greater prioritization of this group by hematologists, to ensure their physical and mental health needs are addressed as part of an optimal disease management plan.

THE PATIENT PERSPECTIVE

"The more time a person spends interacting with someone the more they begin to understand one another. Patients receiving zero transfusions have not developed the same relationship with the hematologist as those who have regular consultations and more frequent transfusions. Those patients that hematologists see often, have a relationship with, have added clinical needs or are children are dealt with in a different way to the occasional patient passing through the office."

Lily Cannon,
Thalassaemia International Federation

Conclusion

PK deficiency is a genetic, chronic disease that lasts a lifetime and takes a heavy toll on the patient and their family, both physically and mentally. It is clear from the survey that there are unmet needs for both patients and caregivers that must be addressed: in particular, relating to hematologist understanding of the disease and what it's like to live with PK deficiency, as well as the emotional and psychosocial impact of the disorder. These needs appear to be amplified among those who receive no transfusions, and further gaps are perceptible within this group, for example, the lack of dialogue between patients and their hematologist on the critical topic of aging.

While there are no 'easy' solutions, the data point to practical actions that can be adopted to improve patients' and caregivers' experiences. A number of clear key calls to action emerge from the data.

CALLS TO ACTION FOR HEMATOLOGISTS

1. **Seek medical training to improve your own understanding** of PK deficiency as a disease, and the life-long burden for the patient and caregiver.
2. **Prioritize well-rounded care** for those affected by PK deficiency, that attends to emotional and psychosocial health aspects, along with physical health needs throughout the lifespan.
3. **Consult with other medical specialists** including hematologists who specialize in pediatric and adult care of people with PK deficiency as routine practice, to ensure complications are effectively monitored and managed. Support these actions by opening a Pyruvate Kinase Deficiency Center of Excellence in each country where PK deficiency patients live.
4. **Provide additional support for non-transfused patients,** with further touchpoints to ensure effective disease management.
5. **Improve resources for patients and caregivers,** through the delivery of tools and resources designed to empower those living with this chronic, debilitating disease.
6. Create an environment in which PK deficiency **patients and caregivers feel empowered.**
7. **Become familiar with local and regional PK deficiency groups and support services** and make referrals.

Conclusion Continued

CALLS TO ACTION FOR PATIENTS & CAREGIVERS

1. **Be confident in advocating** for yourself or your loved one.
2. **Share your experiences** and take **advantage of focus groups.**
3. Reach out to members of the **PK Deficiency Advocacy Advisory Council** to make your voice heard through advocacy initiatives and educational materials.

More research is needed to build on the survey insights and broaden recognition and understanding of the needs of those living with PK deficiency. In particular, further research and a better understanding of the following areas could help improve care in PK deficiency:

- Patient/caregiver anxiety or worry around hematologist appointments;
- The reasons driving patient and caregiver satisfaction levels in terms of communication with the hematologist;
- Which elements of care for regularly transfused patients lead to perceptions of better communication with the hematologist - in order to transfer these learnings to the care of non-transfusion dependent patients;
- Referral pathways in each country and where improvements need to be made. This research could provide a foundation for developing a standardized treatment/ clinical guidance in collaboration with local hematologists.

By driving awareness among hematologists of the unmet needs highlighted in this report, and ensuring hematologists are equipped to take relevant actions within their local practice, we can improve the experience, as well as the lives and futures, of people living with PK deficiency.

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