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# Starting the conversation on gene therapy for phenylketonuria: Current perspectives of patients, caregivers, and advocates

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ABSTRACT

Phenylketonuria (PKU) is a rare genetic condition caused by inborn error(s) in the gene for the enzyme phenylalanine hydroxylase. Resulting loss of phenylalanine (Phe) metabolism requires strict dietary therapy and/or medication to prevent toxic accumulation of Phe. Novel investigational therapies, including gene therapies that aim to address underlying causes of PKU, are now entering clinical trials. However, perceptions of this technology in the PKU community have not been assessed. We conducted a qualitative survey recruiting adult patients, caregivers, and patient advocates from the US and 3 EU countries to assess the impact of living with PKU and the perceptions of gene therapy. Telephone interviews were conducted for up to 60 min following a standardized discussion guide. Interviewers classified each participant by their level of knowledge regarding gene therapy as either: low (little or no prior awareness); moderate (awareness of gene therapy as a concept in PKU); or high (working knowledge of gene therapy, e.g., vectors). In total, 33 participants were recruited (patients, n = 24; caregivers, n = 5; advocates, n = 4). The patient sample was well balanced among age groups, sex, and US/EU geographies. The participants' experiences and burden of living with PKU were largely negative, characterized by frustrations with current management consistent with prior reports. Most participants (n = 18/33) were identified as displaying moderate gene-therapy knowledge, 10/33 as displaying high knowledge, and 5/33 as displaying low knowledge. Both positive and negative perceptions were observed; positive perceptions were often linked to "hope" that gene therapy may represent a cure, whereas negative perceptions were linked to the "uncertainty" of outcomes. High knowledge of gene therapy appeared to trend with negative perceptions; 7/10 participants from this group reported high levels of concern over gene therapy. In contrast, participants who displayed low knowledge reported low (n = 3/5) or moderate (n = 2/5) concern, with predominantly positive perceptions. These data highlight the need for education around the theoretical risk:benefit profile of gene therapy. Despite current unknowns around gene therapy, our study demonstrates the important role of healthcare providers as educators who can use available data to provide balanced information to patients and caregivers.

## 1. Introduction

Phenylketonuria (PKU) is a genetic disorder caused by inborn error(s) in the gene encoding phenylalanine hydroxylase (PAH), an enzyme that catalyzes the metabolism of the amino acid phenylalanine (Phe) [1,2]. Loss of PAH activity leads to elevated blood Phe and a build-up of Phe in the brain, causing substantial and progressive neurocognitive issues and neurologic disorders in untreated individuals [1,3–5]. Following diagnosis in infancy and throughout life, the standard of care for PKU comprises strict daily dietary therapy to minimize the

*Abbreviations:* BH4, tetrahydrobiopterin; CRISPR, clustered regularly interspaced short palindromic repeats; EMA, European Medicines Agency; LNAA, large neutral amino acid; PAH, phenylalanine hydroxylase; Phe, phenylalanine; PKU, phenylketonuria; US FDA, United States Food and Drug Administration..

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consumption of Phe in food, and the consumption of medical supplements, usually Phe-free L-amino acid formulas, throughout the day to fulfill nutritional requirements [2].

However, many individuals with PKU continue to experience suboptimal outcomes despite initiating early dietary therapy, including the effects on growth and nutrition and increased levels of neurocognitive impairment during adolescence/early adulthood compared with healthy individuals [5–7]. A similar trend is observed for impairments in psychosocial functioning and quality of life for patients on dietary therapy [6]. Studies in adults with PKU, including those with early-treated PKU, have also shown a greater incidence of emotional disorders, including anxiety and depression, compared with the general population [4,5,8]. This relationship is more pronounced in individuals with evidence of high blood Phe levels [4,5].

Alternative medical supplements to conventional Phe-free L-amino acid formulas can be considered in some patients [2] to account for different treatment preferences. Low-Phe glycomacropeptide supplements have been associated with increased palatability and have similar effects on Phe levels compared with L-amino acid formulas [9]. Another treatment option, large neutral amino acid (LNAA) supplementation, can protect against neurocognitive dysfunction through a variety of biologic mechanisms [10,11]. However, not all patients may respond to LNAA [10], and those who do derive benefit would still require lifelong treatment.

Beyond traditional dietary therapy and medical supplements, several non-dietary prescription medications have emerged as treatments for patients with PKU. The PAH enzyme activator sapropterin dihydrochloride (Kuvan®) has been approved by the United States Food and Drug Administration (US FDA) and the European Medicines Agency (EMA) for the treatment of PKU in patients who are responsive to tetrahydrobiopterin (BH4) [12–14]. Treatment with sapropterin dihydrochloride has been shown to reduce the levels of blood Phe over extended periods and to increase Phe tolerance in adult and pediatric patients who respond to treatment [15–18]. However, 50–75% of individuals with classical PKU are not BH4 responsive, and therefore derive minimal to no benefit from treatment [2,19]. Furthermore, even among those who respond to treatment, there is often still a requirement for some level of dietary therapy to maintain target blood Phe levels [1].

More recently, the substitution of defective PAH using enzyme substitution therapy has become a treatment option for PKU. Pegvaliase (Palynziq®) was approved by the US FDA in 2018 and by the EMA in 2019 for the treatment of adult patients with uncontrolled blood Phe (>600 μmol/L) on existing management [20–22]. Pegvaliase provided reductions in blood Phe levels alongside reduced symptoms of inattention and irregular mood in phase 3 clinical trials [23,24]. However, despite advances in PKU management, currently available therapies do not correct the underlying dysfunction of the *PAH* gene and the condition thus remains incurable at present.

Ongoing advancements in the arena of clinical gene therapy have demonstrated that targeted correction of pathogenic genes in monogenic disorders, such as spinal muscular atrophy, has the potential to effectively treat or prevent the onset of disease [25]. PKU represents a prime candidate for gene therapy, as Phe metabolism can be restored by expression of a single gene, while blood Phe is an easily measured biomarker that provides a well-defined therapeutic endpoint [26]. Proof of concept for *PKU* gene therapy in animal models was first established in 1994, using a mouse model of PKU [27]. One historically limiting factor for effective clinical gene therapies has been the inefficient delivery of the necessary therapeutic effectors to target tissues. Developments in the design of viral vectors for gene therapy, including adeno-associated and lentiviral vectors that do not provoke strong immune reactions, have contributed to translating gene therapy into clinical research [28–31]. Several pharmaceutical companies have announced the development of gene-therapy treatments for PKU, with 2 in-human studies listed on Clinicaltrials.gov as of March 2021 [32,33].

As the potential of gene therapy for PKU grows, so too does the need for appropriate patient-focused education around this topic [34]. Societal perceptions of gene therapy among the general population have been the topic of past research [35]; however, to our knowledge, the perception of gene therapy among patients and other members of the PKU community has not been studied. This study aimed to evaluate existing knowledge and perceptions of gene therapy in members of the PKU community in Western Europe and the US, and to identify key educational gaps on the topic for this audience.

## 2. Methods

### 2.1. Study design and setting

This was an interview-based survey conducted in the US, Ireland, Germany, and Spain. The study was conducted in accordance with all national data protection laws and relevant industry guidelines in each participating country, including the European Society for Opinion and Marketing Research, the European Pharmaceutical Market Research Association, the British Healthcare Business Intelligence Association, the Arbeitskreis Deutscher Markt/Berufsverband Deutscher Markt, and the Insights Association in the United States. All participants provided their consent to take part in the interview and received financial compensation for their time.

### 2.2. Participants

Potential participants were recruited by referral from clinicians of adult PKU clinics and patient advocacy organizations in the 4 target countries. Screening questionnaires were issued to all potential participants to verify their eligibility for the study. Eligible study participants were patients, caregivers, or patient advocates who met the inclusion criteria. Eligible patients were aged 18–55 years with a positive diagnosis of PKU confirmed through newborn screening and were actively managing their condition. Caregivers were required to be aged ≥18 years and be a parent, guardian, family member, or friend of a person aged ≥15 years with a PKU diagnosis confirmed through newborn screening. The person with PKU was required to be actively managing their condition, and the caregiver must have helped the patient take care of themselves and their condition and have spent ≥20 h per week with them. Patients were defined as actively managing their PKU if a positive response was obtained when asked if they were using non-dietary prescription PKU medication, dietary therapy or special supplements, and/or regularly monitoring their Phe levels.

Patient advocates were currently active, patient-facing members of a national, regional, or local PKU advocacy organization or association that represented ≥300 patients. Advocates were required to be involved in either: decision-making at the board level associated with decisions about the organization's services/offerings for members or providing input into the strategic direction for the organization related to PKU; managing or coordinating the production of support/education materials, and/or running events for PKU; or educating all types of stakeholders about PKU such as patients, families, grantees, and healthcare institutions. In addition to having direct contact with patients with PKU, advocates were also required to have direct contact with at least 1 other stakeholder, who could include caregivers/families, healthcare providers at institutions or schools, social workers, municipal leaders, grantees, or legislators.

All participants were required to be cognitively capable of understanding and answering questions, and able to speak clearly and express themselves. Patients, caregivers, and advocates who were affiliated with a pharmaceutical company, other than in the context of participation in a clinical trial, were excluded from the study. Patient, caregiver, and advocate sample sizes could vary by country, but a minimum of 6 caregivers and advocates and 24 patients across all countries were required. The aim was for an equal distribution of patients across the age groups 18–29 years and 30–55 years.

### 2.3. Interview format

In-depth telephone interviews were conducted following 1 of 3 standardized discussion guides developed for this study, based on participant status as a patient, caregiver, or patient advocate. Interviews were conducted for a duration of up to 60 min. The interviews were conducted by THE PLANNING SHOP, an Adelphi Group company (London UK and Philadelphia US), which is an independent healthcare market research agency. Support personnel including technical support staff and transcribers were permitted to assist as necessary during the interview.

All interviews were structured into 2 parts: a discussion on living with PKU, assessing the patient's and caregiver's personal experience and the role of patient advocates with regard to their respective organizations; and a discussion exploring the participant's level of knowledge and perceptions of gene therapy, and identifying potential educational gaps.

A short educational primer on gene therapy was used as a discussion aid, which was provided to participants partway through the second part of each discussion. The primer consisted of a 2-page brochure outlining information about gene therapy in lay-friendly language shown via computer screen to each participant. To summarize, the primer contained: a basic description of the mechanism of action for vector-based somatic gene transfer; the general goals of clinical trials of gene therapy, such as to investigate the potential for gene therapy to reduce or eliminate the need for treatment; and an overview of potential risks posed by gene therapy, including immunogenicity, off-target gene transfer, and unknowns regarding treatment response and durability.

Participation in the interviews was entirely voluntary, and participants had the right to refuse to answer a question or completely withdraw from the research at any time. Any information provided during the interviews was treated as confidential and remained anonymous unless consent was provided by the relevant participant.

### 2.4. Data analysis

Responses to each discussion question were grouped by observed themes and supported using direct quotes from participants. Word clouds were generated from patient responses using an online "Wordle"-based application.

## 3. Results

### 3.1. Participants

Interviews were conducted between October 5 and November 11, 2020. In total, 33 individuals participated in the study, comprising 24 adult patients, 5 caregivers, and 4 patient advocates (Table 1). Of the adult patient group, 12 (50%) were based in the US, and 4 each were from Ireland, Germany, and Spain. The adult patient sample was well balanced between male (n = 11) and female (n = 13) participants and contained an equal proportion of patients aged 18–29 and 30–55 years (n = 12 each). Half of all patients had prior or current use of at least 1 non-dietary prescription PKU medication (sapropterin dihydrochloride and/or pegvaliase), but this experience was largely restricted to individuals in the US (n = 10). One patient advocate from each study country was enrolled; all were involved in board-level decision-making within their respective organizations.

### 3.2. Living with PKU and perceptions of current management: "it affects me all day long"

All patients and caregivers reported that PKU had some deleterious effects on their quality of life, despite conventional treatments such as dietary therapy and daily medical supplement consumption (Suppl Box A.1). Exploration of emotional perceptions of living with PKU revealed primarily negative word associations, with "frustration" being the most frequent response (Suppl Box A.2; Suppl Fig. A.1).

**Table 1**
Participant baseline characteristics.

| | Patients (n = 24) | Caregivers (n = 5) | Patient advocates (n = 4) |
|---|---|---|---|
| Age group, n (%) | | | |
| 18–29 | 12 (50) | 0 (0) | 0 (0) |
| 30–55 | 12 (50) | 2 (40) | 0 (0) |
| 55+ | 0 (0) | 2 (40) | 0 (0) |
| Not stated | 0 (0) | 1 (20) | 4 (100) |
| Sex, n (%) | | | |
| Male | 11 (46) | 3 (60) | 0 (0) |
| Female | 13 (54) | 2 (40) | 2 (50) |
| Not stated | 0 (0) | 0 (0) | 2 (50) |
| Geography, n (%) | | | |
| US | 12 (50) | 2 (40) | 1 (25) |
| EU[a] | 12 (50) | 3 (60) | 3 (75) |
| Employment status, n (%) | | | |
| Employed[b] | 10 (42) | 4 (80) | 4 (100) |
| Unemployed | 5 (21) | 1 (20) | 0 (0) |
| In education[b] | 9 (38) | 0 (0) | 0 (0) |
| Not stated | 0 (0) | 0 (0) | 0 (0) |
| Experience with ≥ 1 non-dietary prescription PKU medication,[c] n (%) | 12 (50) | – | – |

Abbreviation: PKU, phenylketonuria.
[a] Aggregates participants from Ireland, Germany, and Spain.
[b] Part-time or full-time.
[c] Non-dietary prescription medications: sapropterin dihydrochloride and pegvaliase.

Perceptions of conventional dietary therapy and amino acid supplementation were generally negative and associated with a lack of freedom and restrictions on activities of daily life (Suppl Box A.3). In contrast, perceptions of non-dietary prescription medications were largely positive, albeit concerns regarding lack of response to treatment and potential adverse effects were also voiced (Suppl Box A.4).

### 3.3. Knowledge and perspectives on gene therapy: balancing hope with concern

Prior to delivery of the educational primer document, interviewers classified participants by their level of knowledge regarding gene therapy based on their responses: little or no prior knowledge of gene therapy; moderate knowledge, which included awareness of gene therapy as a concept and that it is being explored in PKU; or high knowledge, which included working knowledge of gene-therapy technology such as vectors, gene editing, or clustered regularly interspaced short palindromic repeats (CRISPR).

The group with low initial knowledge of gene therapy included the fewest participants (15%, 5/33) (Table 2). This group was mostly composed of patients in the younger age group (n = 3/5 aged 18–29 years). The majority (55%, 18/33) of participants had moderate awareness of gene therapy as a concept (Table 2). This group contained a mix of patients, caregivers, and patient advocates who were predominantly members of older age groups, the majority aged 30–55 years (44%, 8/18). The remaining 10 participants (30%), 9 patients and 1 advocate, demonstrated high baseline levels of knowledge (Table 2). Level of concern and emotional associations with gene therapy prior to reading the educational primer for each knowledge group are shown in Fig. 1.

Overall, 1 of the predominant positive perceptions of gene therapy was "hope" (Fig. 1), as many expressed optimism at the concept of gene therapy as a potential cure for PKU (Box 1). In contrast, negative perceptions of gene therapy were related to "uncertainty" (Fig. 1); concerns regarding the perceived risks involved with the procedure, the uncertainty of its outcome, and fear of side effects or loss of identity (Box 1). A

**Table 2**
Participant characteristics in respondents with low, moderate, or high knowledge of gene therapy prior to the provision of an educational primer.

| | Low (n = 5) | Moderate (n = 18) | High (n = 10) |
|---|---|---|---|
| Identity, n (%) | | | |
| Patient | 5 (100) | 10 (56) | 9 (90) |
| Caregiver | 0 (0) | 5 (28) | 0 (0) |
| Patient advocate | 0 (0) | 3 (17) | 1 (10) |
| Age group, n (%) | | | |
| 18–29 | 3 (60) | 4 (22) | 5 (50) |
| 30–55 | 2 (40) | 8 (44) | 4 (40) |
| 55+ | 0 (0) | 2 (11) | 0 (0) |
| Not stated | 0 (0) | 4 (22) | 1 (10) |
| Sex, n (%) | | | |
| Male | 2 (40) | 7 (39) | 5 (50) |
| Female | 3 (60) | 9 (50) | 5 (50) |
| Not stated | 0 (0) | 2 (11) | 0 (0) |
| Geography, n (%) | | | |
| US | 1 (20) | 10 (56) | 4 (40) |
| EU[a] | 4 (80) | 8 (44) | 6 (60) |

Abbreviations: CRISPR, clustered regularly interspaced short palindromic repeats; PKU, phenylketonuria.

[a] Aggregates participants from Ireland, Germany, and Spain. Low defined as little/vague or no prior knowledge; moderate defined as awareness of gene therapy as a concept and that it is being explored in PKU; high defined as working knowledge of gene-therapy technology such as vectors, gene editing, or CRISPR.

common theme among participants who expressed negative perceptions was a reluctance to be an early adopter of gene therapy, in general due to the uncertainty of risk for potential side effects.

Comparing participants by geographic origin, a greater proportion of European participants were classified in the low baseline knowledge of the gene-therapy group in comparison with US participants (22% [4/18] vs 7% [1/15]), with a corresponding lower proportion in the moderate knowledge group (44% [8/18] vs 67% [10/15]) (Suppl Table 1). Observed patterns of level of concern regarding gene therapy were generally similar between US and European participants, although the small sample size limits conclusions which could be drawn from subgroup analysis by individual country.

### 3.4. *Gene-therapy educational needs: "before having this treatment, people should know what they're putting into their body"*

Following the provision and reading of the educational primer on gene therapy, generally greater concerns were observed from participants, including the emergence of new concerns and hesitance from previously less informed individuals (Box 2). These concerns were thematically similar to those initially reported by participants with a high baseline level of knowledge, generally linked to potential side effects and skepticism about perceived benefits. These themes may have been influenced by the content of the primer, as exemplified by 1 EU patient who was able to articulate their concerns around treatment durability, a topic briefly covered in the educational document.

When asked for feedback around education on the concept of gene therapy, several themes emerged from participants' responses including the need for transparent communication of the risks of gene therapy and the use of plain language (Box 3). One US patient, when discussing the concept of gene-therapy research, identified "barriers" of getting through "jargon" when independently researching gene therapy.

### 3.5. *Emotional triggers when discussing gene therapy: "you hear virus and alarms start to go off"*

Reactions to viral-vector terminology used in the educational document incited feelings of fear and associations with COVID-19 (Box 4). Negative perceptions of the concept of viral vectors in 1 participant also stemmed from the representation of viruses in the media, specifically in films. Evidence of respondent anxiety also emerged when using

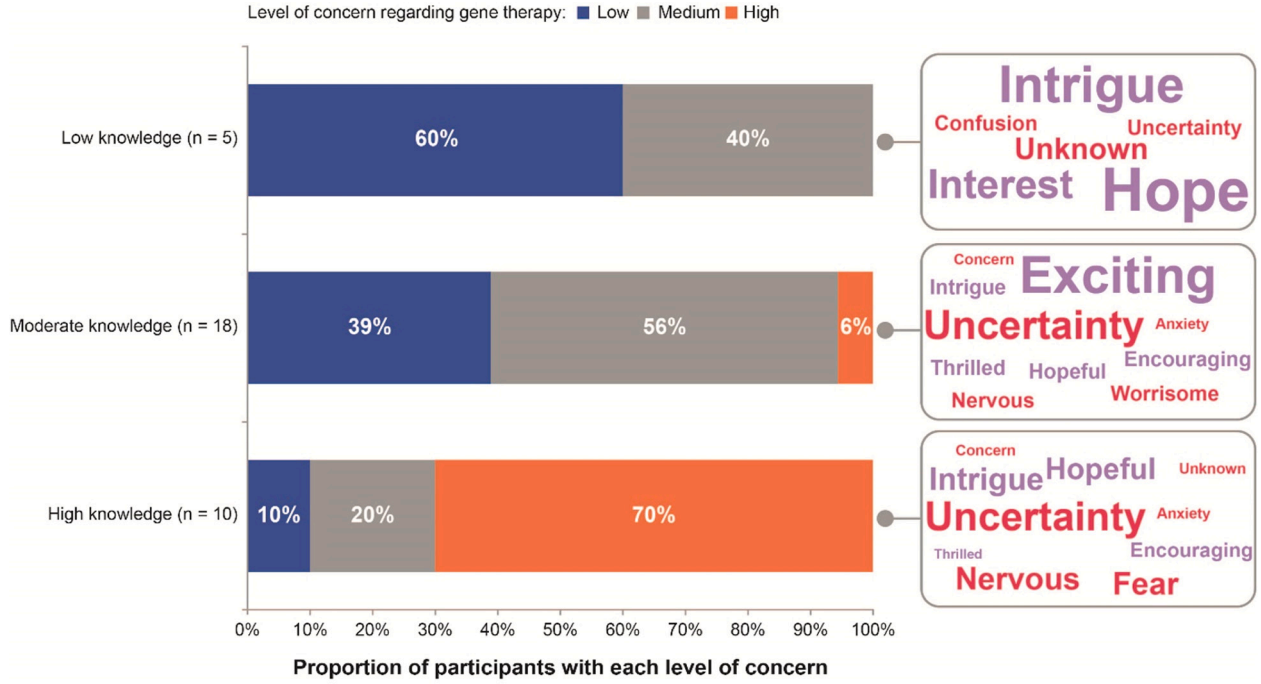


**Fig. 1.** Perceptions and observed level of concern related to the concept of gene therapy in respondents with low, moderate, or high knowledge of gene therapy prior to the provision of an educational primer. The word clouds correspond to words associated with positive (purple) and negative (red) perceptions of gene therapy provided by each knowledge group. Low knowledge defined as little/vague or no prior knowledge; moderate defined as awareness of gene therapy as a concept and that it is being explored in PKU; high defined as working knowledge of gene-therapy technology such as vectors, gene editing, or CRISPR. Due to rounding, percentages in the bars may not equal 100%.
Abbreviations: CRISPR, clustered regularly interspaced short palindromic repeats; PKU, phenylketonuria.

**Box 1**
Excerpts from patient and caregiver interviews around baseline perceptions of gene therapy.

**Positive perceptions**

"*It creates hope and positivity*" EU patient

"*Generally a feeling of optimism; it would be great if it worked because it would be life-changing for so many people*" EU patient

"*When I hear about gene therapy I think of it as something more promising than a drug*" EU patient

"*Wow what would life be like if I could go anywhere I wanted and not have to worry about what my medical treatment would be like*" US patient

"*I think it could easily be the future of medicine; this could help with a lot of problems that people are having with everything; more than just PKU*" US patient

"*I am thrilled about it just knowing there are companies and scientists who are doing their best to discover better treatments*" US advocate

**Negative perceptions**

"*If I knew it worked, I'd want to try it myself as I'd be healthy then, but I am fairly skeptical and just don't know enough about it*" EU advocate

"*I am a bit leery about the side effects; I would not want to go on the trial to be honest until later on when side effects have been looked at*" US patient

"*I would definitely let other people go on it before I would volunteer my husband for it*" US caregiver

"*I think it frightens me a bit. I prefer someone else to have it first and then they can tell me how it goes because the side effects issue is something that you need to bear in mind*" EU patient

"*It would feel like I have been changed and it is no longer me*" EU patient

**Box 2**
Excerpts from patient and caregiver interviews around perceptions of gene therapy following reading an educational primer document.

**Positive perceptions**

"*I think gene therapy can give me a new lease on life; to be more emotionally sound; to speak clearly; just to be a well-rounded person; to be the person I can be; more patient, more loving; I just feel like it is going to allow me to be the person I am inside*" US patient

"*It would be liberating; it would change my life if PKU is cured; I would have the ability to function as a normal person*" EU patient

"*You would have greater freedom with your food. You wouldn't have to be thinking, 'I have to eat this' or 'I can't eat this.' You wouldn't have to worry as much*" EU patient

**Mixed perceptions**

"*I think we are often cautious when we don't know things, so I think the potential joy at having this option will be tempered by the concern over something new*" EU advocate

"*If it had shown that it can work in me and over time, then I would feel strong about it too*" EU patient

"*I feel skeptical not about the gene therapy itself but more about it getting rolled out*" EU patient

**Negative perceptions**

"*I suppose it would be good for those 5 years but when those 5 years came to an end, and you had to go back to how you were before, I suppose it wouldn't be so good—it would be hard having to get used to it again*" EU patient on treatment durability

"*My skepticism and my fear would outweigh my hope for the treatment*" EU caregiver

"*I think the side effects are too high, which makes it too risky*" EU patient

"*This is scary territory, what are we getting into?*" US patient

terminology such as "protein" to refer to the PAH enzyme expressed through gene therapy; protein was referred to as an "enemy."

## 4. Discussion

In this study, we present results from a cross-sectional survey among members of the PKU community that qualitatively assessed the impact of living with PKU, perceptions of current treatments, and surveyed existing knowledge and perceptions of PKU gene therapy. This study sheds light on a topic for which there is a relative paucity of literature, despite the advancement of gene-therapy technology into human trials in PKU.

The persistent burden of PKU reported by the participants in this study was consistent with previous reports in the literature, including difficulties adhering to diet [36–38]; issues with reimbursement for PKU foodstuffs [39]; unpalatable medical supplements [36]; and impact on mood and daily life, including perceived social difficulties [36,37,40,41]. These perceptions culminated in a common theme of "frustration" indicating awareness of an unmet therapeutic need, with hope for future treatment options for PKU emerging from this.

Most participants exhibited a moderate, pre-existing awareness of gene therapy as a concept being investigated in PKU. Interviewers noted

**Box 3**
Excerpts from interview responses providing insights into educational needs.

"*Many patients have this big hope that their lives will get so much better, and they need to see this all in the context of the risks associated*" EU patient

"*Before having this treatment, people should know what they're putting into their body*" EU patient

"*One of the barriers for me was just getting through all the jargon and the information and getting to the meat about what this is about*" US patient, referring to past experience engaging with information about gene-therapy research

"*To give someone at least a reason to at least consider it maybe you want to communicate some of the potential benefits, and I don't just mean medical benefits I mean some of the lifestyle benefits*" US patient

**Box 4**
Excerpts from interview responses reacting to viral-vector concept.

"*Especially now, with what we're going through, you hear 'virus' and alarms start to go off!*" EU patient

"*I couldn't help but think about coronavirus because that is going on at the moment; I suppose it has got me thinking more about side effects and is there side effects and the pros and cons of the treatment*" EU patient

"*There are movies about this—'I Am Legend' comes to mind—where they put a new gene in the body using a measles virus to try and cure cancer but instead everyone became zombies*" US caregiver

the greatest range of knowledge level among participants in the younger age group (18–29 years). A possible contributing factor to this range was differences in patients' circumstances, such as caregiver-guided management versus independent management, which could influence behavior toward the exploration of alternative treatment options. This may partially factor into low awareness of gene therapy among 3 young patients who were on the cusp of transition from caregiver-guided management to greater independence. Differences in educational background may also contribute to this range, as certain members of the younger age group in the high baseline knowledge group were currently in education in a Science, Technology, Engineering, or Mathematics-related field.

Our results suggest that existing knowledge of gene therapy may predispose individuals to a greater level of hesitation and concerns around its implementation, and vice versa. Indeed, following the provision of an educational document, previously less informed participants began to express concerns about gene therapy. A similar relationship between knowledge and hesitancy around gene therapy was identified in a single-center qualitative study in patients with sickle cell disease [42]. However, results from a systematic review and narrative synthesis of the literature identified an inverse relationship, wherein provision of additional information generally resulted in increased acceptance of gene or cell therapy among patients from several studies [34]. One possible explanation for this discrepancy between studies may result from variations in the perceived risk:benefit profile of gene therapy. More severe clinical consequences and greater therapeutic unmet need in other disease states may differently impact patient perspectives on gene therapy compared with PKU, a condition that, while burdensome, can generally be managed with current therapies.

The effect of wider social contexts and the media on patients' perceptions of gene therapy is demonstrated in our results. For example, the COVID-19 pandemic has generated wider cultural awareness and stigma around viruses that may transfer to negative associations toward gene therapy. It is, however, unclear to what extent and for how long these existing cultural attitudes will persist. Research in the field of behavioral psychology suggests 1 major challenge to scientific communications around topics as potentially polarizing as gene therapy may result from tackling ingrained cultural biases [43]. Even when balanced arguments are provided, research has shown that information may be selectively interpreted to reinforce a person's original viewpoint [43]. With this factor in mind, the potential impact of previously publicized gene-therapy trials should also not be discounted. High-profile adverse events such as the emergence of cancer in clinical trials of gene therapy for X-linked severe combined immunodeficiency in the 1990s have been shown to affect public perception of potential risks of gene therapy in other disease areas [35]. However, there was little evidence in our cohort of a direct impact from these results on the perception of gene therapy in PKU.

The possibility that discussion of gene therapy will arise in clinical practice is likely to increase as research into investigational gene therapies for PKU continues. Currently, discussion of these topics must navigate a difficult territory of conceptualizing the theoretical risk: benefit of gene therapy while clinical data are sparse in PKU. Data from gene-therapy research in other disease states provide a potential resource for physicians to draw on, while remaining aware of the nuances of specific gene-therapy strategies in PKU when compared with strategies in other diseases.

Reactions to the educational primer provided during this study indicate several potential findings for physicians discussing PKU gene therapy with patients and their caregivers. These include concerns over specific terminology, including scientific language and words that are difficult for the lay person to understand, or even words that act as negative emotional triggers, such as "virus" and "protein." Our participants indicated a desire for balanced information that equally weighed the potential benefits and risks of gene therapy. In discussing gene therapy, as with any other medical advancement, particular care should be taken around discussing concepts that remain unknown such as the potential durability of treatment effect. In this case, transparent information that explains how gene therapy may not represent a single dose "cure," but without presuming a definite duration of effect, should be provided to manage patients' expectations. These findings also indicate the responsibility on the industrial sponsors of gene-therapy studies to provide balanced educational materials to support physicians, patients, and caregivers.

This study has several limitations that may affect the generalizability of our conclusions. The small sample size obtained for this study represents a primary limitation; however, this number was prespecified in the protocol given the status of PKU as a rare disease [44], and is a

similar sample size to other qualitative studies in rare diseases [42]. The participants in this study may also represent a group more engaged with their health care and who possess greater knowledge about their condition than the general population with PKU. Despite this, a range of gene-therapy knowledge was observed in the participants. Additionally, although unavoidable due to the COVID-19 pandemic, the use of telephone interviews removed the possibility of gaining information from body language that could have been achieved with face-to-face interviews. The COVID-19 pandemic may have also had an acute impact on patients' perceptions of viral-vector gene therapy.

## 5. Conclusions

PKU remains burdensome for patients and their caregivers despite recent progress made toward expanding treatment options. As a potential new therapeutic modality, most participants had some awareness of gene therapy, and we observed an apparent trend of increased knowledge of gene therapy with higher levels of concern. Awareness will likely continue to grow as trials progress, so healthcare providers and patient advocate organizations face a mounting challenge in how to approach patient education around gene therapy. Education on novel scientific concepts should be both clear and balanced, drawing on sound scientific hypotheses to educate around the potential risks and benefits, and thus allowing patients to make informed conclusions while acknowledging the impact of pre-existing perceptions.

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## Declaration of Competing Interest

Heather Bausell has acted as a paid consultant for BioMarin Pharmaceutical Inc., Ultragenyx, Horizon, and Nutricia; has received speaker fees from BioMarin Pharmaceutical Inc., Ultragenyx, Vitaflo International Ltd., and Cambrooke Therapeutics; and has received financial support for travel from BioMarin Pharmaceutical Inc and Vitaflo. Agata Bąk has received consultancy fees from BioMarin Pharmaceutical Inc. The other authors declare no competing interests.

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## Appendix A. Supplementary data

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