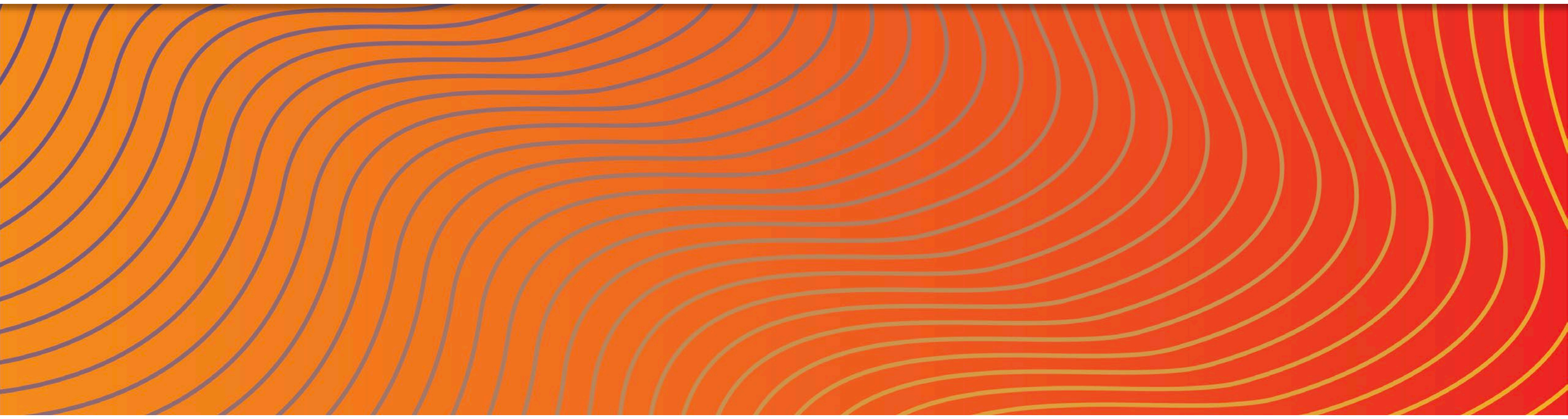

THE VOICE OF THE PATIENT

Externally–Led Patient–Focused Drug Development Meeting on Kidney Xenotransplantation

Public Meeting: November 9, 2023
Report Date: November 12, 2024

Submitted as patient experience data for consideration pursuant to section 569C of the Federal Food, Drug and Cosmetic Act to:
Center for Biologics Evaluation and Research (CBER),
U.S. Food and Drug Administration (FDA).

This report reflects the National Kidney Foundation's accounts of the perspectives of patients and care partners who participated in an Externally Led Patient-Focused Drug Development Meeting, an effort to support the FDA's Patient-Focused Drug Development (PFDD) Initiative.

VOICE OF THE PATIENT

Report on the Externally Led Patient-Focused Drug Development Meeting on Kidney Xenotransplantation

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November 12, 2024. This report has not been revised or modified since November 12, 2024.

STATEMENT OF USE

The National Kidney Foundation has permission to submit this Voice of the Patient report to the FDA External Resources webpage; linking to the FDA website will not violate the proprietary rights of others.

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XENOTRANSPLANTATION DEVELOPMENTS

This Fall 2023 meeting took place before the approval of the first two approved expanded access applications and the experimental kidney xenotransplants (into living recipients) conducted in Spring 2024 at Massachusetts General Hospital and NYU Langone. Consequently, patients were not able to share their perspectives within the context of these developments. As scientific progress advances, patient perspectives may also evolve.

CONTENTS

Introduction

On November 9, 2023, the National Kidney Foundation (NKF) held an Externally Led Patient-Focused Drug Development (EL-PFDD) Meeting on Kidney Xenotransplantation. The goal of the meeting was to provide the U.S. Food and Drug Administration (FDA), xenotransplant companies, clinicians, academic researchers, and the public a forum in which to learn from kidney disease and transplant patients about their experiences and perspectives on living with kidney disease and kidney transplantation, and their views on kidney xenotransplantation. The goals of this meeting were to afford the FDA with an overall understanding of:

- patient perspectives on living with kidney disease and what factors may influence a patient to consider a kidney xenotransplant
- patient perspectives on the potential risks and challenges of kidney xenotransplantation
- factors that influence patient willingness to enter a kidney xenotransplant clinical trials, including patient and caregiver perspectives on how to minimize potential risks and burdens of participation

This meeting was conducted as a parallel effort to the FDA-led PFDD meetings that were first conducted under the Prescription Drug User Fee Act (PDUFA V) from 2013-2017. These meetings aim to gather patient perspectives more systematically on their conditions and the available therapies to treat their conditions. To help expand the benefits of FDA's PFDD initiative, in 2015, FDA announced the opportunity for EL-PFDD meetings. EL-PFDD meetings are planned and hosted by patient organizations, with the input of FDA staff, and use the process established by FDA-led PFDD meetings as a model.

More information on this initiative can be found at https://www.fda.gov/industry/prescription-drug-user-fee-amendments/externally-led-patient-focused-drug-development-meetings.

Overview of Xenotransplantation

Definition of Xenotransplantation

Xenotransplantation is the direct transplantation, implantation, or infusion of nonhuman animal products (e.g., live cells, tissues, or organs) or the transplantation, implantation, or infusion of human cells, tissues, organs, or body fluids that have had ex vivo contact with live nonhuman animal products into a human recipient.[1] This conference was only concerned with xeno-organ transplantation.

Need for Xenotransplantation

An estimated 35.5 million patients in the United States have chronic kidney disease (CKD), 808,000 of whom are in end-stage kidney disease (ESKD), requiring some method of renal replacement therapy (RRT). The available options for RRT include dialysis and allotransplantation. Roughly 560,000 (67%) of those are on dialysis, about 90,000 patients are on the transplant list.[2,3] While 2022 marked the first year that a landmark 25,500 kidney transplants were performed, in 2023, it is estimated that 14 patients still die each day waiting to receive a kidney transplant.[3,4] Efforts are being made to improve both deceased and living kidney donation, but the demand for human organs for clinical transplantation far exceeds the supply.[3,5] Xenotransplantation using nonhuman animal donors—pigs—may be an answer to the donor kidney organ shortage. [1,3]

Benefits and Risks of Xenotransplantation

The use of organs from nonhuman animals has many potential benefits. [6] Dr. Kumar presented some reasons pig organs are preferred, including:

- pig organs are appropriately sized and function similarly to human kidneys;
- can be genetically engineered to lower rejection risk;
- provide a reliable and unlimited supply of quality-controlled donor organs;
- pig source is already in use for other reasons (e.g., heart valves, cornea, skin)

In the early days of xenotransplantation investigations, transplant clinicians recovered donor kidneys from chimpanzees and nonhuman primates. Current efforts are focused on the pig as a donor organ source, given their overall larger litter size and body size (and, correspondingly, organ size), compared with nonhuman primates' availability and breeding characteristics. [6] Of particular note to kidney transplant candidates, the internal structure of pig and human kidneys share many similarities, in addition to demonstrating a similar blood flow, ability to balance fluids and electrolytes, dietary and digestive capability, and estimated glomerular filtration rate (eGFR).[3,6]

Xenotransplantation also carries several known and unknown risks.[1,7] While it is not possible to accurately estimate the risks and benefits at this stage, Dr. Reese presented some of the potential risks and potential *catastrophic* outcomes, including:

- potential for xeno-organ recipients who be infected by zoonotic organisms, for instance a cross-species infection by latent retroviruses, as well as potential infection transmission to people who are in close contact and the general population;
- risk of organ dysfunction for transplant recipients including rejection; poorly functioning organ; organ loss. Bleeding and blood clotting disorders;
- If the kidney does not work, the patient could return to dialysis;
- It is uncertain if the patient would be eligible for an allotransplant after receiving a xenotransplant for various reasons including: they could be too frail for another transplant procedure, or their immune system is now too sensitized for another transplant;
- recipient's quality of life might be worse than with dialysis;
- complications of xenotransplant could cause death.

While the risks of xenotransplantation cannot be accurately predicted at this stage, alternative treatments also involve risks and poor quality of life. The patient testimonies and audience discussion explore the risks and complications of the currently available treatments for kidney failure. Some complications of available treatments, presented by Dr. Reese, are listed below:

- **Chronic dialysis** has a high death rate, reduced quality of life, limited ability to participate in meaningful activities; complications are common;
- **Human Kidney Transplant (allotransplant)** has known complications after transplant including of limited function, infections, and organ rejection. Due to the lack of available human organs, many people die on the waiting list.

Barriers to Kidney Xenotransplantation

Before xenotransplantation can become a mainstay in the treatment of chronic and end-stage kidney disease, multiple physiological and immunological barriers must be overcome. Nonhuman animal cells, tissues, and organs are susceptible to rapid and robust hyperacute organ rejection and destruction within minutes, to hours after transplantation. Notably, recent evidence generated over the past 3 years from xeno-transplanted kidneys and hearts into decedents and human patients suggests that this hyperacute rejection may be circumvented through the genetic engineering of tissues that lack major targets of the hyperacute immune response.[8-10] Nonetheless, published reports from these xenotransplants also support the concern that xeno-organ rejection remains a substantial risk. Multiple scientific groups are focused on the process of diagnosing, categorizing, and treating xeno-organ rejection. Additionally, some enzymes and proteins, particularly several that are involved in coagulation, are incompatible between pigs and humans.[6,8] These incompatibilities may result in the development of thromboses within the graft, affecting the health and function of the donor organ.[6,8,11] In addition, intact innate and adaptive immune responses require the administration of immunosuppressive treatment protocols, although genetic engineering may yet prevail as a method for preventing longer-term rejection responses. [6,8-10]

Ethical Considerations for Xenotransplantation

The prospect of xenotransplantation raises a number of unique ethical considerations.

Some relevant ethical considerations presented by Dr. Reese and discussed during the audience discussions include[12]:

- **Respect for Persons:** The need for robust multi-step education and informed consent; also, **Loss of Privacy**: despite best efforts by hospitals, medical privacy may be impossible to protect;
- **Beneficence**: Selecting patients with few good treatment options;
- **Risk/Benefit Ratio**: considering whether benefits of the procedure outweigh potential individual and societal risks/burdens, and how the risk threshold may differ among differing patient experiences;
- **Equity**: how equitably can xenotransplant resources be distributed to patients who may benefit from them the most?
- **Autonomy**: Potential lifelong requirement for public health surveillance. Additionally, if the public health is at risk, the patient and close contacts may be required to quarantine;

Importantly, as with any new drug therapy or technology, safety and efficacy must be evaluated by clinical trials.[6,12] Although, as of the date of the meeting, two pig heart-to-human xenotransplants were performed in living, end-stage *cardiac* disease patients,[13] pig *kidney*-to-human xenotransplantation had been evaluated in decedent recipients only.[10,14,15] In both types of xenotransplant, 1 to 2 recipients received pig organs, preventing assessment of the significance of outcomes. [10,13-15] Despite the much-deserved enthusiasm for the technologies that have made this possible, xenotransplantation is not an established medical practice, and therefore should be subject to rigorous clinical research.[12] However, it is important to consider how this may be approached in an ethical manner.[6,12] As many of the potential risks of xenotransplantation are fundamentally different from allotransplant, xenotransplantation studies should be evaluated as phase 1 trials, which are subject to more stringent requirements than standard Phase 3 trials, for which extensive evidence from previous human experiments exists (data which are lacking for xenotransplants).[12] The meeting discussions did not address animal rights, natural law, and religious considerations. The full scope of considerations and clinical evaluation of xenotransplantation protocols lie beyond this meeting summary. [6,12,16]

Meeting Overview

This EL-PFDD Meeting on Kidney Xenotransplantation provided the FDA, xenotransplant companies, clinicians, academic researchers, and the public the opportunity to hear directly from patients and their care partners about their experiences living with kidney disease and their views on the potential risks and benefits of xenotransplantation. Specifically, the goals of this meeting were to afford the FDA with an overall understanding of:

- patient perspectives on living with kidney disease and what factors may influence a patient to consider a kidney xenotransplant
- patient perspectives on the potential risks and challenges of kidney xenotransplantation
- factors that influence patient willingness to enter a kidney xenotransplant clinical trials, including patient and caregiver perspectives on how to minimize potential risks and burdens of participation

The meeting was preceded by two webinars. The first webinar ("EL-PFDD meetings with the FDA") provided background about EL-PFDD meetings and the different clinical trial stages of the FDA drug approval process; the second webinar ("Overview of Xenotransplantation") provided background information about xenotransplantation including ethical considerations and the known and unknown risks associated with this experimental procedure.

Meeting Format

This meeting, led by a moderator, had both in-person and virtual attendees. Patient input was gathered through dialogue with the live and virtual audiences via in-person discussion, emails, and online comment submissions before, during, and after the meeting. Only patients and care partners were asked to participate in the dialogue.

Discussions during the meeting focused on three key topics: 1) the daily effects of living with kidney disease and why patients would consider xenotransplantation; 2) patients' perspectives on the potential risks and other downsides to xenotransplantation; and 3) patients' perspectives and considerations for participation in kidney xenotransplantation clinical trials (Appendix 2). The discussion questions used to guide the audience discussions are found in Appendix 3.

Patient Panels and Moderated Discussion

Patient voices were heard through patient/care partner Testimony and Discussion Panels (Appendix 4.1) and moderated audience discussions. These were conducted as described below.

Testimony Panel

A patient Testimony Panel was heard in which 7 patients and care partners gave five-minute presentations on their experiences regarding symptoms and daily burdens of living with kidney disease and why they might (or might not) be willing to consider a kidney xenotransplant (Appendix 4.2). Panelists were selected by NKF representatives. Criteria for selecting panelists were set to maximize clinical and demographic diversity on each panel.

Discussion Panel

A patient Discussion Panel was heard in which two patients shared their experiences regarding the allotransplant process and post-transplant monitoring. The meeting moderator engaged with the panelists and audience during the discussion panel. This was the opportunity to explore why two transplant recipients might (or might not) be willing to consider a kidney xenotransplant (Appendix 4.2). Panelists were selected by NKF representatives. Criteria for selecting panelists were set to maximize clinical and demographic diversity on each panel.

Moderated Audience Discussion

Each Testimony Panel was followed by a moderated audience discussion. During the moderated audience discussion, the moderator interacted directly with live and virtual audience members by receiving in-person testimony and reading emailed comments. In Discussion C, two panelists (Appendix 4.1) helped introduce the moderated conversation.

Polling Questions

Polling Questions (Appendix 5) were posed to the participants to reveal the demographics of the attendees and their perspectives on the different discussion topics. Only patients and care partners were asked to participate in polling. Polling questions were based on a pre-meeting survey of prospective attendees, input from the meeting co-chairs, and literature. Care partners were asked to respond on behalf of the patients for whom they provide care (not on behalf of themselves), even if the patient also responded.

Polling was conducted via an online platform, through which attendees could respond. Responses were projected instantly for audience viewing and described simultaneously by the moderator. The results are described in the text and depicted graphically in Appendix 6.

Post-Meeting Comments

To expand on the perspectives gathered at the meeting, patients and care partners were encouraged to submit comments to NKF after the meeting. Comments were accepted until December 10, 2023.

Enduring Documentation of Meeting

The archived meeting recording, this meeting report, and the meeting transcript are available on the National Kidney Foundation website (Appendix 2).

KEY THEMES

The input from the meeting emphasized the challenges of living with kidney disease, its impact on day-to-day life, patient consideration of xenotransplant as a possibility (Discussion A), patient perspectives on potential known and unknown risks of xenotransplantation, and considerations regarding participating in a phase 1 xenotransplantation clinical trials. Several key themes emerged from this meeting:

- **Challenges of dialysis:** Patients frequently spoke about the challenges of living with dialysis as a renal replacement therapy. The participating patients and care partners expressed dissatisfaction with dialysis on multiple levels including limitations on daily living, the long-term health risks, and the general discomforts of (and frequent misery associated with) the procedure itself. When considering choosing between dialysis or a xenokidney transplant, most patients expressed their willingness to try a xenokidney transplant—even when they had serious questions or concerns about the procedure—over having to go back on dialysis.

- **Toll of living with kidney disease**: Similar to the challenges of daily living on dialysis, patients generally spoke of the difficulties of living with kidney disease and how it has impacted their lives or the lives of loved ones. Care partners spoke of the helplessness they felt about not being able to take away this burden from their children living with kidney disease and how this added to the urgency they felt about the need for xenokidney transplantation as a viable treatment option.

- **Waitlist concerns**: Several patients reflected on the emotional toll that being on (or not being eligible for) the allotransplant waitlist can take. They expressed their fear about not moving up the list in time and about what their alternatives were in the face of not being able to receive an allotransplant. At least one patient considered the possibility of using a xenokidney transplantation clinical trial as, if not a direct solution for replacing allotransplantation, but a potential bridge to "buy time" between a failing native or transplanted kidney and having to go on dialysis.

- **Urgency for clinical trial data**: Patients were eager to expand clinical research for xenokidney transplantation to the trial phase. They noted the length of time it takes to start the trial process to its approval, the amount of time already lost, and the number of patients who could have benefited. They emphasized the need for data and answers to their questions about the procedure. This could alleviate concerns and improve outcomes. They voiced frustration with federal regulations of the procedure, suggesting guidelines have been too strict and too cautious. Other patients noted that we are only where we are today with allotransplantation because of the risks taken decades ago.

- **Family/loved ones**: Patients spoke of the role their families and friends play in their decision-making process regarding xenokidney transplantation. They expressed their frustrations with kidney disease restricting their ability to spend time with their families and loved ones and how xenokidney transplantation would help give them better quality of life. Some also stated their desire to avoid putting additional stress on their families and the need to protect family from potential risks, especially zoonotic infection. They spoke of xenotransplantation enabling them to have more time with loved ones, and of how they might be willing to risk a clinical trial if they did not have any family.

- **Living donor concerns**: Multiple patients spoke of the emotional toll of having a living donor. Although patients appreciated the better outcomes and reduced number of immunosuppressants associated with living donor transplantation, they spoke of the stress of looking for and approaching living donors. They have concerns about the impact of the procedure on the living donor (even with the best outcomes), and guilt when thinking about someone closer to the living donor eventually needing a transplant.

- **Patient-voice**: Patients emphasized the importance of patient-voice in the decision-making process. They expressed their desire to do their own risk-benefit analysis and felt that research should not be held back because of overconcern about patient apprehension. They also voiced the importance of deciding how much monitoring was appropriate after xenokidney transplantation, and how to decide when to terminate participation in a trial when a kidney xenotransplant fails.

- **Quality of life**: Much of the risk-benefit analysis focused on their perception of what the benefit of xenokidney transplant to their quality of life versus potential risks. Patients were generally willing to consider the risk of xenokidney transplant if it could provide opportunities for improved quality of life. Patients considered the limited availability of data regarding potential risks seriously and did not assess risk lightly, but most we were willing to take some risks over accepting the poor quality of life they know they will have on dialysis.

ATTENDEES

The Meeting was open to the public and a total of 72 people attended the in-person meeting, 122 viewers joined the livestream. These attendees included patients, care partners, FDA representatives, xenotransplant companies, researchers, nephrologists, transplant surgeons, ethicists, and anyone interested in observing the meeting. Only patients and care partners were invited to participate in the polling and audience discussion, and participation was anonymous and optional.

The composition of the patient and care partner attendees was revealed by demographic polling questions (Appendix 5.1). Based on their responses, most participants (60%) were patients who have experienced kidney disease and 30% were care partners of someone who has experienced kidney disease (Appendix 6; Figure 1). The majority (63%) of attendees resided on the East Coast (Eastern Time Zone), followed by 26% in the Midwest (Central Time Zone), 5% in the West (Mountain Time Zone), and 7% on the West Coast (Pacific, Alaskan, Hawaiian Time Zones). No participants were from Canada, Mexico, Caribbean Islands, or outside of North America (Europe, South America, etc.). (Appendix 6; Figure 2).

Most respondents were between 40-49 (23%), 60-69 (23%), 50-59 (21%), or 18-29 (19%) years old. Approximately 7% were 30-39 years old and 2% were between 2-12, 70-79, or >80 years old. No participants were under 2 years (Appendix 6; Figure 3). Most respondents were White (74%), 16% were Black or African American, 5% were Asian American, and 2% selected Other or Hispanic or Latino to describe their race or ethnicity. No respondents were American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, or indicated they were opting out of answering (Appendix 6; Figure 4).

Participants predominantly were nearly equally split by gender: 47% were male; 53% were female (Appendix 6; Figure 5). Nearly a third (27%) of respondents were unsure or did not know the cause of their kidney condition, while 18% of respondents each selected focal segmental glomerulosclerosis (FSGS), immunoglobulin A (IgA) nephropathy (IgAN), or polycystic kidney disease (PKD). Respondents also indicated lupus nephritis or diabetic and/or hypertensive kidney disease (7% each) and Alport syndrome or atypical hemolytic uremic syndrome (aHUS) (2% each) as causes of their kidney condition; no respondents selected acute kidney injury (AKI), C3 glomerulopathy (complement 3 glomerulopathy; C3G) or membranoproliferative glomerulonephritis (MPGN), Fabry disease, or membranous nephropathy (MN) (Appendix 6; Figure 6).

REPORT OVERVIEW

This report summarizes the perspectives shared by kidney disease patients and care partners at the EL-PFDD Meeting on Kidney Xenotransplantation, including patient testimonies, moderated audience discussions, and responses to live polling questions posed during the meeting.

This Voice of the Patient report intends to support the understanding of patient perspectives of those living with kidney disease, including symptom burdens, views on xenotransplantation risks, and perspectives on xenotransplantation phase 1 clinical trial participation, by the FDA, xenotransplant companies, clinicians, academic researchers, and the public. Through firsthand statements, this document also highlights the unmet needs of kidney disease patients, particularly with regard to kidney transplant eligibility and access. Thus, this report may aid the FDA in considering the patient voice as the agency fulfills its role in the xenotransplantation phase 1 clinical trial program development process. This process includes advising sponsors on their xenotransplantation programs and clinical trial design, evaluating known and unknown risks to clinical trial participants and their families, and assessing benefit-risk for clinical trial participation.

Input from this report may also be valuable to the xenotransplantation program development process more broadly. For example, it may guide pharmaceutical companies in their development process by uncovering previously unappreciated and unmet burdens of living with kidney disease. This report can direct research decisions toward targeting xenotransplantation support mechanisms that may address or alleviate such challenges.

In addition, this report may describe barriers to clinical trial participation by kidney disease patients and may inform the determination of clinical trial guidelines that are inherently meaningful to patients.

In this report, patients and care partners are collectively referred to as *"patients and/or care partners," "participants," "attendees," or "respondents."* When responses to polling questions are reported, the responses are from patients and care partners in the live and virtual audiences. *"Care partner"* refers to a family member, partner, or friend who provides direct care to the patient.

Percentages from polling questions reported in the text and as numerals in the Appendix figures are rounded-off from the original data. Consequently, the sum of percentages for a given graph may not total 100% and the bar heights may not always precisely reflect the percentages within.

We note that, while the participants at this meeting represented a clinically and demographically diverse group, the extent to which this group reflected the kidney disease patient population at large is unknown. Moreover, there may be symptoms, impacts, treatments, or other aspects of kidney disease that are not included in the narrative. Therefore, this report is not meant to represent the views and experiences of any specific group of individuals or entities, or to be comprehensive or definitive. The terms and language used in this report to describe kidney disease symptoms and impacts, views about xenotransplantation, and/or participation in xenotransplantation clinical trials reflect those of attendees.

Quotes from patients and care partners in this report were taken from patient testimonies, remarks from live audience members, online comments, and statements transcribed from emails.

PERSPECTIVES FROM PATIENTS

Quotes have been edited for grammar, punctuation, and clarity.

Discussion A: Patient Experiences with Kidney Disease: Why Patients May Consider Kidney Xenotransplantation (Expectations and Outcomes)

Testimony Panel

Following the first expert presentation from Dr. Vineeta Kumar, an overview of xenotransplantation, testimonies from seven patients (or care partners of patients) currently living with kidney disease were presented. The patients and care partners described the symptoms and the daily burdens of living with kidney disease. Noteworthy excerpts from these presentations are below. Full testimonies are found in Appendix 4.2.

Brie *(adult transplant recipient (aHUS))*

> *"I prayed for many years to be a mother. However, during my 2.5 years on dialysis* ***I felt less than a mother. 2.5 years is a long time to miss out on life moments,*** *especially with young children.*
>
> *"When I was diagnosed (with aHUS) and immediately placed on dialysis, I had a 6-month-old, a 3-year-old, and a 5-year-old. Two years later … I received my transplant …. Those were 2 crucial years, and during that time,* ***I sat in the background while my family created memories without me."***
>
> *"****No matter how they spin it, dialysis is not a pleasant option****. The years spent only being able to consume 32 ounces of liquid a day, the struggle over which shoes to wear because you don't know how badly your ankles will swell, the random throwing up spells, and so on …"*
>
> *"****You can't live a normal life on dialysis****."*
>
> *"****The heartbreak I felt while waiting on dialysis for a transplant was almost unbearable****."*

Sandi *(adult patient, ineligible for transplant wait list (currently on in-center dialysis))*

> *"Since I have end-stage renal disease,* ***I don't know how long dialysis will work for me****."*

Ed *(adult patient, history of failed transplant, current functioning transplant (IgAN))*

> *"****Dialysis saved my life. It also negatively impacted the quality of my life. I felt a sense of hopelessness and doom. I was surviving on dialysis, not thriving****."*

*“**I longed for the freedom from dialysis** AND to spend quality time with family and friends, go to work or go to school or travel the world.*

*“**Waiting for my kidney transplants was terrible**.”*

*“**The uncertainty of not knowing when I would get a kidney, or even if I could survive** the years long wait, was extremely taxing on the body, mind, and spirit**.***

*“**My marriages suffered (I was divorced twice). My careers were derailed, and my family’s dreams were crushed**.”*

Katherine *(adult patient, on transplant waitlist, currently on in-center dialysis)*

*“**The time spent on hemodialysis is difficult mentally, physically and it is time consuming**.”*

*“**Being on the waitlist is another burden** because I am on the inactive transplant waitlist until I can transition over to the active list, and **I fear that I may not live long enough to see all my grandchildren grow up** …”*

Wendy *(adult care partner (now adult daughter has lupus nephritis & recurring kidney failure))*

*“**While on dialysis,*** **[my daughter]** ***endured multiple procedures for access that kept clotting and ended with a failed graft and fistula**. It was found her lupus was the cause of the failed dialysis access points and was only able to receive her treatments through a temporary tunnel catheter, which led to **two bacterial infections and sepsis**.”*

*“Samantha’s health journey has been **traumatic for her to experience**, and as her mother, it has been **excruciating to watch**.*

*“***[My daughter’s]** ***nephrologist expects her kidney function to decline again*** *and plans to place her back on the transplant list, once her renal function falls to 20% to avoid going back on dialysis.”*

Maria *(adult patient, rare/recurring disease (IgAN))*

“[To treat my IgAN], *I undertook a **grueling regimen of high-dose prednisone in 2021** but **have not been able to leave stage 4, with my kidneys functioning at less than 30%**.”*

*“I have not done dialysis yet, but **the need could arise at any time**. Any infection I contract could kick off an autoimmune response that could **damage my kidneys further and push me***

> ***into end-stage renal failure**—where **the only options available today remain dialysis or transplant**.”*
>
> *“The two available options come with their own set of issues, concerns, and inconveniences that **may keep me alive, but perhaps not really living**.”*

Victoria *(adult care partner for pediatric kidney transplant patient)*

> *“The* [13 months are my son was diagnosed with acute kidney failure] *were an **emotional and tumultuous time** for my son and our family. We were so thankful he was alive, but **the dialysis he had to endure was torture**.”*
>
> *“He’d often say he **felt like a human water balloon** … the primary reason that **prevented him from enjoying 6th grade with his peers**.”*
>
> *“**Our family was, and is, traumatized by the journey** **[our son]** **has endured**. As a mother and primary caregiver, **I felt helpless I couldn’t fix this for him. He lost a vital part of his childhood to his kidney failure**.”*
>
> *“**Being so young, who knows how long his current kidney will last**. If it fails, I hope he gets priority on the living donor list from my non-directed kidney donation and our National Kidney Registry Voucher.”*
>
> ***“But what if that second kidney fails soon after? I worry one, two or even three transplants later—will he be out of options?”***

Discussion A: Polling Questions and Audience Discussion

After the panel presentations, Polling Questions (Appendix 5.2) were posed to the audience (via live polling software) to gather broader patient input on the symptoms and daily impacts of kidney disease as well as their thoughts and concerns about xenokidney transplantation as a treatment option. Polling results were displayed in real-time and supported the moderated audience discussion. The meeting moderator utilized the Discussion Questions (Appendix 3) to further explore the patients’ experiences with kidney disease, and how that may influence their perspectives of xenotransplantation. During this discussion, patients and care partners of the in-person and livestream audiences provided verbal and written comments on their perspectives on the physical, emotional, and social impacts of kidney disease on their daily lives. Participants also discussed their worries about kidney disease, how it has affected their extended and immediate families, and what it means for themselves or their loved ones' futures.

Following are the results of the Polling Questions, quotes from testimonies, examples of verbal and written comments during the discussion, and quotes from a pre-meeting survey shared with participants.

Effects of Kidney Disease on Daily Life and Considerations for Kidney Xenotransplantation

Attendees were asked to share their or their loved one's current level of kidney function/disease stage (Appendix 5.2; Discussion A: Question 1). Most respondents had an eGFR between 30 to 59 (CKD stage 3) or <15 (CKD stage 5) (both 24%), with 14% of respondents reporting an eGFR or 15 to 29 (CKD stage 4) or not knowing their eGFR/stage of disease, and 12% having an eGFR ≤90 (CKD stage 1) or between 60-89 (stage 2) (Appendix 6; Figure 7).

When asked to describe their dialysis, transplant waitlist, and/or kidney transplant experience (Appendix 5.2; Discussion A: Question 2), most respondents (72%) indicated they currently had a functioning transplant and were not on dialysis or a transplant waitlist; 12% of respondents had end-stage disease with a native kidney (on dialysis and/or a transplant waitlist); 9% reported having end-stage disease with a kidney transplant (on dialysis and/or transplant waitlist); and 7% reported having a functioning kidney (not on dialysis or transplant waitlist) (Appendix 6; Figure 8).

Attendees who ever had been or who were currently on dialysis were asked to share how long they had been/were on dialysis (Appendix 5.2; Discussion A: Question 3). The majority (47%) of the participants indicated they had been/were on dialysis for 1-5 years, with 22% of participants with dialysis experience reporting 7-11 months of treatment, 16% reporting 6-10 years on dialysis, 13% reporting <6 months of dialysis, and 3% indicating 11-15 years utilizing this type of renal replacement therapy. No respondents indicated the use of dialysis for 16-20 or >20 years (Appendix 6; Figure 9).

For participants who reported having been on the transplant waitlist (Appendix 5.2; Discussion A: Question 4), 41% indicated a 1-5-year wait time, 27% of respondents reported <6 months on the waitlist, 15% selected 7-11 months of waiting, and 12% reported 6-10 years. No respondents indicated they were or ever had been on the waitlist 11-15 or >20 years, while 5% of respondents indicated being on the waitlist between 16-20 years (Appendix 6; Figure 10).

Attendees were then asked to consider a panel of reasons that might motivate them to consider a xenokidney transplant (now or in the future) and to select their top three possible reasons (Appendix 5.2; Discussion A: Question 5). The top four reasons selected were "avoiding/shortening time on dialysis" (123% of responses), "improving quality of life" (85%), "avoiding/shortening time on the transplant waitlist" (82%), and "age, including the number of future transplants they or their loved one might need" (82%). "No matched living donor and concern with matching on waitlist" and "interest in helping advance science/treatments" were motivators for 72% each. "Ineligibility for allotransplant/waitlist" (33%), "concern for losing eligibility for any transplant in the future (e.g., declining health)" (26%), "no interest in a xenokidney transplant" (21%), or "other" (5%) were less motivating to respondents as reasons to consider a xenokidney transplant (Appendix 6; Figure 11).

The live audience discussion following further explored the impact of kidney disease on attendees' lives or the lives of their loved ones, whether or not they would consider a xenokidney transplant, and what factors might impact their consideration. Patient experiences and expectations uncovered by these discussions are detailed below.

Kidney Disease Experience

Attendees reported their difficulties and concerns about being on dialysis, especially after a failed allotransplant and/or for an extended period, and the risks associated with this type of therapy. They also shared their experiences with barriers to being approved for a donor kidney, eligibility to be a living donor, and their experiences with a transplant failing. Care partners shared their parallel experiences.

> *"I've now been on dialysis for a year* [with a failing/failed kidney allotransplant] *and* ***pretty sick for about 3 years****."*
>
> *"****I was on dialysis for 9 years****. Part of the reason I was on* [it] *for that period of time was* [that] *I was also diagnosed with cancer in between that so "luckily" with thyroid cancer … But it took me off the transplant list for 3 years, and* ***I had to jump through many, many hurdles*** *to prove to*

> *the transplant team that I was cancer-free at that point, and that giving me a transplant and putting me on immunosuppressants was not going to be a major factor in me, you know, losing my transplant later on."*
>
> *"**I had a heart attack when I was 42**, in part because of the new immunosuppressants that I'm on."*
>
> *"**I personally was turned down at 2 transplant centers*** [for being a kidney donor for my son] *before getting another opinion and* [then] *I was taken immediately. So ... I think that has to be looked into. Because in my own case, for about 5 or 6 months, I sort of just said, 'Well, I can't be a living donor. My son's gonna have to be on the* [waitlist] *for a deceased kidney ...' So, I think, you know, **if you have CKD, you cannot give up** ... You have to ask for a second opinion... a third, and a fourth and keep going."*
>
> *"My son is 16 ... He had a kidney transplant when he was 2 ... He's had a wonderful life.* [You] *would never know he has had a transplant. It's been fantastic—just, you know, medicine 2 times a day. **He's, like, totally normal, but his kidney is failing**. He's had it for 12 years. I have ... been rejected for donating, so **we're now in the process of sort-of just a huge amount of work**."*
>
> *"*[I was] *consistently tired, and over time, became underweight due to lack of appetite.* [I] ***had a hard time thinking about the future and only felt hope when thinking about transplant**."*
>
> *"I think that people don't understand that **you need more than one*** [transplant], ***and it's hard to ask a second time**."*
>
> *"**My life revolves around my polycystic kidney disease**. I never know how I am going to feel after my dialysis treatment."*
>
> *"**He is sad and tired all the time**."*

In particular, patients stressed the general misery and challenges of having any kind of quality of life while on dialysis. While they appreciated the necessity of the procedure to stay alive, they stressed over and over the negative impact that dialysis has had on their general health and ability to lead a full life with their loved ones.

> *"There's a big difference between being on dialysis in your 20s—you know* [the odds] *you're likely to survive on dialysis is* [sic] *much longer* [in your 20s]*. By the time you hit 30 or 40, you know**, those odds starts coming down pretty quickly**."*

*"**I had to take a break from college** while being on dialysis."*

"When I was young, [dialysis] *wasn't difficult, except for the amount of time it took. The 2nd time, I was 20 years older, and **the process caused headaches and exhaustion, and I had to deal with infections**."*

*"Peritoneal dialysis caused me to gain weight and **led to my being sicker than I'd ever been in my life**."*

"Even with this [lifesaving] *treatment, one is often very tired and does not feel well. **It's a long process that severely challenges one's ability to hold a job, spend time with family, and enjoy life**."*

*"Having a child on hemodialysis and living 2 hours from her treatment center was **an extreme hardship for our family**."*

*"**Daily life*** **[on dialysis]** ***was a cyclical struggle**."*

*"**I would never have wished my daily life on dialysis on my worst enemy**."*

*"**I describe my life on dialysis as living hell**."*

*"**Dialysis is a miserable experience**."*

*"Horrible. **Dialysis is the last resort**. It keeps you alive, but the emotional, physical, and metal injuries remain because you never feel well on dialysis."*

*"**Life was very stressful** on peritoneal dialysis. It took up a lot of time."*

*"Peritoneal dialysis was **beginning to lose effectiveness** the last few months."*

"[Being on peritoneal dialysis was the] ***WORST YEAR OF MY LIFE."***

"[On dialysis,] *I was so very sick and sick of being sick!"*

"My life was miserable. I was existing and not living. I felt terrible all the time."

*"My daughter was on peritoneal dialysis for 2.5 years before receiving a kidney transplant. **Her life was tethered to being on a machine** every night for 10 hours and **her quality of life was diminished,** due to the effects of end-stage kidney failure* [sic]*."*

*"**I could have saved myself seven years of dialysis** if xenotransplantation was available."*

*"**Dialysis made it difficult to work full time**. Work followed by dialysis left me exhausted."*

> *"**Following a dialysis diet was a challenge."***
>
> *"My life was extremely limited. I was on dialysis for almost 10 years, **and I would have died if I had to wait*** **[for a transplant]** ***much longer**."*
>
> *"Daily life on dialysis is exhausting and difficult. Patients like [me] on dialysis are a **vulnerable population with needs for extensive support. Trying to live a more 'normal' life is nearly impossible**, as is holding a full-time job."*
>
> *"Although* [dialysis is a] *lifesaving treatment, **it removes quality of life**."*
>
> *"**Being on dialysis is a very exhausting experience**. I have low energy, weakness, and hope that I can sleep until I feel better. Dialysis days are always difficult. The other days can be good or bad."*
>
> *"**My life has been destroyed by dialysis, even as it has been saved**."*
>
> *"My husband does peritoneal dialysis ... **It's been heartbreaking to see the dialysis ruin his life, but he has no choice or he would die.**"*
>
> *"I am, and was at the time, a working mom of 3 little children, and **living on dialysis was hell**.... As a mother, having to tell your 2-year-old who is crying after skinning his knee that you don't have the strength or ability to pick him up off the ground **will break you.**"*
>
> *"When it came to holidays, there were Christmases and Easters when I could not physically walk to our living room to set up gifts for our children because **my dialysis cord wouldn't reach that far**."*

Xenokidney Transplant Interest

Multiple participants expressed their interest the success of xenotransplantation, and some expressed interest in signing up themselves. Patients relayed their sense of urgency; they feel they may be running out of time.

> *"There are so many individuals who are dying (literally) for a kidney transplant. The demand far exceeds the* [number] *of kidneys available. **Having alternative ways to have a functioning kidney is the ONLY way to prevent the loss of life due to kidney failure**."*
>
> *"My daughter was on the transplant list for over 5 years before receiving a kidney. She went through 4 potential donors prior, who were all rejected for one reason or another. **This could, potentially, speed up the process and eliminate dialysis**."*

*“***Pig heart transplants offer hope for success in kidney transplants*** *with the use of gene engineering.”*

*“***I do think clinical trials should start as soon as possible***, so that there is another option for those who can’t receive* [a kidney] *with* [the regular] *type of allotransplant.”*

“There are not enough human kidneys. ***Marginalized patients have greater difficulty procuring kidneys****.”*

“Any alternative weighed against the real possibility of death in any situation is worth it.”

“I try my best [as a physician] *to encourage live kidney donation, but* ***there’s not enough kidneys****, and we have to start a clinical trial and answer all the questions … How safe is it? Is it* [safe]*? What are the risks? … we don’t know what will happen 10 years from now, 20 years from now.* ***We have to advance science****.”*

“Because I am a firm believer in the advancement of science, medicine, and technologies for the improvement and betterment of we, humans. ***This is a step in the right direction.****”*

*“***As long as extensive scientific research is done***, xenotransplantation could potentially greatly benefit a huge amount of people needing a kidney transplant.”*

*“***Kidney patients need as many options as possible***, and even more-so for critical organs like* [the] *heart and liver.”*

*“***I think it’s a wonderful idea***. This would cut down the wait time for a donor.”*

“We didn't have kidney transplants years and years ago. I mean, ***just think of what if someone didn't investigate this years ago; we wouldn't even be where we are now****.”*

“We have to start. You have to start. ***I would encourage the FDA to please consider it.****”*

*“***I am also one of those who are waiting on a phase 1 trial***. Not just for me, but for all the people who I love and care for and who are in need, who are on that* [transplant wait]*list who are … 14 dying every day. Yeah,* ***it’s time to move forward.*** *”*

*“***If xenotransplantation had been available,*** *I most likely wouldn’t have spent that time waiting on the transplant list.* ***I could have rejoined my life as a mother much quicker****.”*

*“***I would have volunteered to be in the first xeno clinical trials****; my quality of life had diminished to the point* [that]*, other than losing my life,* ***no risk would have been too great.****“*

*"**Xenotransplantation could cut down on the months/years patients are waiting on dialysis while the clock ticks** by on a kidney hopefully to come."*

*"**You can't live a normal life on dialysis.** You can with a transplant, and a **xenotransplanted kidney could fill that need.**"*

*"**Advancements in xenotransplantation would give hope to many with kidney disease,** and possibly avoid dialysis. We, as humans, have the intelligence to recognize change in order to evolve."*

*"I have experienced an allotransplant. I'm very well aware of the surgery itself, the post-transplant medication regimen, the follow-up appointments, the physical pain, and anxiety that come with receiving a human kidney transplant. **I would happily go through all that again if it meant I didn't have to suffer on dialysis, and I could get back to living a normal life.**"*

"I know a human transplanted kidney lasts an average of 12 years. I stand here today, at 40, so most likely I will need another transplant or 2. I would wholeheartedly volunteer for a xenokidney, if it meant my time on dialysis would be cut down."

*"**I would consider it if dialysis was no longer working for me, and I had absolutely no other options."***

*"I assume there would be many more follow-up visits, the possibility of added post-transplant medications and more blood work, even daily monitoring for some time, but **I would gladly accept that if it meant I would be able to return to my life as a wife, mother, and friend**."*

*"Risks of xenotransplantation—**of course there would be risks**—I knew them going into my own transplant, but as a mother**, I would risk everything for the chance to actually be there for my children**—honestly I would."*

*"**If I knew my time on dialysis was running out and xeno was an option, I would seize it.** The way I see it, **my only other option would be death.**"*

***"If studies are done that prove the rejection rate is the same as human kidney transplant**, then I would definitely participate in the program."*

*"Without a transplant, I would have suffered and eventually died. **If the option is a horrible death or a xenotransplantation, it's a no brainer**."*

*"I would accept an approved kidney xenotransplant if I needed another kidney to live **because there was no other alternative, and** **[if I]** **was assured that it would effectively replace my kidney function.**"*

*"**Reducing or eliminating the wait for a human kidney, with all the associated trauma of that wait**, would have driven me to strongly consider entering a trial for kidney xenotransplantation."*

*"Reflecting back on my dialysis experiences, if the opportunity was available back then to be a part of xenotransplantation trials, **I most certainly would have moved beyond the fears—with medical guidance—and had the transplant in the hopes of getting my life back.**"*

*"When I consider the risks of xenotransplantation, **I think of the potential benefits,** such **as increased freedom in my life, less pain, and** **[fewer]** **of the numerous medications** I take. When I think of it this way, **I am willing to endure a xenokidney** that would last for even a few years to allow me time off dialysis."*

*"**My hope for a xenotransplant is stronger than my fear of the risks**."*

*"I do not want fear to stand in my way. I understand and accept no one is promised tomorrow, but when you have a condition where the only options for staying alive are dialysis or transplant, **I want the transplant (whether it be human or pig).**"*

*"When I think about it from a grandmother's perspective, **I would join the first clinical trial to help advance science for future generations**. When I think of my grandchildren, if they are ever confronted with kidney failure, **I want them to know their grandmother offered her life to improve the number of treatment options to extend their lives with xenotransplantation.**"*

*"**I think xenotransplantation would be a good match for my daughter, and I would encourage her to enter a clinical trial** because I've seen the effects dialysis has had on her quality of life. **She doesn't want to live the rest of her life on dialysis or waiting for an allotransplant, which may never happen**."*

*"Without xenotransplant, **I don't know if my daughter will have a future that allows her the freedom of living that most of us take for granted**."*

*"If xenotransplantation achieves FDA approval, I believe it will make these dreams a reality for my daughter, because **she will have an option to receive a functioning kidney without***

***prolonged wait times or chronic dialysis**. Even the possibility that she may be monitored several hours daily is not a deal breaker, as she has already been hooked to a machine for several hours during chemo and dialysis.”*

*“**Breakthroughs don't come without doing research**. If patients are willing to participate in trials, it's important to build scientific experience and knowledge.”*

*“I’m not going to lie, **I’m nervous about zoonotic infection**, because I could make others sick if I get it, **but if they have safety precautions, and I’m able to enjoy living again, it’s worth it and I would be willing to participate in a phase I trial**. Being hooked up to a machine multiple times per week for hours with no end in sight isn’t living and **I want to live**.”*

*“For us, **the benefits and the hope of living a full life once more outweigh the risks and dread** of watching* [our daughter] *live hooked up to a machine and simply existing.”*

*“Xenotransplantation would help ensure my son would have a transplant when he is in need; **that alone seems a good reason to try**.”*

*“Xenotransplantation makes tremendous sense—**filling the gap between the number of deceased and living donors**.”*

*“**Too many people die on the waiting list**.”*

*“Being a young patient and **at my last days of life, I would certainly try all means of transplant possible. I want to live.**”*

*“My nephew and my twin sons all have Alport syndrome. My sons are CKD stage 1. They are only 3 years old, but **we are very interested in any and all advances in kidney transplantation,** as they will both need kidneys.”*

*“Too many people die while waiting for an organ. **There are too few organs available and too few people donating**. This is what is next. We must explore other options.”*

*“I have 5 children. 2 of them have the same rare kidney disease that I have**. If I had any option that would save them from dialysis, pain and/or death...I would take it**. I think most parents would.”*

*“I'm not confident that cross-species transplantation will ever be successful, but **if patients know the risks and are willing to try, why not try to move forward with studies**?”*

*"**I really believe that xenotransplantation would make a huge difference** in reducing the waitlist and allowing CKD stage 5 patients have the opportunity to a better quality of life."*

*"**I never want my son to be one of those waiting—and dying—on the transplant list**."*

*"There is a huge shortage of kidney donors. **The more kidneys available, be it human or pig, the more people can be saved."***

*"More people need transplants in order to survive. **If research shows a pig's kidney could save lives it should be trialed**."*

*"If human kidneys are not available, **we must institute an alternative**."*

*"If you ever experienced the tragedy of life on dialysis, you would understand that **the quicker a dialysis or kidney disease patient receives a transplant, human or animal, the quicker that person can return to being a more positive influence** and strong support mechanism for her spouse, family, employer, community and self."*

*"**The difference between transplant and dialysis is transformative**. I feel like a normal person now, as opposed to a very clinical life of trying to keep yourself alive and well. My only goal was to receive a transplant and **I would have openly received a pig kidney**."*

*"**It's the best option** for patients who cannot get a human transplant."*

*"**People need transplants right now, and xenotransplantation can give it**."*

"However, if we were faced with needing a kidney while [my son] *is still under 18, and none was available, I would strongly consider alternatives like xenotransplantation. **A xenokidney would offer a timely solution to years on dialysis**, allow him to be free of fear of complications and restrictions, and **he could get on with living his life**!"*

*"Having been on the transplant list, I know that the long wait time is frustrating. **If there is any way to decrease the wait times, I am all for it**."*

*"**I am supportive of anything that would get someone off of dialysis**."*

"Many people die on the [allotransplant waitlist]*, and **xeno could change that unnecessary outcome.**"*

> *"The waitlists are long and the needs is 'very high.'* ***Anything that can be safely done to help reduce the number of deaths and shorten the wait time should be considered****. What else might be discovered while trialing xenotransplantation?"*
>
> *"I would accept one! I have been following the science for a decade.* ***If we can use xenotransplantation for heart valves, then why not kidneys****?"*
>
> *"****Advances like*** **[xenotransplantation]** ***can dramatically change life for patients with kidney disease****."*

Xenokidney Transplant Concerns

While respondents were interested in seeing xenokidney transplantation move forward into the clinical trial investigation phase, not every participant who shared in the discussion was equally eager to sign up. One participant in particular shared his concerns about entering his son into a clinical trial, both for the potential effects of medications associated with the treatment as well as the presumed diversion of resources from improving currently approved therapies.

> *"I will say that* ***I would not, of course, not put*** **[my 16-year-old son]** ***in a clinical trial*** *for, you know, transplantation. I know the more kidneys into the system, the better. I will say it's a little vaguely distasteful to me."*
>
> *"****I would worry about medicines. I already am worried about the medicines*** **[my son]** ***takes. I'm also worried about kind-of taking the taking our foot off the gas on other options****, man-made organs, improving medicines for donated kidneys."*
>
> *"****If it were*** **[my son's]** ***last option, I would take it****, so I'm in favor of the research. I just hope we continue and surpass this phase and get something better."*
>
> *"Even when receiving a cadaver*[ic] *kidney* [donation] *and the markers are there, there is still a chance of it never working or going thru* [sic] *rejection.* ***Until we can successfully make the body not reject a foreign entity, I don't see a big success****."*
>
> *"My major concern at this time would be rejection of the foreign object by my body.* ***I need to know the percentage rate for rejection before agreeing to participate. If the rejection percentage is too high, I don't think I would be willing to take that chance****—especially at my age."*

*"I want to live a full, productive, and useful life with the time I have left**. I won't go out willy-nilly to accept something with a high failure rate 'just because**.'"*

*"**I don't like the idea of animal transplants**. Scares me on what the future issues may be."*

*"**The idea of having a pig organ inside of me or others is frightening.** Even putting someone in a clinical trial **makes me nervous considering the risks of infection and rejection**."*

"I hope the first trials begin and are successful, so [my son] *and all those in need, can get a kidney when deemed necessary. **I just don't think I am ready now** to enter my son in one of those early trials."*

"We don't know if [xenotransplantation] *is safe or healthy for patients in the short-term, or the long-term effects on the bodies. **Pigs kidneys do not seem like the safe route to take on**."*

*"**I'm a bit apprehensive because the man with the pig heart didn't live very long**."*

*"**The potential benefit is great, but so is the risk**. Xenotransplantation has been studied for decades with a promise of helping dialysis patients, and **it doesn't appear much real progress has been made**."*

"[Spending time with my friends and family] *is something that I* [have] *love for and that I love doing, and **being among the first to undertake a xenokidney transplant would most likely render that life extinct**."*

*"There are numerous risks associated with xenotransplantation, known and unknown, and **if you asked me today to participate in the first human clinical trial, I'd simply say no**."*

*"**What worries me** **[are]** **the unknown risks with xenotransplants**. Throughout my daughter's life, I have researched everything I could about her disease, so that I could better understand each phase of treatment she has undergone, and the risks involved. **With xenotransplantation, there isn't much public information available for me to research with due diligence**."*

*"I also worry that **I would be more willing to take risks in order to sustain my life without fully thinking through the long-term implications** of xenotransplantation."*

*"As a mother, I want my son to live a long and healthy life, so in the early trials, **I would hesitate to sign him up as one of the first patients. We cannot know if xenotransplant will lead to a better quality of life until we learn more about it**."*

> *“**Seems unnatural**. What about allergies? I was given a strong immunosuppressant to counteract rejection and had a severe reaction. One version made from pig, the other from horse.”*
>
> *“Another worry is, after xenotransplant, would* [my son] *be in **much worse physical state** and be subject to **more intensive, daily testing**?”*
>
> *“As of right now, **until I learn more, I find it hard to be 100% supportive**. But that could change.”*
>
> ***“[I] have heard of a virus that can come with xenotransplant**.”*
>
> *“If* [my son] *received a xenotransplant and it failed, **would his body reject a human kidney** if one became available?”*
>
> *“*[If my fears] *proved true, I think **xenotransplantation would have to be a last option**.”*
>
> *“**I would not feel particularly comfortable personally with** xenotransplantation but would consider it **as a last resort**. I would think other human stem cell options should be explored first.”*
>
> *“*[I am] ***concerned about reduced survival time vs human transplant**. Possible use as an intermediate stopgap while waiting for an allograft. Perhaps for elderly?”*
>
> *“I would hesitate. I received a pig loop for dialysis which my body rejected and left me with too many antibodies in my system. **It would scare me, but if last hope, maybe**.”*
>
> *“I've had a cadaver*[ic] *transplant for 45.25 years. I was the second person in the world to be given ATGAM® (currently made by Pfizer, I believe), so **I'm no stranger to clinical trials and the risks they present**. In regard to kidney xenotransplantation, **I'm not sure if I would accept any risks unless it was a last resort**.”*

Some participants shared their discomfort with using animals in medicine or for scientific research, but also noted the importance of not letting personal ethics stand in the way of scientific and medical advancement.

> *“**I feel sorry for the pig**.”*
>
> *“I am an animal lover, and hate animal research, so **I am not sure how I feel about the implications of raising animals for organs**,* [but] *I also know that **we have too many people dying while waiting for human organs** … Animal organs might be a bridge.”*

> *"I don't like killing an animal for a kidney, but **I also want patients to get to make their own decisions**."*

> *"**I put 'neutral' because while I am opposed to** [xenotransplantation]**, why should I impose my ethics on someone else?** But in a civil society, many laws are ethics-based to ensure the society is functional. So, **I have a lot of mixed feelings about this**."*

Another consideration involves religious ethics of xenotransplantation. This nuanced issue needs further exploration.

> *"Not sure religion-wise where this fits, but **it has to be better than dialysis**."*

> *"**As a religionist,** [some individuals] **may disapprove** [of xenotransplantation]. However, I believe … any extreme measure may be taken to save* [a life]. *Hence, again, **I am fully supportive and advocate of the idea of kidney xenotransplantation**."*

Discussion A: Important Factors for Considering Kidney Xenotransplant

Despite the better outcomes associated with living kidney donation, participants expressed their reluctance to approach potential living donors due to the risks to the living donor's health or to the possibility of receiving a kidney from a living donor that could have gone to a recipient closer to the donor. Participants noted how xenotransplantation could alleviate those concerns. Participants also highlighted the difficulties of needing multiple transplants over their lifetimes and the lack of transplant options for patients not eligible for the list as factors that affect their willingness to consider xenotransplantation.

> *"It's really hard to get a living donor.* **[My living donor]** ***had some trouble**. It ruined a friendship of 20 years … That is **much more complicated for me this time around**, now that I've seen what could happen … So, for me, **the idea of xenotransplantation removes a lot of that**."*

> *"**I need to hear a lot more about it.** Advantages, disadvantages. What life looks like 2 years, 5 years, 10 years into the future."*

> *"I have to go over all the information. It sounds ok, **but I would have to see how many people accepted a pig kidney and how long would the kidney last**."*

"I have fears about xenotransplantation; they are based on ***not fully understanding the evidence that it will be safe and effective for humans****."*

"[If xenotransplantation carried a] *threat of porcine or other infections to my loved ones—I am around family members with immunocompromised health—****I would not want to jeopardize their health****."*

"The risk of a serious porcine disease being contracted by me, or passed on to anyone close to me, is simply not something my family or I would take on today."

*"****If xenotransplantation required extensive long-term monitoring that would prohibit living a full-quality life, it would be a deal-breaker for me****."*

"Even if death or disease were not risks, the close monitoring, severe medication, loss of privacy and other demands of ***'being first,' would take away too much of the life I am still able to enjoy with my loved ones****."*

"With xenotransplant, ***what scares me most is the possibility of*** **[my son's]** ***other organs failing, leading to death.****"*

*"****I have reservations about the procedure****. Those include infection and other unforeseeable side effects."*

"I am supportive, but I am ***concerned about diseases and rejection possibilities****."*

*"****How can we be sure that the pigs are treated well****, and that we would, indeed, be given healthy kidneys?"*

"It sounds like a good idea. However, ***since there are no clinical trials, there is no information on the success of the xenotransplantation****."*

*"****Need to know more about safety of xenotransplantation****, but I would have considered it if no one had donated a kidney to me."*

*"****Until it's proven that it works, I wouldn't submit myself to unnecessary surgery****. Plus, I have concerns with* ***diseases that could possibly come up****? The 'unknown,' basically."*

*"****I have questions*** *regarding size of* [a] *pig kidney, how many we will receive, life expectancy of* [the] *life* [of the] *kidney, what type of antirejection drugs are needed, insurance coverages, etc."*

*"**I would have to know more about the treatment of the source animal, and details surrounding the process,** to be fully supportive."*

*"**Until I am able to educate myself, I am hesitant**."*

*"**I'm still young enough that if I do get a transplant now, I might still need a third one. That makes a difference.**"*

*"I am also concerned about **the time it will take for the necessary studies to be completed before the first xenotransplantation would even begin**."*

*"**Rejection potential would need to be carefully understood** and the immunosuppressant (sic; -sive) therapies and **any risks would need to be communicated to the patient**. A benefit-risk analysis would be needed per patient."*

*"Medication is another concern. Are the medications the same as those for a human kidney transplant? I've been told there are many. I've also been told that the medications are harsh. What does 'harsh' mean? **I will need to make a comparison of the medications to determine whether this would be an option for me**."*

*"Some of the risks I would be more concerned about are if the kidney fails or needs additional surgery to remove it, life-threatening infections, extreme pain, and **if I was worse off than if I did not endure a xenotransplant.**"*

*"You may ask, 'What rejection percentage is acceptable for me?' To be honest, I don't know at this time. **I would need to compare the acceptance/rejection percentage statistics before making a final decision**."*

*"**I would want to know more information about the immunosuppressive protocol's side effects,** both in the short-term and the long-term. It is possible that **the only risk I would accept is rejection, as that is the same risk one undergoes in an allotransplant**."*

*"I would also like to know, **if the xenotransplant rejected, would I still be able to receive an allotransplant** or would my body be sensitized against it?"*

“[I have fears about] *animal-to-human transplantation unknowns, including infections or potential diseases or unanticipated viruses that could emerge in the future.* ***This is the biggest fear I have about xenotransplantation but it would not deter me.***”

“***I would accept xenotransplantation*** **[if I could be assured there was a]** ***0%*** **[zoonotic]** ***infection risk.***”

“***What defines a ‘successful’ xenotransplant****? I think the definition should include answers to questions like: how long will the pig kidney last? Will there be side effects and/or increased immunosuppressive medications? Will these side effects be more tolerable than the effects of kidney disease and dialysis? In my view,* ***at least one year free from dialysis, minimal pain and sickness would be a successful definition and beneficial result for a xenotransplant****.*”

“[Because of my experience with a living donor], *if I had the option of a xenotransplant, and* **[if]** ***we were at a place where we knew it was safe enough****, I would go for that before a living donor, maybe before a deceased donor, but for sure, before a living donor.*”

“I'm not sure an animal's organ should be inside a human. A pig's makeup is totally different then a human, and ***we don't know how long it would last****.*”

“Another major concern regards the infection risks—specifically zoonosis—for the patient and for those around them. ***Xenotransplantation would not be an option for me if nothing was done about this problem.***”

“***Need more info like stats on the procedure and likelihood of rejection****.*”

”I would be most interested in knowing if the disease had resurfaced in the xenokidneys or not.”

“If there was evidence that a xenokidney transplant did not pose a significantly higher risk of death, infection, or rejection than an allotransplant AND could provide a kidney that would not be damaged by IgAN [IgA nephropathy], ***I could definitely see us saying ‘yes.’”***

“It would depend on my personal situation, meaning [that] *if I did or didn’t have a match for an allotransplant, and how much of my busy and full life was already fading away with age and disease.* ***The truth is, when I need to make the choice, I will choose*** **[xeno]*****transplant over dialysis****. Period.*”

> *"I think I would take a xenotransplant just because I am either at an age* [that] *I wouldn't be put on a transplant list, or I'm soon approaching that age, and* ***I certainly would take a pig kidney****. There would really be no question about that for me."*
>
> *"Dialysis at my age is a huge risk compared to when I was 20. And so that that is, you know, something in the back of my mind of* [that] ***I may not actually survive that long on dialysis if I*** **[don't have]** ***another transplant.****"*

> *"I also had a lot of apprehension, and I still do about, you know, if I had a relative that could donate to me, I do not want that person to have to go through any of the stuff that I went through of dealing with even CKD. And, so, for me,* ***the only options are it's a deceased donor or it's a xenotransplant****."*

> *"****If there are no IgAN or similar rare kidney disease patients being assessed*** *in the early trial phases, I am not sure what we'd say to participating in a later trial."*

> *"I think about my donor who is living, who told me 10 years prior to me, needing it, that she would give it to me. Her mother-in-law now is on dialysis.* ***I haven't been able to call her since I found out cause there's a guilt that she gave*** **[her kidney]** ***to me****. And now her mother-in-law is in need... having* **[xenokidney transplantation as an]** ***option will just save so many lives****."*

> *"If you asked me again in a few years, and* **[if]** ***my health had declined to the point that I was eligible and seeking a living donor transplant, and the xeno' trials had entered a later phase, the answer would be 'maybe****.'"*

> *"I would want to know if any IgA nephropathy patients had participated in the earlier phases of the trials. I would want to know more about the particular experiences of any patients with rare kidney diseases and understand those unique data points."*

Patients also spoke of how, though they had reservations, under certain circumstances they still might be interested, and how knowledge of their contributions to advancing the science would help make up for the risks and/or challenges of xenotransplantation.

> *"If I had no living donor match and the waiting was requiring me to do dialysis****, my life would probably no longer feel like my own. I would feel like a burden*** *to my husband, my aging*

> *parents, my adult children, and my friends, and* ***I believe we would all say 'yes' for joining a clinical trial for a xenotransplant****."*
>
> *"****I would want my participation to specifically collect any data points that could be used to help IgA nephropathy and similar rare kidney disease research*** *move forward in any way possible."*
>
> *"I'm older at this point, and for me* ***it's a way of giving back****. It's a way of 'let's see what happens'...****I'll go for it because we need the information****."*
>
> *"it's also contributing to science. It's contributing to the legacy of transplant*[ation]*, and that* ***hopefully later on, some kid in their twenties doesn't have to sit on dialysis for 10 years waiting for a transplant****."*

Discussion B: Patient Considerations of Risk and Other Downsides of Kidney Xenotransplantation

Discussion B: Polling Questions and Audience Discussion

The second discussion focused on patient considerations for potentially receiving a xenotransplant, focusing on specific risks associated with the procedure. The discussion was preceded by an expert presentation about the known and unknown risks of kidney xenotransplantation. Patients were asked to consider the risks discussed in the presentation and what information they would need to consider a xenotransplant in light of those risks. Polling questions (Appendix 5.2) and audience discussion disclosed patients' concerns about xenotransplantation risks, and what factors might affect their consideration of a xenotransplant.

During the discussion, patients shared their concerns about potential known and unknown risks to xenokidney transplantation. Patients felt that some risks (ie, a catastrophic event, increased risk of failure or rejection requiring surgical removal) were tolerable and would not prevent them from considering a kidney xenotransplant, while other risks (ie, zoonotic disease transmission) might take xenokidney transplant completely off the table for them—at least without significant reassurances.

Patient Concerns About Potential Risks of Xenokidney Transplantation

Participants were first asked to indicate their likelihood of being willing to accept a xenokidney transplant if there was a known risk of a catastrophic event (eg, severe organ damage or a life-threatening event) occurring with the procedure (Appendix 5.2: Discussion B: Question 1). Most (41%) of respondents were unsure if they would still consider undergoing a xenokidney transplant with this risk. Respondents were then split nearly equally in likelihood of accepting a xenotransplant if there was a risk of a catastrophic event, with 10% indicating they would be very likely to still receive a xenokidney, 15% indicating they would be moderately likely, 18% being somewhat likely, and 15% not at all likely to receive a xenotransplant. No respondent indicated they were not interested in a xenokidney transplant (Appendix 6; Figure 12).

Next, participants were asked how willing they would be to accept a xenotransplant if it meant they would not be eligible for the allotransplant waitlist in the future (Appendix 5.2; Discussion B: Question 2). Nearly one-third (31%) of respondents indicated they would not at all be likely to accept a xenotransplant if it affected their eligibility for being listed for a future allotransplant, while 23% indicated they would be somewhat likely to do so. Respondents were then nearly equally unsure (18%), moderately likely (15%), or very likely (13%) to accept a xenotransplant even if it meant they would no longer be eligible to be placed on the allotransplant waitlist; no respondent indicated they were not interested in a xenokidney transplant (Appendix 6; Figure 13)..

When asked their likelihood of accepting a xenokidney transplant if there was a risk of transmission of a zoonotic infection to their friends or family (Appendix 5.2; Discussion B: Question 3), most (44%) respondents indicated they would be not at all likely to agree to receive a xenotransplant and 20% were unsure. The rest of the respondents were somewhat likely (15%), very likely (15%), or moderately likely (7%) to accept a xenokidney if the procedure carried the risk of a zoonotic disease transmission to the patient’s loved ones. Again, no respondent indicated they were not interested in a xenokidney transplant (Appendix 6; Figure 14).

If there was an increased risk of failure or rejection of the kidney requiring surgery to remove the xenokidney (Appendix 5.2; Discussion B: Question 4), 40% of respondents indicated they would be very likely to still accept a xenotransplant, followed by 28% of respondents who indicated they would be moderately likely to agree to be xenotransplant recipients. Just over a third of patients were unsure (12%), not at all likely (12%), or somewhat likely (9%) to receive a xenokidney transplant if there was an increased risk of failure or rejection requiring surgical remove of the donor organ; no respondent indicated they were not interested in a xenokidney transplant (Appendix 6; Figure 15).

Participants were then asked how interested they were overall in receiving a xenokidney now or in the future (Appendix 5.2; Discussion B: Question 5). Most (43%) respondents shared they were very likely to be interested in receiving a xenokidney, either now or in the future, even after the discussion about potential risks, with 29% of respondents maintaining some interest (somewhat interested) and 19% continuing to demonstrate a moderate amount of interest. Some (10%) respondents indicated they were not interested due to the risk discussion and no (0%) of patients were "unsure" or "not interested for other reasons" (Appendix 6; Figure 16).

Patient Considerations for Catastrophic Risk and Risk in General

In the audience discussion, participants noted their impatience with the time that it is taking for xenotransplantation to be studied and approved as a human renal replacement therapy. They emphasized the importance of including the patient voice and considering patient willingness to assess and accept risk for a therapy that could help many people in need.

> *"I picked 'moderately* [interested]*,' but it's because the question wasn't worded perfectly right—* ***if you told me the [catastrophic] risk is 1%, my answer will be different; if you tell me the risk is 10%, my answer will be different; if you tell me the risk is 50%, my answer will be different****. So, I think there's a lot of different answers I could have given to that question if it had been asked in a slightly different way."*

> *"****I think we're wasting a lot** **[in general]** ***and a lot of opportunity of*** [sic] ***life for a lot of people, just because monitoring has become too tight****."*

> *"If we embark on xenotransplantation, which I think we should, we need to approach this with a mind of 'Where were we 50 years ago?'; 'Where were we 100 years ago?'; and 'What expectations [do] people have?'* ***If this helps, in the beginning, 20 more people*** [participating]***, I'm okay with that.*** **[If]** ***that's a risk,*** **[that]** ***I think, is fine****."*

“Without studying [xenotransplantation] *we won’t get to the point* of [xenotransplantation being able to solve all our problems] ***… I think we’ve been held up far too long***. *I was hoping that, by the time I’m 30, we’d have ‘xenos’ available or artificial organs available.”*

“I think we’ve lost control of autonomy for patients. ***5 years ago, I would have said ‘yes’ to this, but I wasn’t given the opportunity***. *The field has become extremely paternalistic, from an institutional review board (IRB) and regulatory standpoint, and I think that’s wrong.”*

“ ***For organ failure, I would have accepted 100% at 3 months***, *because I don’t think that the first few will be super-successful. But* ***if we don’t study it in humans, we will not figure out what’s different*** *between humans and primates and* [how] *the immune systems between those differ without having done research with that.”*

“In terms of ‘catastrophic events,’ when I go under general anesthesia, I have a <1% threshold for heart attack, stroke, pulmonary embolism, and death. ***It’s never zero, even for the best option available***. *I’m a healthy patient. I know my own mortality on dialysis at age 40 … I’m not sensitized; I could easily get another transplant.* ***I know all these details about my own healthcare, and I think the decision has to be informed by what’s the risk of waiting***.*”*

“There's a lot of individualized decisions that go into these kinds of things, and the [person’s] *willingness to take a risk … I think* ***there needs to be some allowance for differences in people's risk-taking and willingness***.*”*

“ ***I don't want to become a burden. I don't want my responsibilities to fall into the hands of others***.*”*

“ ***I appreciate that these risk***[s] ***are unknown … We will never know them if we don’t try, and there are people willing to take those risks, and we need to give them the chance to do that if they want***.*”*

“[The potential for catastrophic risk] *balances against other options—* ***the risk of death on dialysis is obviously a part of that***. *But the* ***quality of life on dialysis is also so bad.”***

“ I would weigh [life on dialysis], *too, as in,* ***‘What is the life that I have if I just stay the course and would I rather take a chance?’*** *And I know that* ***there will be a point at which I am willing***

> ***to take that chance, even if the risk is greater than*** **[with]** ***a human transplant***. *Because it's no life* [on dialysis]. ***After a certain point, really, it's no life of your own on dialysis***.*"*

> *"If all other options were unavailable, even assuming a catastrophic outcome could be possible,* **[I]** ***would be willing to do*** **[a xenokidney transplant for my son]** ***if the other options were worse***.*"*

> *"**I would be willing to*** **[consider]** ***the options for*** **[xenotransplantation].** *Of course,* ***I'm scared about the possible outcomes****, but I have been fortunate. I have not had to be on peritoneal dialysis as long as many others have.* ***But the process can wear you down****; you lose your energy, your dreams, your ability to travel, etc."*

Participants also noted their reluctance to accept the risk of xenotransplantation at this time. They spoke of how they appreciated the willingness of others to take that risk. They shared their perspectives on questions they have about receiving a xenotransplant and reasons they do not feel the risks were worth considering at the moment.

> *"**I think that there needs to be the freedom to make*** **[the]** ***decision*** **[*to risk* xenotransplantation or not]**. [I have] *2 young kids****. I'm not gonna take a xenotransplant even if my kidney failed tomorrow***. *I would say, 'no,' but* **that will change over the course of my *life***. *I anticipate needing more kidneys at some point. Hopefully, as few as possible."*

> *"In terms of risk,* ***I don't want to put that [decision] on the patient,*** *to allow patients to hear those things and make those decisions, rather than saying 'I, your physician.' Or 'I, the FDA—I am going to make that decision for you.'"*

One patient had questions about how xenotransplantation might affect pregnancy and childbirth. She noted that there were not questions about assessing these types of risks and emphasized the importance of collecting this data to share with potential recipients, as it would likely affect patients who were interested in becoming pregnant.

> *"**What about women who were to receive this*** **[type of]** ***transplant? [If] they decide to have children, how would that affect them****?"*

> *"If we did have* [xenokidney transplantation] *as an option right now … how would that transplant affect me? The medications, how would that affect the baby?* ***And how would it affect me carrying a child? I'm not sure that risk was even considered.****"*

> *"****I would only consider*** **[kidney xenotransplantation]** ***if there were minimal-to-no complications to the baby****. I know* [that] *with the human transplant, it's already a high-risk pregnancy. So, I'm also probably expecting that would probably be a high-risk pregnancy. But I would be more concerned* [with], *'****What are the complications and how would that affect the baby? Would I have a very small baby? Would I miscarry****? What kind of medications would I take or not take?'"*

Patient Considerations for Risk of Ineligibility for Future Placement on the Allotransplant Waitlist

Participants shared their reluctance toward receiving a xenokidney transplant if it prevented them from being eligible for a future allotransplant, as well as the need to balance potential known and unknown risks of xenotransplantation with the known risks of remaining on dialysis.

> *"I was very fast on the 'no way'. For me,* [being ineligible for the allotransplant waitlist] *was a dealbreaker.* ***Don't fix me and break me, and then not be able to fix me****."*

> *"I answered very quickly and said that* ***I would, in that case, not enroll in a trial for xenotransplantation if I knew that it was gonna prevent me from getting allotransplant in the future.****"*

> *"For me, I think about … how long I have been on dialysis and how old I am. Because* ***taking these risks would likely save my life at the time. The longer I am on dialysis, the sicker I am going to get.****"*

> *"I lost my spleen. I have arthritis. I have a bunch of other stuff going on. And so, these risks,* ***if it's going to save my life as opposed to living the poor quality of life that many of us live on dialysis, I am more apt to say, 'Let me take these risks****.'"*

> *"It makes a big difference for me to say, well, 'How much of a risk am I willing to take to stay on dialysis?' as opposed to say*[ing], *'****Let me increase the quality of my life through a xenotransplant****.'"*

> **“[I want to]** ***spend quality time with my family and my friends, travel the world, go to school***. *Those kinds of things are important to me. But* **staying on dialysis, you don’t have those options** *very much. Most of, you know, talking to several of the transplant recipients here, it’s the same thing.* ***We want a quality of life. We want a good quality of life, just like anybody else***.*”*

> *“****I’m not a big risk-taker, but when my life is on the line,*** **[I]** ***think differently*** *… I’d be more willing to take risks, and that’s a concern for me. Am I willing to take too much risk? But when your life’s on the line …* [the more risk you are willing to take.]*”*

> **“[If]** ***I help hundreds of thousands of other people and I die a few days sooner, to me, that’s a life worth-lived*** *… How long you live is not the end* **…** ***but how well you lived and what you did with the time you had matters just as much***.*”*

> *“There are young people who are relatively healthy … in whom a human kidney transplant would likely fail* **… [who]** ***might actually have a better outcome with*** **[xenotransplantation]** ***than with current options*** *for transplant or not even being able to be listed.”*

> *“I didn’t hear an option that would have made a difference for me, which is,* ***if I wasn’t able to do a*** **[future]** ***human transplant,*** **[I would still be able]** ***to do another pig transplant. That would change my risk-benefit*** **[equation].** ***A lot.”***

One participant cautioned against the use of incentives, noting it may lead to coercion of clinical trial participants, preventing true free choice.

> *“If we incentivize, then* ***people will be pressured into*** **[participating]** *And I think* ***that poses a lot of ethical issues of, you know, if there hadn’t been an incentive, would you have still done it?”***

> *“*[There are] *patients* [who] *don’t currently stand a chance on* [sic] *having a living donor or a* [deceased donor kidney] *… to be transplanted in a timely frame* [sic]*, so* ***I don’t think there is any need to incentivize*** **[to get clinical trial participants]** ***in the current system***.*”*

Patient Considerations for Risk of Zoonotic Infection Transmission

Participants spoke of their experience of quarantine with the COVID-19 pandemic and how quarantining to manage zoonotic infection transmission risk would be a familiar measure and not a particular burden. They also suggested that zoonotic infections may not be as much of a risk for non-immunocompromised people (ie, friends and family vs the transplant patients themselves), and not be as much of a concern to them as other risks. One patient noted she would be more open to considering a xenokidney transplantation if the risk for potential zoonotic infections could be definitively lowered.

> “*I* [already] *wear a mask quite often today…. How long* [would] *that last?* ***Is there going to be eventually vaccines that could possibly be developed to overcome*** **[potential zoonotic diseases] just** ***like we did in a very short amount of time for*** **[COVID-19]**?”
>
> “***In terms of managing*** **[a zoonotic infection]** ***and need to quarantine, it's something that*** **[I can deal with].”**
>
> “***I'm just very concerned about pig-borne illnesses,*** *such as the type of parasites that can come from undercooked pork* [trichinosis]. *Will that type of disease be an issue?”*
>
> “*Love the idea of scientific advancements, but* ***concerned about an animal/human crossover***.”
>
> “***I think this is a remote risk*** *… The one patient at highest risk from these infections is the recipient of the organ because they'll be immunocompromised. Once your immune system is weak, that infection will harm you and hurt you more than anyone who has a normal, healthy, immune system … Normal, healthy people are unlikely to get super-sick from it.”*
>
> “*Viral replication* [and mutations] *are higher* [in people who are] *immunocompromised. That is very well-proven and true. And could something crazy happen? Yes. But* ***I think the chance of that happening is much, much lower than other of the other risks we've previously discussed***.”
>
> “*If there was a way they could quarantine the pigs and do something different to lower the risk of zoonosis … that would be different for me …* ***I would consider it, but only if the risk could be lowered so that it would not affect me, my family and friends, and my support team***.”

Other participants shared their concern about the ability to fully contain a potential zoonotic infection, even with risk management efforts in place. They felt the risk of transmission to their friends and family was too high to consider a xenokidney transplant.

> *"We tried to prevent* [the spread of COVID-19], *but couldn't prevent* [it], *and that is something you want to try to prevent but can't prevent.* **[It makes you think]** ***'What could be the long-term ramifications from*** **[a zoonotic infection]** ***that could be passed onto*** **[sic]** ***members of our family****?"*

> *"You have to give a lot of weight to this particular risk of* [passing a zoonotic infection to friends/family members], *because then* ***they'll possibly be in the same situation as*** **[I am],** ***needing a transplant because of organ failure to a disease that could have been prevented if I didn't bring this to them****."*

> *"I indicated that I was not interested at all …* ***Bringing in something like zoonosis into the picture would not be good for me****, first of all because of my age, and secondly, because it would put it out there for my family, and—****even though it's my life—I don't think that's fair to them****."*

Patient Considerations for Increased Risk of Xenokidney Failure or Rejection Requiring Surgical Removal

Risk of the need for surgical removal of a failed or rejected xenokidney felt like a "normal" risk to most participants that is similar to what they expect as a risk with an allotransplant. They felt this risk was generally not a deterrent, and did not consider this a reason not to receive a xenokidney. They also stressed the importance of this risk not holding back xenokidney research and approval.

> *"****To me, this feels like a kind of normal risk****. This feels really similar to the risk that I took on when I got a kidney* [allo]*transplant—it could fail. And, honestly, if you need a surgery to take out dialysis like I* [did], *I may have needed a surgery to get a catheter out, I may have needed a surgery for 1 million other reasons if I was on dialysis. This one kind of just feels like it comes with the territory for me."*

> *"****This one actually feels like the more manageable risk****, because to me, if this was the worst-case scenario,* ***this is a risk I'm willing to take to not be on dialysis****,* [especially] *relative to dying or giving my family a disease, or something like that."*

> *"****That*** **[risk of donor organ rejection or failure]** ***is something in the transplant world you are aware of****."*

> *“It’s even a crapshoot for allotransplants. Who gets sensitized and by what and when is something that none of us even understand. For allotransplants, you can have one transplant and next have a panel reactive antibody (PRA) of 99% and be almost impossible to match or you can still be close to 0%. So,* ***if we don’t predict it or know it for what we do currently, I think we are just in the same place*** **[with xenotransplants]***.”*

> *“If you’re talking in a trial situation, and I’m a patient enrolling in a trial, I’m honestly fine, if the kidney works for a month.* ***I’m honestly fine, if it never works at all, because we won’t move the science forward if we don’t take that risk up front****.”*

> *“****I don’t think that we need to have superiority****, we need to have something somewhere close … to 5% of* [xenokidney transplants] *don’t work. But you have to have the next kidney available the next month.”*

Other patients, however, were more cautious about a potential increased risk of failure or rejection of a xenokidney. Some of these patients were older, and the idea that the only transplant option left to them might fail more quickly than an allotransplant left them feeling more hopeless. Others expressed their reluctance to put their loved ones (or themselves) through the trauma of having to support them through the preparation and recovery of a transplant surgery that might not last for very long.

> *“****It depends on what stage you are at****; so I answered this question ‘somewhat likely,’ because, statistically speaking, I’m in the fourth quarter of my life, and* ***this surgery, it’s so traumatic, I wouldn’t want to do it again and again*** *… At this point in my life, here’s my one shot.”*

> *“****I feel like maybe you get one bite at the apple****. You’ve kind of lived 60 years, statistically speaking, you know your estimated like might be 80 years, so it’s like, okay****, I’ve had my chance, I don’t want to put myself or my loved ones through this kind of trauma again if it does not work****. And so that would go into my thinking. It’s not completely ‘not at all,’ but it’s ‘somewhat likely’ that I would just say ‘Okay.’”*

> *“****I don’t want the cure to be worse than the disease, so to speak****.”*

> *"**I would hate to finally get a transplant, and then, two months later or one month later, it's rejected, or I get an infection, or I pass away**. I think that's one of my concerns: **how healthy is that pig's kidney and would it work for me**?"*

> *"**Getting a kidney to me is improving my quality of life and to live as long as possible**, so I would be a little nervous. **If the pig's kidney would fail or my body rejects it in 2 months, or even a year, I would be really sad and hurt by that**."*

> *"My age* [is a concern]. ***If I have this surgery and it doesn't work, what's left for me?** I'm not on the list where I get another xenotransplantation. That bothers me. I don't know what I would do."*

Some participants also had questions about the science about the transplants, and what information is currently known about potential risks, or what additional measures could be taken to reduce these risks.

> ***"When you talk about rejection*** **[and]** ***not*** **[being]** ***eligible for a human kidney after you do the xenotransplantation,*** **[are the factors that might cause that ineligibility]** ***knowable?"***

> ***"Can*** **[these donor pigs]** ***be genetically modified*** **[to be better matches]*****?** Can't we do this from birth?"*

Discussion C: Considerations for Participating in Kidney Xenotransplantation Clinical Trials

Following the discussion of potential risks of xenokidney transplantation, the audience spoke about their considerations for participating in kidney xenotransplantation clinical trials (Appendix 5.2). During the discussion, many patients voiced their concerns about the potential level of monitoring that might be required after a xenotransplant. When discussing their willingness to participate in clinical trials, many patients voiced their support for clinical studies and expressed their willingness to participate. Others expressed more caution about their own or their loved ones' participation, but all agreed that clinical trials should move forward to find some of the answers about the feasibility and safety of xenokidney transplants. This section included a discussion panel, polling questions, and audience discussion. Noteworthy excerpts from the discussion panelist comments are below. Full testimonies are found in Appendix 4.2.

Discussion C: Discussion Panel, Polling Questions, and Audience Discussion

Carey *(adult kidney transplant recipient)*

> *“**The idea of in-patient monitoring for a month makes me throw up right in my mouth**. I’ve been in in-patient quite a bit. **It’s not fun**.”*

> *“**I would do it for the research. I would do it under the right circumstances**. Right now, I’m fairly healthy, so I wouldn’t go do that today. But, under the right circumstances, I absolutely would put up with pretty much any of that, not only to help me, but to help move* [xenokidney transplantation] *forward.”*

> *“*[For longer than a month of in-patient monitoring]*, we get into burden-benefit questions. **If it’s gonna give me 5 years of healthy life, sure, I’ll stay almost as long as you need me**. If it’s short-term, and I’m ending up spending 2 months in the hospital, and then I have a year?”*

Gregory *(adult kidney transplant recipient)*

> *“If I enrolled* [in a xenokidney transplant clinical trial]*, which could still be a large ‘if’ for me, depends on … **where you are in your lifespan and how you’re doing healthwise, and what do you think your other comparative options are, or other types of transplants, etc**.”*

> *“**I would be willing to stay in for a month. That would probably be the max**. Then, I’d be glad to do daily home monitoring.”*

> *“I think it has more to do with, ‘Are they keeping you in the hospital for observation?’ ‘You’re healthy enough to leave’ versus ‘We’re still concerned.’”*

> *“What’s the protocol for? **Is there a specific cutoff or milestone that you have to reach** to be able to get out of the hospital? I think if I knew what those clearly were, I would have a much more likely chance to say, ‘**Sure, I can stay for daily monitoring for a month … but if I reach these goals, let me out**.’”*

> *“**Is there a maximum amount of time? I think it’s still right along that month**. I think one month is when you start to get mentally—**it starts to affect you more than***

> ***anything*** … [you're bored and] *starting to get antsy and depressed; this is now* ***affecting the overall output and outcomes you're looking at***.*"*

Participating in Clinical Trials

When asked in a Polling Question (Appendix 5.2; Discussion C: Question 1) about the greatest level of monitoring they would be willing to accept (for an extended period of time) as part of the requirements for a clinical trial, respondents were nearly equally split between weekly monitoring (35%) and inpatient or other 24/7 (33%), followed closely by daily monitoring (eg, a few hours a day) (23%). Some patients indicated they would prefer a level of monitoring that is less frequent than those suggested (7%), and 2% indicated they were not interested in enrolling in a phase 1 clinical trial (Appendix 6; Figure 17).

Patients were then invited to select from a panel of factors that would be most likely to influence their decision to participate in a phase 1 clinical trial (Appendix 5.2; Discussion C: Question 2). The most important factor to respondents was urgency/immediacy of the need for a transplant (83%). Respondents also rated increased medications/immunosuppression compared to allotransplant (38%), unknown/potential risks (as per the earlier discussion) (35%), and unknown duration of transplant lifespan (33%) as factors likely to impact their decision to participate. Respondents also indicated that it would be important for themselves/their doctor to have a general understanding about xenotransplantation (20%); other factors (15%) and inability to withdraw from the study due to need for follow-up (13%) were also selected, but in few numbers. Some (8%) respondents also once again indicated their disinterest in participating in a clinical trial (Appendix 6; Figure 18).

Patient Considerations of the Level of Monitoring in Clinical Trials

Two panelists helped to start the discussion about clinical trial monitoring. They, as well as audience members, expressed concerns about having a prolonged stay in the hospital for monitoring, expressing particular concern about impatience and maintaining good mental and general health if they are restricted to a hospital room for too long. Most patients agreed they could tolerate in-patient monitoring for up to a month if they had opportunities for movement and exercise and/or entertainment. All patients who shared their thoughts agreed that longer than a month would be too difficult to bear in most cases. Some patients felt that daily or weekly monitoring would be preferable. One patient suggested remote monitoring should be an option, given the technological advances we have available today.

> *"**It's time we start with a phase 1 trial**. We have to do this, because it takes a long, long time to see the result of this."*

> *"I went with 'daily monitoring,' even if was for hours, (1) **because of mental health of being in the hospital**, but also (2) I know hospitals can be very germy, and so I think not only of myself in the hospital for that amount of time, but then family coming to visit me, especially having small kids showing up there. **What if they were to contract something … because they came to see me in the hospital**?"*

> *"I think it depends on the hospital setting. **If I'm lying in bed and deteriorating—you lose a lot of strength by just lying around—that would disincentivizing**."*

> *"**I'm cool with daily intensive monitoring** … Vitals hourly, please automate it. I can walk around with a line in. Put a Peloton® in there. Give me good streaming TV services. Give me a yoga mat and something to do, and **I'll be happy as a clam to be observed for 3 months. But if I need to be lying in bed and treated like I can't walk—I can't get out of my room because of infection concerns, I have no place to move and I am stuck in bed—that's not gonna go so hot**."*

> *"I chose 'weekly.' I think I would consider daily, [but] **only if there was a way to go outside, get some fresh air, or do exercises, have some entertainment, better food. But not if we're gonna be just in bed and being treated—I don't think I will be able to survive just staying in the hospital bed for a month or even longer than that.**"*

> *"**[Coming] in for, like, a day for a few hours every week—that's something I could do and commit to for a long period of time**. I wouldn't mind doing that if we had the trial for about 3 months, 6 months, coming in once a week for a couple of hours to be monitored."*

> *"**If you have a job or a career to which you are really devoted, it would be hard to do some of this monitoring**."*

> *"With today's technology, as long as your labs are good,* ***you can be monitored at home daily better than you can in the hospital****."*

Influencers of Clinical Trial Participation

The panelists discussed factors that would most affect their decision to participate in a clinical trial. The panelists both shared they would more likely participate if they felt a sense of urgency about their immediate health or need for a transplant, noting they would be less inclined if they were in a good place with their health. They emphasized quality of life as part of their risk-benefit analysis. Patients who expressed interest in a clinical trial emphasized their desire to contribute to the research so that kidney disease patients might have better treatment opportunities. Those who were reluctant suggested potential motivators to alleviate some patient concerns. They also expressed the importance of having a broad range of potential xenokidney transplant recipients—including more than just those ineligible for allotransplant—to be able to get the best data and opportunities for patient voices in the processes.

Gregory *(adult kidney transplant recipient)*

> *"****I'm driven quite a bit by the appeal of quality of life as opposed to just strictly the quantity of life****. So, I put the duration* [of the xenokidney transplant] *fairly high,* ***because I would not necessarily want to go through the same process again****."*
>
> *"****An unknown duration itself is a risk*** *because there's a need then to have a surgery to potentially remove it. And then,* ***being kind of put back in the cycle of another meeting, another transplant. You want to avoid that****."*
>
> *"In terms of attracting me to enrolling … related to the urgency* [of the need for a transplant], *it would be* ***knowing that I could still qualify, at least theoretically, for an allotransplant****, either a living donor preferably, or else a deceased donor."*
>
> *"If I knew that* [by] *going [into a clinical trial] that I couldn't* [get a future allotransplant], ***I think the really biggest driver for me personally would be to say, rather than just dying for no good reason, I could help to advance*** **[xenokidney transplantation research***,* and] *it would be going in with the knowledge or expectation that this is going to be a really*

> *terrible quality of life and I’m just gonna put up with it for ‘X’ amount of time and I’ll look forward to dying …* [to] *moving onto something a little bit more pleasant.”*

Carey *(adult kidney transplant recipient)*

> *“**If my only option was dialysis,** I probably* would [do a xenokidney transplant clinical trial].*”*

> *“**I would see*** **[enrolling in a xenokidney transplant clinical trial]** ***as a bridge**… If I thought this would buy me more time, I would do it for that. No, you totally will not quality* [sic; qualify] *for a kidney … but **let me buy some more time if I can**.”*

> ***“If I don’t have another option, why would I not do something that could help other people, and further*** **[xenokidney transplant research]**, *if it’s my only option.”*

> *“The thing that is a big consideration for me is **quality of life and how long it takes to recover.**”*

> *“If I were in a situation where peritoneal dialysis still worked and I could have a quality of life, I wouldn’t go in* [for a clinical trial]. *But **if I was really sick, which can very much be the case, then, yeah, I would do it**.”*

Audience Discussion

> *“As a scientist, **I would appreciate being a member of a clinical trial for the aspect of extending the science** and my own comfort benefit* [would be] *secondary.”*

> *“My family is just my mom and myself. And, **let’s say my mom is deceased and it’s just me**. Then, definitely, **I would make the decisions to be part of a phase 1 clinical trial…** be part of medical research so that others don’t have to walk down that same road and street.”*

> *“**It is extremely important to pursue this research** to prevent additional loss of life due to lack of acceptable kidneys.”*

As patients considered the risks and benefits of participating in a clinical trial, some patients again suggested different incentives that might make it more appealing or more likely to motivate eligible patients.

> *"Not a guarantee, because you can't guarantee anything in life. But* ***at least an assurance from authorities that there is an option for another transplant as a 'rescue therapy****.'"*

> *"We have this currently for people who are living kidney donors—that because they've donated, they get extra points ... on the waitlist.* ***I think if you're willing to take a risk to further the science, maybe there should be extra points given****, either within the [New Kidney Allocation System], or possibly within other systems that involve living donor kidneys that become available later."*

> *"There's always naturally gonna be a risk that the health will deteriorate, cardiac health, vascular health, the place to implant the kidney might not be there in the future. But I think* **[extra points on the waitlist]** ***should be one consideration****."*

One patient emphasized the importance of opening up eligibility to a wide range of patients with kidney disease to get the largest pool of potential participants possible.

> *"****The trials should be open to a broad population of different backgrounds and in different disease states and in different states of*** **health** [not just patients who are risk takers and/or who are ineligible for allotransplant]*."*

> *"With the proper consent, respecting patient autonomy, and understanding of where they are in life,* **[patients]** ***should have the ability to participate even if another transplant down the road may*** **[not]** ***be a possibility****."*

Two participants noted the importance of considering at what point participation in the clinical should be able to be terminated, and the importance of allowing patients to be a part of that decision-making process, both regarding the health of the donor kidney itself and the health of the patients themselves.

“**[When]** ***do we decide to end this organ by taking it out***? *Do we keep it in and continue to have the patient forced to be taking immunosuppression?* ***There should be some input from the patient***.”

“***At what point do we have a patient where they’re like, ‘I’m done’***? How do [protocols and] *clinicians come to the conclusion that, okay, we’re gonna take everything off?* ***That has to be the patient’s choice***. *And I think that’s something that* ***should be a conversation*** **[with doctors]*****, even prior to going into any of these clinical trials***.”

CONCLUSIONS

This Externally Led Patient-Focused Drug Development (EL-PFDD) Meeting held by the National Kidney Foundation provided the FDA, product developers, clinicians, academic researchers, and the public an opportunity to hear in-depth patient views on the challenges of living with kidney disease, the impact on patients' daily lives, their views on xenotransplantation, concerns about potential risks of the procedure, and concerns about clinical trials and the factors most likely to affect their willingness to receive a xenokidney transplant and/or participate in a xenokidney transplant clinical trial.

Major themes that emerged from patient discussions in the meeting were:

- **Dialysis** has a significant **negative impact on patient quality of life** and many patients would consider a xenokidney transplant or participation in a xenokidney transplant trial to avoid the discomforts and long-term health risks of going on (or back on) dialysis, even if they had questions, fears, or concerns about xenotransplantation.
- The impacts of **kidney disease** are wide and varied but are ultimately all **limiting** to patient daily life and quality of life.
- While patients consider the direct impacts of kidney disease and risks of xenokidney transplantation on their own **quality of life** and livelihoods, disease **treatments**, and potential **risks** of xenokidney transplantation are major factors in how much risk they are willing to accept when considering whether to receive a xenokidney transplant and/or participate in a clinical trial.
- Many patients were open to the idea of xenokidney transplantation after it has been approved, or to participate in later trials, but were **reluctant to participate in initial trials**.
- Patients had many questions about xenokidney transplantation and were eager to have clinical trials get started to **find answers about the potential risks and benefits about the experimental procedure**. They expressed their concerns about the risks of zoonotic disease, risks to their personal health, risks of not being able to receive a future allotransplant, and potential risks to unborn children. For some patients, these concerns were unsurmountable if not addressed; for others, the risks were acceptable if xenokidney transplantation meant a better quality of life.
- Patients were **reluctant** to take more and potentially less tolerable **medications**, and expressed **concerns about potentially lengthy monitoring post-xenotransplant**. They shared fears about the procedure having a more detrimental impact on their quality of life than their disease. However, these **fears were often outweighed by fear of dialysis, and often superseded their reluctance**.

- Overall, despite their concerns, nearly all patients would have accepted the risks if faced with **no alternatives**. Even patients who were not ready would accept a xenokidney transplant--even if all of their concerns had not yet been addressed—if it meant the difference between **reduced quality of life on dialysis**, versus the **freedom with a transplant**, even a xenotransplant.

The FDA expressed sincere thanks and admiration for the patients' courage and willingness to share their experiences and insights at the meeting.

Incorporating Patient Input into a Benefit-Risk Assessment Framework for Kidney Xenotransplantation

In recent years, the FDA has adopted an enhanced approach to benefit-risk assessment in regulatory decision-making for human drugs and biologics to support certain regulatory decisions about NDAs or BLAs, from premarket approval through the postmarket setting.[17] The Benefit-Risk Assessment Framework involves assessing four key benefit-risk dimensions: *Analysis of Condition*, *Current Treatment Options*, *Benefit*, and *Risk and Risk Management*. When completed for a particular product, the Framework provides a succinct summary of each decision factor and explains the FDA's rationale for its regulatory decision.

In the Framework table, the *Analysis of Condition* and *Current Treatment Options* rows summarize both the severity of the condition as well as the nature and impact of the therapies currently available to treat the condition. The assessment provides an important context for drug regulatory decision-making, providing information that can help inform the weighing of specific benefits and risks of a particular medical product under review (the other 2 dimensions of the framework).

The input provided by patients and care partners through the EL-PFDD Meeting on Kidney Xenotransplantation may inform the FDA's understanding of the *Analysis of Condition* and *Current Treatment Options* dimensions for kidney disease.

The information for *Analysis of Condition* and *Current Treatment Options* in the following sample Framework table for xenotransplantation draws from patient contributions at the Voice of the Patient: EL-PFDD Meeting on Kidney Xenotransplantation held on November 9, 2023. This sample Framework table contains the kind of information that may be included in a Framework completed for kidney xenotransplantation.

Dimension Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Kidney disease affects children and adults. • Varied causes of disease, but all negatively affect quality of life.	• Early kidney disease can be managed with diet and medication in some cases, but few management options exist when patients are in later stages of the disease
Current Treatment Options	• Treatments that are available for treating end-stage kidney disease (ESKD) include: - dialysis - kidney allotransplantation • Dialysis negatively affects patient quality of life in both the short- and long-term. • There is a shortage of both living and deceased donor kidneys. - Patients on the waitlist may never receive a kidney. - No standardized living donor guidelines between transplant centers, which can be a barrier to living kidney donation. - End-stage kidney disease (ESKD) patients have no option but dialysis while they wait for a kidney. - Patients who are ineligible for the allotransplant waitlist have no option but dialysis once they reach end-stage kidney disease.	• Patients expressed **willingness** to accept a xenokidney transplant if: - It would improve their quality of life. - It was shown to be safe for them/their families. - It was shown to have some longevity in the patient. - It was shown it would <u>not</u> affect their ability to receive a future allotransplant. - There were more data available to answer their questions/address their concerns. - The risk of zoonotic infection could be definitively reduced or eliminated. • Patients expressed some **concern** about receiving a xenotransplant including: - Fears regarding increased risk of rejection or failure - Fears about zoonotic infection (affecting their family/care partners as well) - Impacts of prolonged inpatient monitoring - Fears regarding potential catastrophic events, leaving them worse off than before the xenotransplant • Patients expressed willingness to participate in a xenokidney transplant **clinical trial** if: - It would provide a bridge between end-stage kidney disease and going on dialysis. - It would advance the science for future kidney disease patients. - It would improve their quality of life. - They were not the first patients to participate in the trial. • Patients hoped for the clinical trial and eventual approval of xenokidney transplantation as a treatment option. Xenotransplantation could improve patient quality of life and address organ shortages.

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APPENDIX 2: RESOURCE MATERIALS

MEETING AGENDA

Agenda | EL-PFDD Meeting on Kidney Xenotransplantation

SLIDE PRESENTATIONS

Slide Presentations (PDF) | EL-PFDD Meeting on Kidney Xenotransplantation

MEETING TRANSCRIPT

Meeting Transcript (PDF) | EL-PFDD Meeting on Kidney Xenotransplantation

MEETING RECORDING

The meeting recording can be viewed on the *Patient-Focused Drug Development Meeting on Kidney Xenotransplantation* page of the National Kidney Foundation website.

APPENDIX 3: DISCUSSION QUESTIONS

Discussion A: Patient Experiences with Kidney Disease: Why Patients May Consider Kidney Xenotransplantation (Expectations and Outcomes)

1. Based on your kidney disease to date and currently available treatment options for you, are you interested in a xenokidney transplant? In other words, if you are interested, tell us about why you think it would be a good option for you (eg, time on waitlist, availability of matched organ, alternative treatments like dialysis).
2. What factors would be important to you in deciding to seek a xenokidney transplant?
    a. Whether or not it functions as well and/or as long as an allotransplant
    b. Whether or not you would be able to get a xenokidney much faster than a human kidney

Discussion B: Patient Considerations of Risk and Other Downsides of Kidney Xenotransplantation

1. For each of the following risks that were discussed in the presentation, what information would you need to know and how likely would they be to impact your decisions to undergo a xenokidney transplant?
    a. Organ rejection
    b. Zoonosis (infection), to both you and your family/friends
    c. Delayed graft function
    d. Incomplete functioning provided by human kidney
    e. Catastrophic failure (e.g., damage to other organ systems, death)
2. If the above issues could be managed but required intensive medical treatment and monitoring, would that impact your decision to undergo a xenokidney transplant?
    a. What if this required hours of daily monitoring and treatment?
3. If having a xenokidney transplant caused issues that made it so you would not be eligible to receive another kidney (xeno or human) in the future, how would this impact your decision to undergo a xenokidney transplant?

Discussion C: Considerations for Participating in Kidney Xenotransplantation Clinical Trials

1. Please provide your thoughts about each of the following aspects of participating in a potential first-in-human, Phase 1 clinical trial:
    a. Design (adaptive, one patient at a time, very small)
    b. Monitoring, biopsies, and other in-patient and additional follow-up, including autonomy/privacy concerns & need to continue/inability to withdrawal
    c. Efforts to keep xenokidney functioning (e.g., managing pain, rejection)
    d. Unknown benefits (how well or how long the organ will function)
    e. Unknown risks (any and all of the previously discussed risks could manifest)

APPENDIX 4: PATIENT PARTICIPANTS AND TESTIMONIES

APPENDIX 4.1: PATIENT PARTICIPANTS

Testimony Panelists

- Brie — Adult transplant recipient [aHUS]
- Sandi — Adult patient, ineligible for transplant waitlist, currently on in-center dialysis
- Ed — Adult patient with a history of failed transplant, current functioning transplant [IgAN]
- Katherine — Adult patient on transplant waitlist (currently on in-center dialysis)
- Wendy — Adult care partner (now adult daughter has lupus nephritis & recurring kidney failure)
- Maria — Adult patient with rare/recurring disease [IgAN]
- Victoria — Adult care partner for pediatric kidney transplant patient

Clinical Trial Discussion Panelists

- Carey — Adult kidney transplant recipient
- Gregory — Adult kidney transplant recipient

APPENDIX 4.2: PATIENT TESTIMONIES

Brie

Adult transplant recipient [aHUS]

Hi! I'm Briana from Birmingham, Alabama, I’m a wife and mother to 3 young children, 2 daughters and a son. I’m the director of marketing for an Alabama-based pharmacy, and in May 2019 I was diagnosed with aHUS, a very rare, genetic disease that causes blood clots to form in your blood vessels, blocking blood flow to the kidney, and I received a kidney transplant in August 2021.

I prayed for many years to be a mother. However, during my 2.5 years on dialysis, I felt less than a mother. 2.5 years is a long time to “miss out” on life moments especially with young children. When I was diagnosed and immediately placed on dialysis, I had a 6-month-old, a 3-year-old, and a 5-year-old. Two years later, when I received my transplant, my kids were then 3, 5, and 7. Those were 2 crucial years, and during that time, I sat in the background while my family created memories without me, such as building sandcastles at the beach or simple neighborhood walks.

During those 2 years, I was forced to wait on an allotransplant due to COVID-19, as well as finding a matching donor. If xenotransplantation had been available, I most likely wouldn’t have spent that time waiting on the transplant list. I could have rejoined my life as a mother much quicker. I would have volunteered to be in the first “xeno” clinical trials; my quality of life had diminished to the point, other than losing my life, no risk would have been too great.

No matter how they spin it, dialysis is not a pleasant option. The years spent only being able to consume 32 ounces of liquid a day, the struggle over which shoes to wear, because you don’t know how badly your ankles will swell, the random throwing up spells, and so on—all of that could have been reduced had xenotransplantation been an option. Everything mentioned, and living that life, would have greatly influenced me to volunteer for xenotransplantation. I would have seen it as a life raft in the tumultuous sea I was living in.

Xenotransplantation could cut down on the months/years patients are waiting on dialysis while the clock ticks by on a kidney, hopefully, to come. You can't live a normal life on dialysis. You can with a transplant, and a xenotransplanted kidney could fill that need.

I have experienced an allotransplant. I’m very well aware of the surgery itself, the posttransplant medication regimen, the follow up appointments, the physical pain and anxiety that come with receiving a human kidney transplant. I would happily go through all that again if it meant I didn’t have to suffer on dialysis and I could get back to living a normal life.

I know a human transplanted kidney lasts an average of 12 years (according to the Cleveland Clinic, a kidney from a living donor lasts about 12 to 20 years, while a kidney from a deceased donor lasts about eight to 12 years.) I stand here today at 40, so most likely I will need another transplant or 2. I would wholeheartedly volunteer for a xenokidney, if it meant my time on dialysis would be cut down. I assume there would be many more follow-up visits, the possibility of added post-transplant medications, and more blood work, even daily monitoring for some time, but I would gladly accept that if it meant I would be able to return to my life as a wife, mother, and friend.

Risks of xenotransplantation, of course there would be risks, I knew them going into my own [allo-] transplant [previously], but as a mother, I would risk everything for the chance to actually be there for my children; honestly, I would. Only 47% of those on dialysis are still alive 5 years out. If I knew my time on dialysis was running out and xeno was an option, I would seize it. The way I see it my only other option would be death.

In the years since my transplant, I’ve taken advantage of my second chance: I’m room mother for my kids’ classes; I’ve blown my work goals out of the water; my husband has his wife back; we’ve taken the family vacations; and I relish in the mundane. I love packing my kids’ lunches; having sleepovers in the den with them; taking them on long walks; and just being an active part of their everyday lives. THIS—THIS type of bonding with my kids is what xenotransplant could provide if I need another transplant!!!

The heartbreak I felt while waiting on dialysis for a transplant was almost unbearable. 2.5 years—that was 2 Christmases I missed out on playing Santa in the middle of the night because my cord wouldn’t stretch that far; 2 Easters I couldn't play the bunny; not to mention I couldn’t be the one to collect the lost teeth; and I couldn't be the one to run to my child as they cried in their beds or their crib. As a mother, that goes against your natural instincts. For those reasons, I would accept the risks, of failure, pain, sickness, and whatever else xenotransplantation could throw at me. I am a mother—that is my God-given blessing, and I wouldn’t let ANYTHING stand in my way.

Sandi

Adult patient, ineligible for transplant waitlist, currently on in-center dialysis

Good morning/afternoon. My name is Sandi. I live in the nation's capital—the District of Columbia—and I'm a native Washingtonian. I retired from the federal government in 1996 after 30 years of service. I suffered from kidney disease for many years before being diagnosed with end-stage kidney disease in 2019. I have been a hemodialysis patient on Monday, Wednesday, and Friday at 3.5 hours for 4 years. I was told by three different hospitals that I was not a viable candidate for the kidney transplant donor list for several reasons:

- my age
- my ethnicity
- my blood type (O+)
- my health challenges, such as diabetes and high blood pressure

Since I am not a viable candidate for the kidney transplant donor list, I must depend on a living donor. I don't have one as yet, so I am open to other options. Xenotransplantation is not something I have heard of until now. If the procedure is approved—and is successful—it could save the lives of many people who would not otherwise receive a kidney transplant—like me.

My major concern at this time would be rejection of the foreign object by my body. I need to know the percentage rate for rejection before agreeing to participate. If the rejection percentage is too high, I don't think I would be willing to take that chance—especially at my age. If I am told that X, Y, and Z would be done to decrease rejection—and if it lowered the percentage rate—then I would reconsider. If the rejection rate is "minimal," I need specific information on the meaning of "minimal." If studies are done that prove the rejection rate is the same as human kidney transplant, then I would definitely participate in the program. You may ask, "What rejection percentage is acceptable for me?" To be honest, I don't know at this time. I would need to compare the acceptance/rejection percentage statistics before making a final decision.

I am looking at things from a different perspective. I am 78 years old. Because of my age, I don't know how much time I have left. I want to live a full, productive, and useful life with the time I have left. I won't go out willy-nilly to accept something with a high failure rate, "just because." I am also concerned about the time it will take for the necessary studies to be completed before the first xenotransplantation would even begin.

At my age, I am unsure if this would even be an option for me. However, I would accept an approved kidney xenotransplantation if I needed another kidney to live because there was no other alternative and was assured that it would effectively replace my kidney function.

Another major concern regards the infection risks—specifically zoonosis—for the patient, and for those around them. Xenotransplantation would not be an option for me if nothing was done about this problem. However, I understand that [if] pigs can be screened and quarantined, [this could reduce] the infection risks to nearly 0%. If this proves to be true, then I would accept xenotransplantation with 0% infection risk.

Since I have end-stage renal disease, I don't know how long dialysis will work for me. I do know that dialysis is what is keeping me alive. At my age, my chances of receiving a kidney donation of any kind are slim. I would consider it if dialysis was no longer working for me, and I had absolutely no other options.

Medication is another concern. Are the medications the same as those for a human kidney transplant? I've been told there are many. I've also been told that the medications are harsh. What does "harsh" mean? I will need to make a comparison of the medications to determine whether this would be an option for me. Thank you for your time and interest!

Ed

Adult patient with a history of failed transplant, current functioning transplant [IgAN]

Good afternoon. My name is Ed. In 1986 while stationed at Howard Air Force base in Panama, I was diagnosed with IGA nephropathy. I was told that I would need dialysis and eventually need a kidney transplant. I was medically retired, and months later started hemodialysis. At that time, I was 23 years old, married and had 2 small children. After nearly 6 years of serving my country, my lifelong dream of having a career in the Air Force was over and the courses of my life and the lives of my wife and children were dramatically changed.

Today, at 60 years old, I am married and have 5 adult children, 4 grandchildren and 2 Yorkie pups that keep my life full. I have had a full and blessed life and I want more.

After 1 year on hemodialysis, I received a kidney transplant which lasted 34 years. When it failed, I went on peritoneal dialysis. Nearly 3 years later I had my second transplant in May of this year. I am doing well now and remain grateful for another chance at embracing life.

Dialysis saved my life. It also negatively impacted the quality of my life. I felt a sense of hopelessness and doom. I was surviving on dialysis, not thriving. I longed for the freedom from dialysis AND to spend quality time with family and friends, go to work or go to school, or travel the world.

Waiting for my kidney transplants was terrible. The uncertainty of not knowing when I would get a kidney or even if I could survive the years-long wait was extremely taxing on the body, mind, and spirit. My marriages suffered (I was divorced twice). My careers were derailed, and my family's dreams were crushed.

I mention all of this because reducing or eliminating the wait for a human kidney, with all the associated trauma of that wait, would have driven me to strongly consider entering a trial for kidney xenotransplantation.

Nevertheless, I have fears about xenotransplantation; they are based on not fully understanding the evidence that it will be safe and effective for humans. Some of these risks are **acceptable** to me:

- Animal to human transplantation unknowns, including infections or potential diseases or unanticipated viruses that could emerge in the future. This is the biggest fear I have about xenotransplantation, but it would not deter me.

- Acute or chronic rejection possibilities. Similar to human kidney transplants, I know these risks exist
- Infections that directly impact only me
- Different or new immunosuppressant medications and potential negative side effects
- Mental health impacts, like depression and anxiety post-transplant

And some risks that are **unacceptable**:

- Threat of porcine or other infections to my loved ones. I am around family members with immunocompromised health and I would not want to jeopardize their health.
- if xenotransplantation required extensive, long-term monitoring that would prohibit living a full quality life; it would be a deal-breaker for me.

Knowing that there are many unknowns to consider and when my life is literally on the line, I also worry that I would be more willing to take risks in order to sustain my life without fully thinking through the long-term implications of xenotransplantation.

Yet, these fears seem almost irrelevant when given the chance to avoid or minimize dialysis treatments and the harsh life I described previously.

Reflecting back on my dialysis experiences, if the opportunity was available back then to be a part of xenotransplantation trials, I most certainly would have moved beyond the fears, with medical guidance, and had the transplant in the hopes of getting my life back.

Finally, as a Latino, it would be important to know that my race and ethnicity was included in preparation for xenotransplantation. Thank you for your time and for hearing my story.

Katherine

Adult patient on transplant waitlist (currently on in-center dialysis)

Only the creator knows when my life will end and, in the past, I took life for granted. However, when I was diagnosed with end-stage renal disease, I began to cherish each day I am graced with. My name is Katherine.

I live in Jacksonville, FL, with my husband, and I have grandchildren living in Atlanta, GA, and Cleveland, OH. In 2021, I was diagnosed with end-stage renal disease and put on the transplant waitlist that same year. I spend three and a half hours on hemodialysis, Tuesday, Thursday, and Saturday. I was on peritoneal dialysis for 6 months, but after an additional 3 surgeries I had to stop because my body rejected the catheters.

The time spent on hemodialysis is difficult mentally, physically and it is time consuming. Being on the waitlist is another burden because I am on the inactive transplant waitlist until I can transition over to the active list and I fear that I may not live long enough to see all my grandchildren grow up, as the youngest is now 4 months old.

Side effects of medications I take, my dialysis treatments, and the emotional effects of my kidney disease are depleting and compromising my quality of life. While the transplant list fills me with hope, having the option[s] of [both] a human or xenotransplant is even better.

Any new treatment or medication has risks and side effects, but when I think of the alternative without treatments, I would rather take the risk. The shortage of kidneys for transplant, time on the waitlist, time on dialysis, and hope to extend my life to be with my family are the reasons why I have no fear of xenotransplantation.

When I consider the risks of xenotransplantation, I think of the potential benefits, such as increased freedom in my life, less pain and less of the numerous medications I take. When I think of it this way, I am willing to endure a xenokidney that would last for even a few years to allow me time off dialysis.

However, some of the risks I would be more concerned about are if the kidney fails or needs additional surgery to remove it, life-threatening infections, extreme pain, and if I was worse off than if I did not endure a xenotransplant.

I believe we need to define what a “successful xenotransplant” is and that definition needs to involve the patients. What defines a “successful xenotransplant”? I think the definition should include answers to questions like: How long will the pig kidney last? Will there be side-effects and/or increased immunosuppressive medications? Will these side effects be more tolerable than the effects of kidney disease and dialysis? In my view at least one year free from dialysis, minimal pain and sickness, would be a successful definition and beneficial result for a xenotransplant.

My hope for a xenotransplant is stronger than my fear of the risks. My future is unknown. Will I receive a human kidney? Will I be on dialysis for the rest of my life? Will treatment like xenotransplantation become available? Or if I will live long enough and stay healthy enough, I do not know. I am living on borrowed time, however whatever time I have left I want to spend it with my spouse, grandchildren and rebuilding relationships with my daughter and sister.

If xenotransplantation is that opportunity, I do not want fear to stand in my way. I understand and accept no one is promised tomorrow, but when you have a condition where the only options for staying alive are dialysis or transplant, I want the transplant (whether it be human or pig).

Science and medicine keep me alive physically, but my strong faith in God and accepting his grace and mercy keep me hopeful to be able to leave a legacy for my grandchildren to remember that I did not give up and I was willing to take one of the biggest risks of my life. When I think about it from a grandmother’s perspective, I would join the first clinical trial to help advance science for future generations. When I think of my grandchildren, if they are ever confronted with kidney failure, I want them to know their grandmother offered her life to improve the number of treatment options to extend their lives with xenotransplantation.

Thank you for your time and the chance to express my opinion.

Wendy

Adult care partner [now adult daughter has lupus nephritis and recurring kidney failure]

Hello. My name is Wendy. I am 50 years old, and I live with my husband and 23-year-old daughter in Hemingway, South Carolina. I am the caregiver to my daughter. In 2012, at age 12, she was diagnosed with systemic lupus erythematosus (SLE) lupus nephritis WHO (World Health Organization) class III which has progressed and is now class V. The highest class is class VI. Last year she went into renal failure and began dialysis.

While on dialysis, she endured multiple procedures for access that kept clotting and ended with a failed graft and fistula. It was found her lupus was the cause of the failed dialysis access points and [she] was only able to receive her treatments through a temporary tunnel catheter, which led to two bacterial infections and sepsis.

A few months ago, her kidneys began functioning around 30% and she is now off dialysis and the transplant list. Samantha's health journey has been traumatic for her to experience, and as her mother, it has been excruciating to watch. Her nephrologist expects her kidney function to decline again and plans to place her back on the transplant list once her renal function falls to 20% to avoid going back on dialysis.

I think xenotransplantation would be a good match for my daughter and I would encourage her to enter a clinical trial because I've seen the effects dialysis has had on her quality of life. She doesn't want to live the rest of her life on dialysis or waiting for an allotransplant which may never happen.

My daughter and I fully understand there are risks with any transplant, such as organ rejection or side effects from immunosuppressants. We are as prepared as we can be to deal with organ rejection. As for side effects, I have talked with the allotransplant team about medications used post-transplant. They are medications she has taken previously to treat her lupus, so I am already familiar with potential side effects.

What worries me is the unknown risks with xenotransplant. Throughout my daughter's life, I have researched everything I could about her disease so that I could better understand each phase of treatment she has undergone, and the risks involved. With xenotransplantation, there isn't much public information available for me to research with due diligence.

However, my daughter has a lifelong condition, and our future is full of unknowns. Without xenotransplant[-ation], I don't know if my daughter will have a future that allows her the freedom of living that most of us take for granted. If xenotransplantation achieves FDA approval, I believe it will make these dreams a reality for my daughter because she will have an option to receive a functioning kidney without prolonged wait times or chronic dialysis. Even the possibility that she may be monitored several hours daily is not a deal-breaker, as she has already been hooked to a machine for several hours during chemo and dialysis.

I would like to share with you a conversation I had with Samantha [daughter] recently after explaining xenotransplantation and its known risks. I asked if she'd be willing to enter a Phase 1 trial if she were selected as a candidate. Her response: "I'm not going to lie. I'm nervous about zoonotic infection because I could make others sick if I get it, but if they have safety precautions and I'm able to enjoy living again, it's worth it and I would be willing to participate in a Phase 1 trial. Being hooked up to a machine multiple times per week for hours with no end in sight isn't living, and I want to live."

In conclusion, I can tell you as a mother and caregiver, although she is not currently on dialysis or the transplant list, I would support and encourage Samantha to be one of the first trial participants, if she is an appropriate candidate and as you just heard, she agrees. I do not want to watch her deteriorate on a machine again. I am certain she would be closely monitored and receive the best of care while undergoing clinical trials. For us, the benefits and the hope of living a full life once more outweigh the risks and dread of watching Samantha live hooked up to a machine and simply existing.

Maria

Adult patient with rare/recurring disease [IgAN]

Hi, I'm Maria. I live in Midlothian Illinois, which is a suburb of Chicago. In 2019, I sought care after a year of suffering with swollen feet and blaming menopause. A primary care doctor noticed several irregularities in my lab work. But it wasn't until 18 months later that I was referred to a nephrologist, biopsied and diagnosed with IgAN [immunoglobulin A nephropathy]—a rare kidney disease that has irreversibly damaged the filtering function of my kidneys. I undertook a grueling regimen of high dose prednisone in 2021 but have not been able to leave stage 4, with my kidneys functioning at less than 30%. I have not done dialysis yet, but the need could arise at any time. Any infection I contract could kick off an autoimmune response that could damage my kidneys further and push me into end-stage renal failure—where the only options available today remain dialysis or transplant.

Talking to you today about xenokidney transplantation is important to me because, with my condition, even after receiving a living donor kidney, the IgAN would still exist within me and could damage that kidney as well. I don't have firsthand experience with either of the treatment options, and I hope to put those decisions off for a long time. But neither of those options would end my battle with IgAN. The two available options come with their own set[s] of issues, concerns and inconveniences that may keep me alive, but perhaps not really living.

There are numerous risks associated with xenotransplantation, known and unknown, and if you asked me today to participate in the first human clinical trial, I'd simply say "no." I am sick. My blood carries 70% more toxicity than most people. I am sluggish and foggy much of the time. But participating in the first human clinical trial would come with way too many risks for someone who has not yet reached that decision-making point.

The risk of a serious porcine disease being contracted by me, or passed on to anyone close to me, is simply not something my family or I would take on today.

Today even in my diminished health, my husband and I enjoy family dinners, game nights and other get-togethers with our adult children. We both come from sizable Greek and Irish families that we entertain A LOT. Each year my siblings and our families spend vacation time with my aging parents. We also have a large array of friends—my five best girlfriends have been by my side for 45 years—we've shared everything together. These are the things I live for and that I love doing, and being among the first to undertake a xenokidney transplant would most likely render that life extinct.

Even if death or disease were not risks, the close monitoring, severe medication, loss of privacy and other demands of 'being first', would take away too much of the life I am still able to enjoy with my loved ones.

If you asked me again in a few years, and my health had declined to the point that I was eligible and seeking a living donor transplant, and the xeno trials had entered a later phase, the answer would be "maybe." I would want to know if any IgAN patients had participated in the earlier phases of the trials. I would want to know more about the particular experiences of any patients with rare kidney diseases, and understand those unique data points. But I think I would be most interested in knowing if the disease had resurfaced in the xenokidney or not. If there was evidence that a xenokidney transplant did not pose a significantly higher risk of death, infection or rejection than an allotransplant AND could provide a kidney that would not be damaged by IgAN, I could definitely see us saying "yes."

However, if there are no IgAN or similar rare kidney disease patients being assessed in the early trial phases, I am not sure what we'd say to participating in a later trial.

I would probably ask a lot of questions of the doctors and expect them to provide data from the trials that was critiqued against my condition. It would then depend on my personal situation, meaning—if I did or didn't have a match for an allotransplant, and how much of my busy and full life was already fading away with age and disease.

The truth is, when I need to make the choice, I will choose transplant over dialysis. Period.

If I had no living donor match and the waiting was requiring me to do dialysis. My life would probably no longer feel like my own. I would feel like a burden to my husband, my aging parents, my adult children and my friends, and I believe we would all say "yes" for joining a clinical trial for a xenotransplant. That being said, I would want my participation to specifically collect any data points that could be used to help IgAN and similar rare kidney disease research move forward in any way possible.

Thank you.

Victoria

Adult care partner for pediatric kidney transplant patient

Hello, my name is Victoria, I live in Howard County, Maryland. Friday, April 5th, 2019, [is] the day my son[’s life] and our family’s lives, changed forever. Prior to that dreadful day, my 12-year-old was the epitome of health—a travel soccer and baseball player, avid mountain biker, skier, and a great student. I couldn’t have imagined flu-like symptoms leading to debilitating dizziness sending us to the ER, was life-threatening low hemoglobin. The cause: acute renal failure.

On that April day in our local ER, we learned he had less than 10% kidney function. Due to the complexity of his case, he was transferred to [Johns] Hopkins, where he endured a series of invasive tests and procedures. This visit, the first of many, ended 37 days later, when we were told he would never regain kidney function and would need a transplant.

The next 13 months were an emotional and tumultuous time for my son and our family. We were so thankful he was alive, but the dialysis he had to endure [peritoneal dialysis] was torture: 9-10 hours per night, his tiny body filled with 1500 ccs of fluid—that’s 50 ounces—filling, dwelling, draining up to 6 times while he “slept.”

In the morning, the last cycle left 1300 ccs of fluid in his body to collect toxins until evening, when he would endure the cycles all over again. He’d often say he felt like a human water balloon—this [was] the primary reason that prevented him from enjoying 6th grade with his peers.

Our family was, and is, traumatized by the journey [my son] has endured. As a mother and primary caregiver, I felt helpless I couldn’t fix this for him. He lost a vital part of his childhood to his kidney failure. But thankfully, after 13 months, he received a deceased donor kidney.

Being so young, who knows how long his current kidney will last? If it fails, I hope he gets priority on the living donor list from my non-directed kidney donation and our National Kidney Registry Voucher. But, what if that second kidney fails soon after? I worry one, two, or even three transplants later—will he be out of options? If faced with the threat of dialysis while waiting for another kidney, we would have to consider the alternatives. In this case, we would consult the xeno research and our transplant team, including xenotransplant surgeons.

My son and our family experienced lasting trauma from his kidney failure and he suffered multiple complications from dialysis, but if a human kidney is not available for a future transplant, we will have to choose between dialysis or experimental procedures like xenotransplantation. We would want to know if a xenotransplant would be a more stable solution and present less complications over dialysis. I don't want to see my son suffer on dialysis or have to endure complications like high blood pressure, seizures, and constant fear of infection.

As a mother, I want my son to live a long and healthy life, so in the early trials, I would hesitate to sign him up as one of the first patients. We cannot know if xenotransplant will lead to a better quality of life until we learn more about it.

With xenotransplant, what scares me most is the possibility of his other organs failing, leading to death. Another worry is [that], after xenotransplant, he would be in much worse physical state and be subject to more intensive daily testing. And lastly, if he received a xenotransplant and it failed, would his body reject a human kidney if one became available? As things stand now, if these proved true, I think xenotransplantation would have to be a last option.

However, if we were faced with needing a kidney while [my son] is still under 18, and none was available, I would strongly consider alternatives like xenotransplantation. A xenokidney would offer a timely solution to years on dialysis, allow him to be free of fear of complications and restrictions, and he could get on with living his life!

If xenotransplantation becomes more predictable and successful in human trials, it seems like a very good alternative for [my son] for these reasons:

- My son was blessed to receive a deceased 19-year-old's kidney, but someone had to die for him to receive it—that comes with conflicting feelings of gratitude and guilt.
- Xenotransplantation would help ensure my son would have a transplant when he is in need; that alone seems a good reason to try.
- Xenotransplantation makes tremendous sense—filling the gap between the number of deceased and living donors. I never want my son to be one of those waiting—and dying—on the transplant list.

I hope the first trials begin and are successful, so he, and all those in need, can get a kidney when deemed necessary. I just don't think I am ready now to enter my son in one of those early trials.

I look forward to a world where my son has a future that doesn't include the impending threat of kidney failure to hold him back. Thank you for your time and consideration.

APPENDIX 5: MEETING POLLING QUESTIONS

APPENDIX 5.1: DEMOGRAPHIC POLLING QUESTIONS

1. I am currently (or in the past):
    a. An individual who has experienced kidney disease
    b. Care partner of someone who has experienced kidney disease
    c. Both a patient and a care partner

2. Where do you or your loved one live?
    a. U.S. East Coast (Eastern time zone)
    b. U.S. Midwest (Central time zone)
    c. U.S. West (Mountain time zone)
    d. U.S. West Coast (Pacific, Alaskan, Hawaii time zones)
    e. Canada
    f. Mexico, Caribbean Islands
    g. Outside of North America (Europe, South America, etc.)

3. What is your or your loved one's age (years)?
    a. Birth to 1
    b. 2-12
    c. 13-17
    d. 18-29
    e. 30-39
    f. 40-49
    g. 50-59
    h. 60-69
    i. 70-79
    j. 80 or greater

4. How would you describe your or your loved one's race or ethnicity?
    a. American Indian or Alaska Native
    b. Asian American
    c. Black or African American
    d. Hispanic or Latino
    e. Native Hawaiian or Other Pacific Islander
    f. White or Caucasian
    g. Other
    h. I prefer not to answer.

5. What is your or your loved one's gender?
    a. Female
    b. Male
    c. Nonbinary
    d. Prefer not to answer.

6. What is the cause of your kidney condition?
    a. Acute kidney injury (AKI)
    b. aHUS (atypical hemolytic uremic syndrome)

    c. Alport syndrome
    d. C3G/membranoproliferative glomerulonephritis (MPGN)
    e. Diabetic and/or hypertensive kidney disease
    f. Fabry disease
    g. FSGS (focal segmental glomerular sclerosis)
    h. IgA nephropathy (IgAN)
    i. Lupus nephritis
    j. Membranous nephropathy (MN)
    k. Polycystic kidney disease (PKD)
    l. Other or unknown/unsure

APPENDIX 5.2: DISCUSSION POLLING QUESTIONS

Discussion A. Patient Experiences with Kidney Disease: Why Patients May Consider Kidney Xenotransplantation (Expectations and Outcomes)

1. What is your or your loved one's current level of kidney function (stage of disease)?
    a. eGFR = 90 or above (CKD stage 1)
    b. eGFR = 60-89 (CKD stage 2)
    c. eGFR = 30-59 (CKD stage 3)
    d. eGFR = 15-29 (CKD stage 4)
    e. eGFR = less than 15 (CKD stage 5)
    f. I don't know.
    g. The patient is deceased.

2. Which best describes your or your loved one's experience?
    a. Functioning native kidney (not on dialysis or transplant waitlist)
    b. End-stage disease with native kidney (on dialysis and/or transplant waitlist)
    c. Functioning transplant (not on dialysis or transplant waitlist)
    d. End-stage disease with transplanted kidney (on dialysis and/or transplant waitlist)

3. If you have ever been or are currently on dialysis, how long are/were you on it?
    a. Less than 6 months
    b. 7-11 months
    c. 1-5 years
    d. 6-10 years
    e. 11-15 years
    f. 16-20 years
    g. Greater than 20 years

4. If you have ever been on the transplant waiting list, how long have you been/were you on it?
    a. Less than 6 months
    b. 7-11 months
    c. 1-5 years
    d. 6-10 years
    e. 11-15 years
    f. 16-20 years
    g. Greater than 20 years

5. What motivates you the most to consider a xenokidney transplant (now or in the future)? Select top 3.
    a. Avoiding/shortening time on dialysis
    b. Avoiding/shortening time on the transplant waitlist
    c. You are ineligible for allotransplant/waitlist
    d. No matched living donor and concerned with matching on waitlist
    e. Concern you may lose eligibility for any transplant in the future (e.g., declining health)
    f. Your age, including the number of future transplants you may need
    g. Improving quality of life
    h. Interest in helping advance science/treatments
    i. Other
    j. N/A; I am not interested in a xenokidney transplant.

Discussion B. Patient Considerations of Risk and Other Downsides of Kidney Xenotransplantation

1. How likely would you be to undergo a xenotransplant if there was a risk of a catastrophic event (e.g., severe organ damage, life-threatening event)?
    a. Not at all (due to the risk of a catastrophic event)
    b. Somewhat likely
    c. Moderately likely
    d. Very likely
    e. Unsure
    f. N/A; I am not interested in a xenokidney transplant [regardless of the risks presented.]

2. How likely would you be to undergo a xenotransplant if there was a risk you would not be eligible for the allotransplant waitlist in the future?
    a. Not at all (due to the risk of ineligibility for the allotransplant waitlist in the future)
    b. Somewhat likely
    c. Moderately likely
    d. Very likely
    e. Unsure
    f. N/A; I am not interested in a xenokidney transplant [regardless of the risks presented.]

3. How likely would you be to undergo a xenotransplant if there was a risk of a zoonotic infection that could be transmitted to friends/family?
    a. Not at all (due to the risk of zoonotic infection)
    b. Somewhat likely
    c. Moderately likely
    d. Very likely
    e. Unsure
    f. N/A; I am not interested in a xenokidney transplant [regardless of the risks presented.]

4. How likely would you be to undergo a xenotransplant if there was an increased risk of a failure or rejection of the kidney requiring a surgery to remove it?
    a. Not at all (due to the increased risk of rejection requiring surgery to remove it)
    b. Somewhat likely

    c. Moderately likely
    d. Very likely
    e. Unsure
    f. N/A; I am not interested in a xenokidney transplant [regardless of the risks presented.]

5. Overall, considering these potential risks, how interested would you be in receiving a xenokidney now or in the future?
    a. Not at all
    b. Somewhat likely
    c. Moderately likely
    d. Very likely
    e. Unsure
    f. N/A; I am not interested for other reasons [not related to the risks discussed]

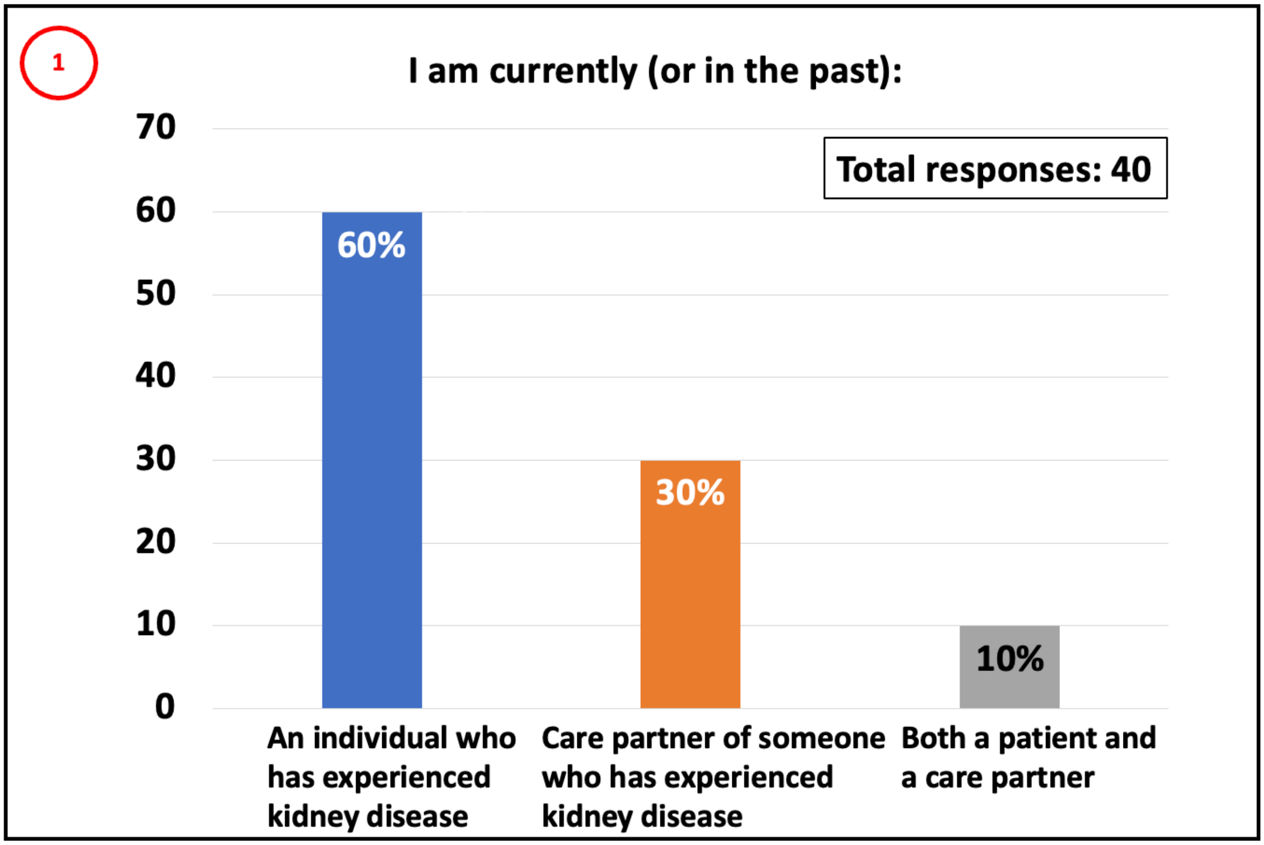
Discussion C. Considerations for Participating in Kidney Xenotransplantation Clinical Trials

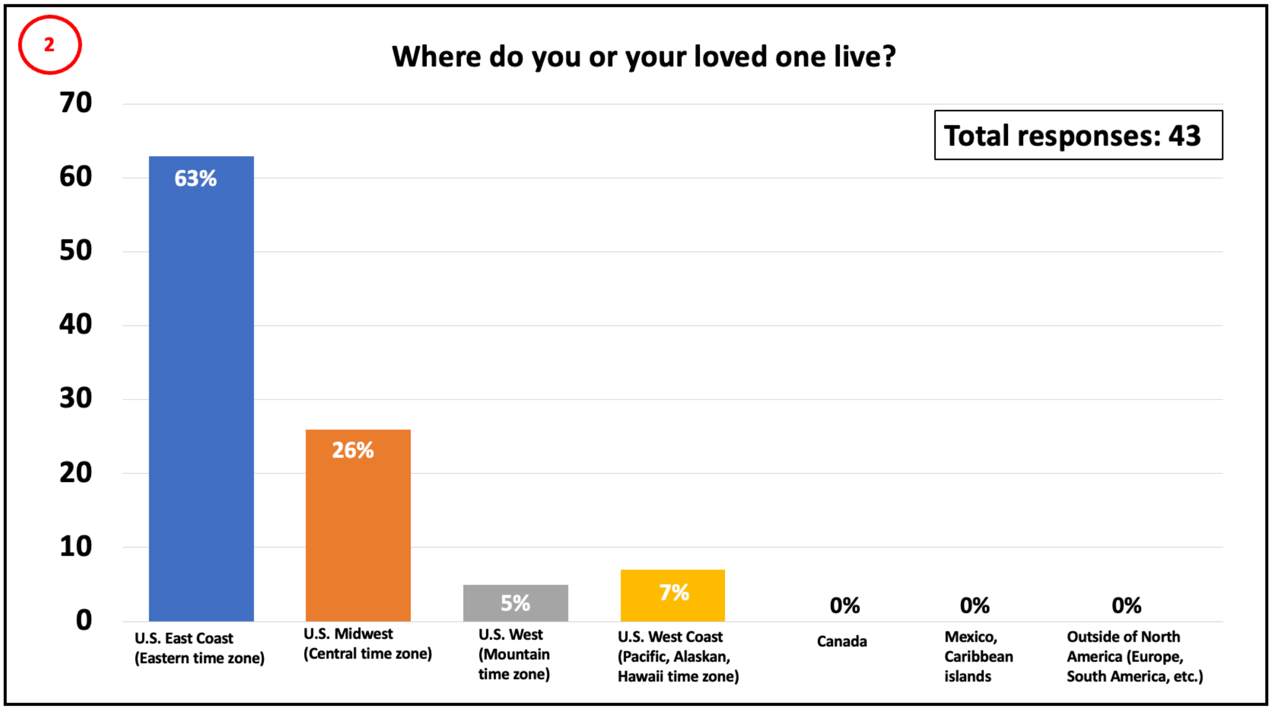
1. What is the greatest level of monitoring you would be willing to accept (for an extended period of time)?
    a. Inpatient or other (24/7)
    b. Daily monitoring (e.g., a few hours a day)
    c. Weekly monitoring
    d. Something less frequent
    e. N/A; I am not interested in enrolling in a phase 1 clinical trial.

2. Which other factors would be most likely to influence your decision to participate in a phase 1 clinical trial? Select all that apply.
    a. Urgency/immediacy of the need for a transplant
    b. Increased medications/immunosuppression compared to allotransplant
    c. Inability to withdraw from the study due to need for follow-up
    d. Unknown duration of transplant lifespan
    e. Unknown/potential risks (discussed earlier)
    f. Your and your doctor's general understanding about xenotransplantation
    g. Other
    h. N/A; I am not interested in enrolling in a phase 1 clinical trial.

APPENDIX 6: RESULTS FROM POLLING QUESTIONS

Demographics of attendees





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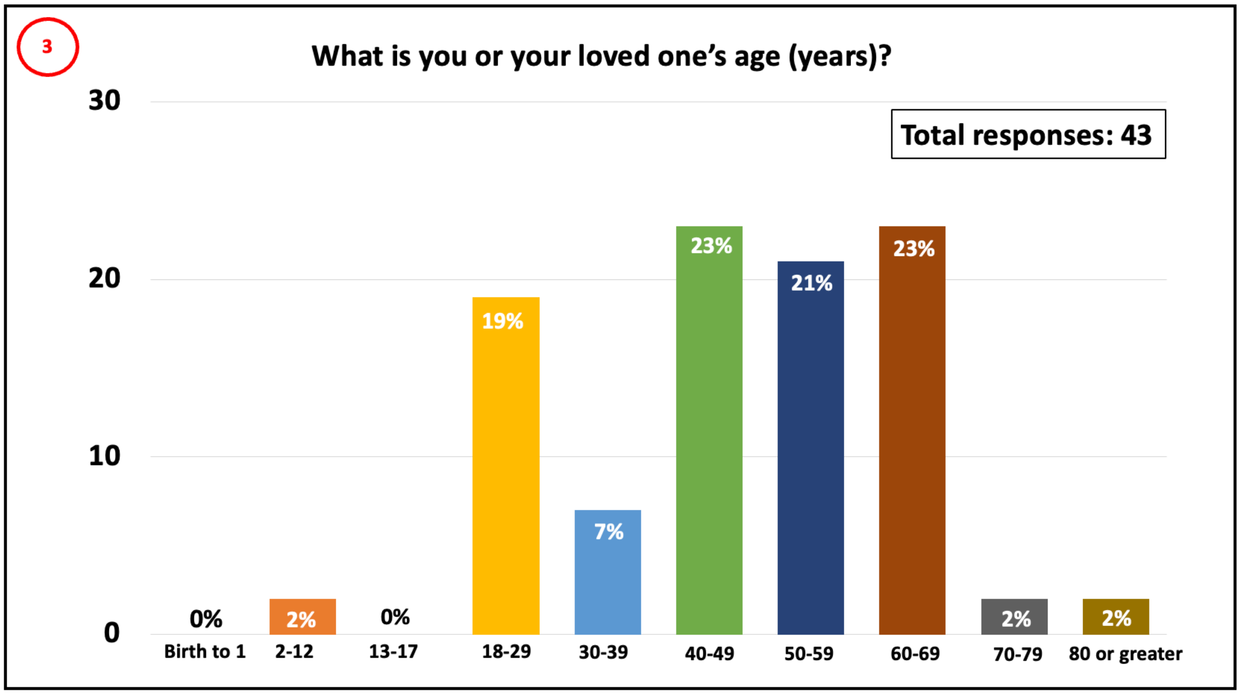

What is you or your loved one’s age (years)?

Total responses: 43

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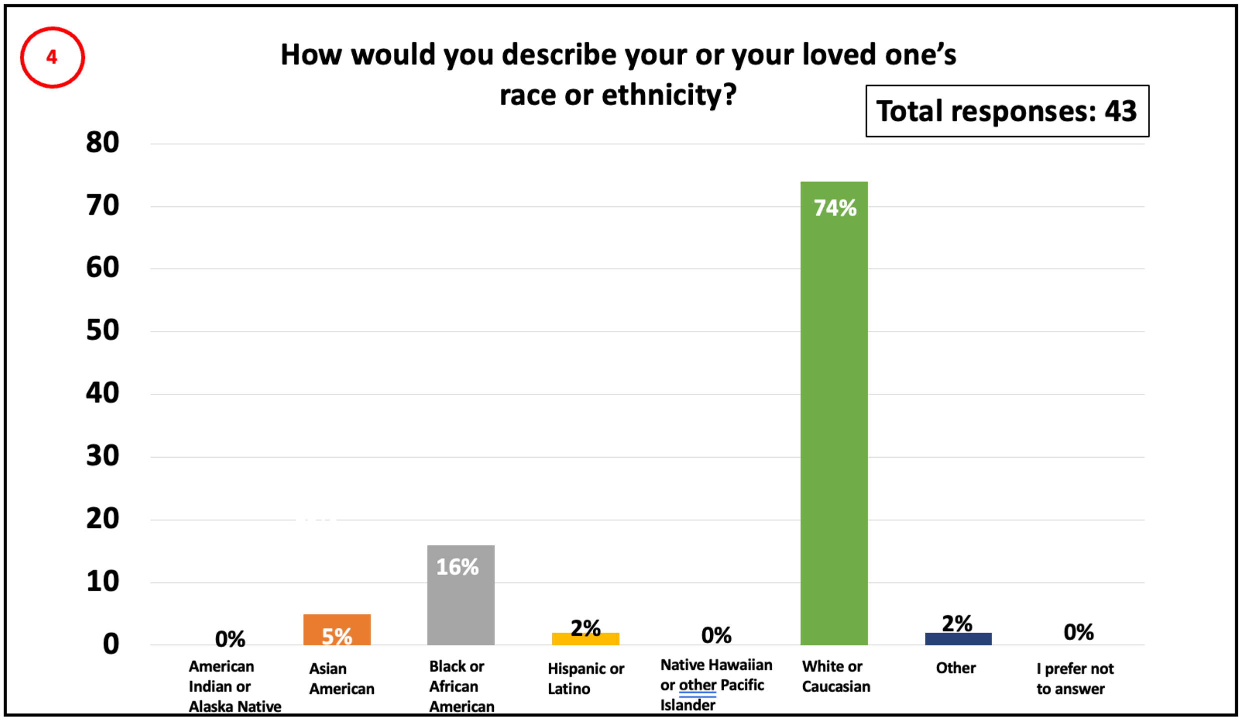
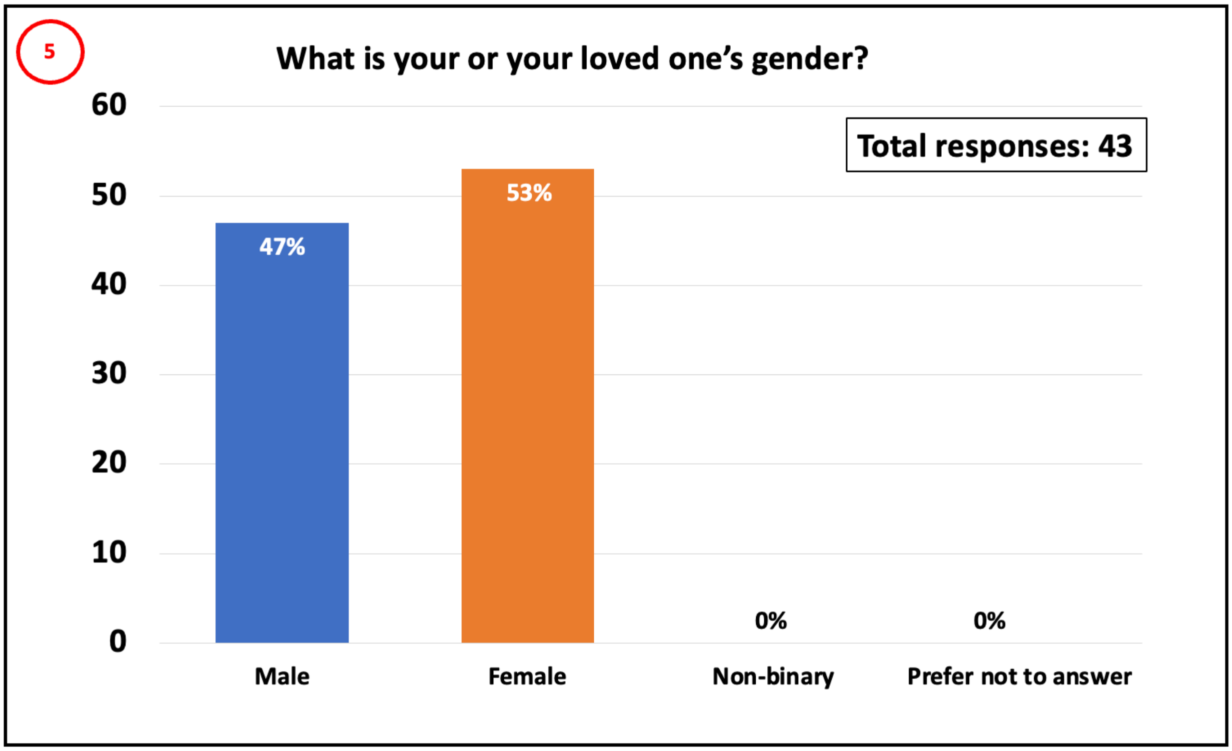


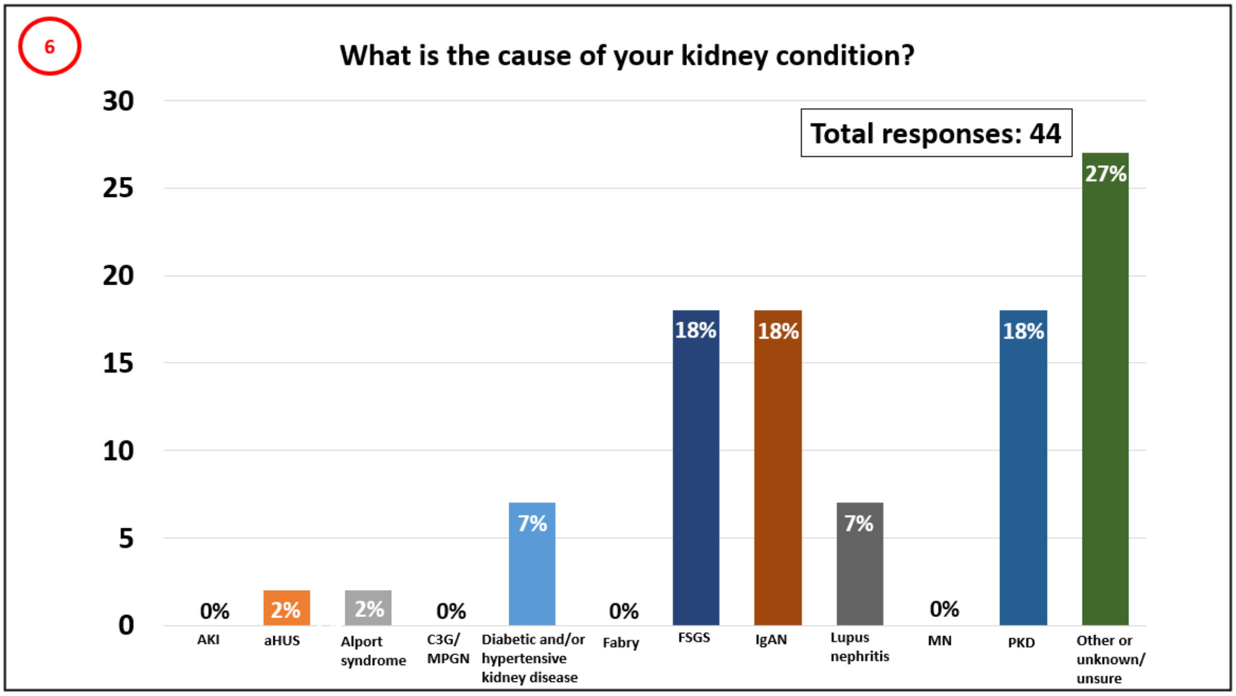
How would you describe your or your loved one’s race or ethnicity?

Total responses: 43



⑤ What is your or your loved one's gender?

Total responses: 43

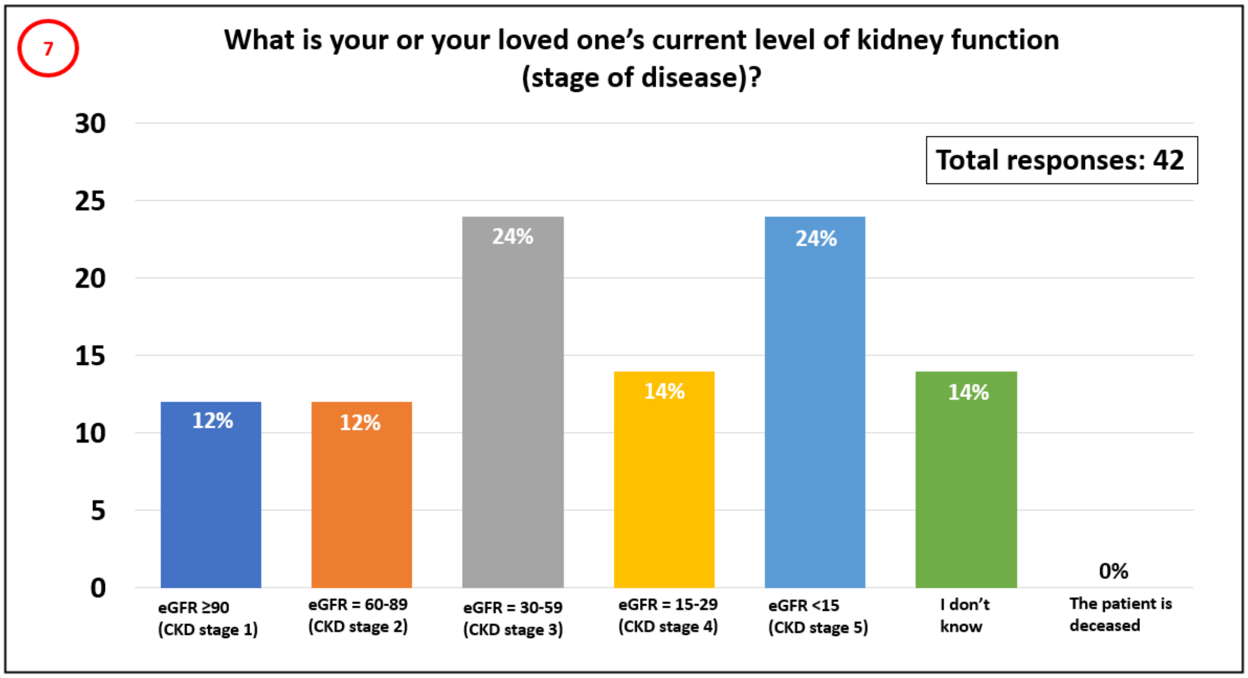


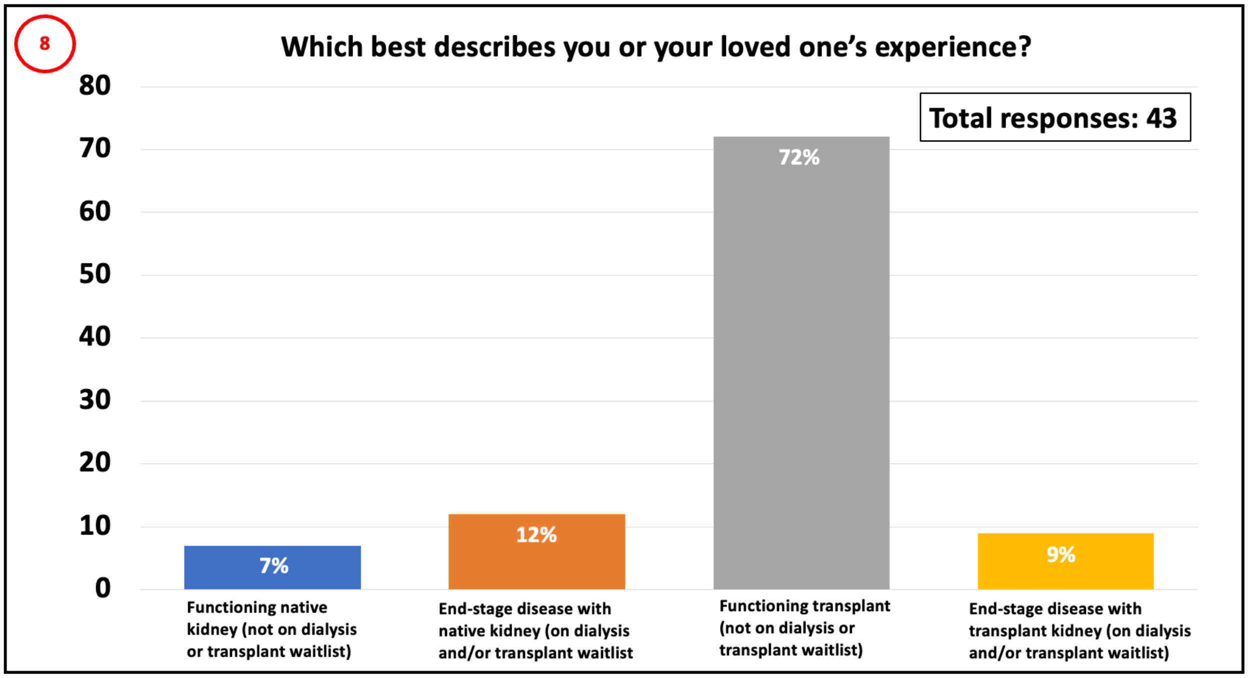
⑥ What is the cause of your kidney condition?

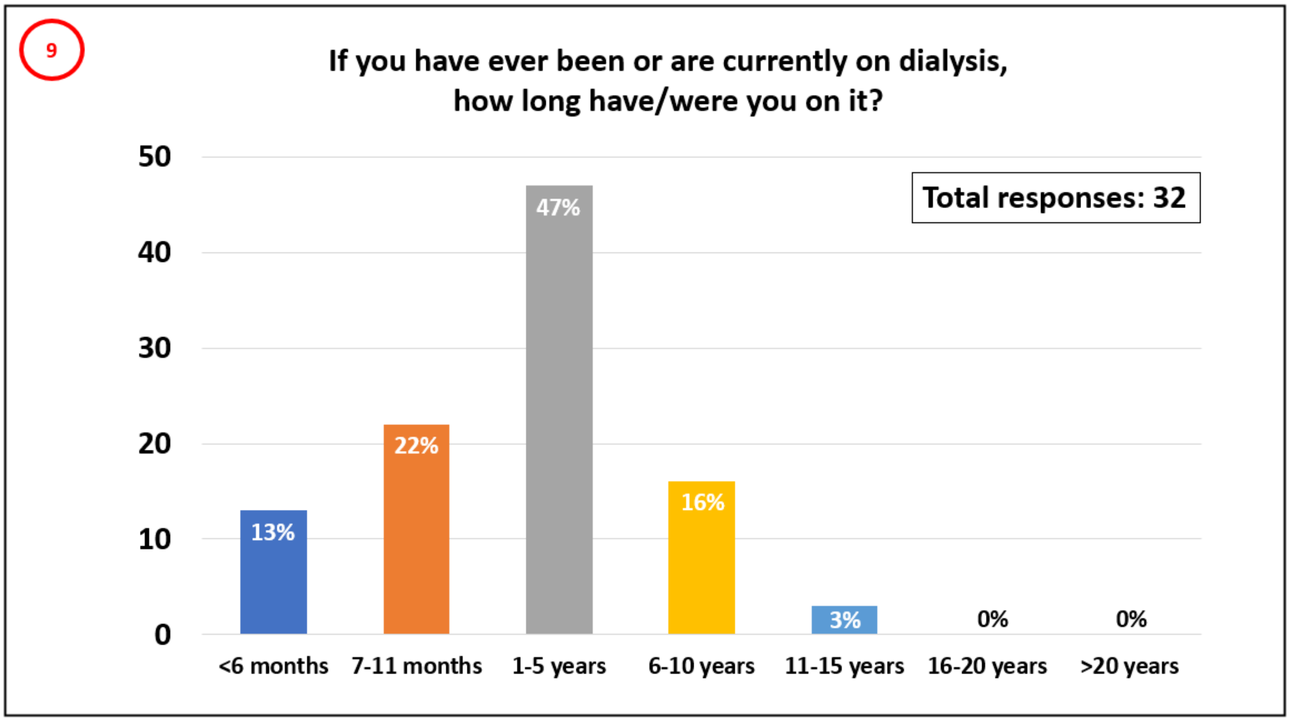
Total responses: 44

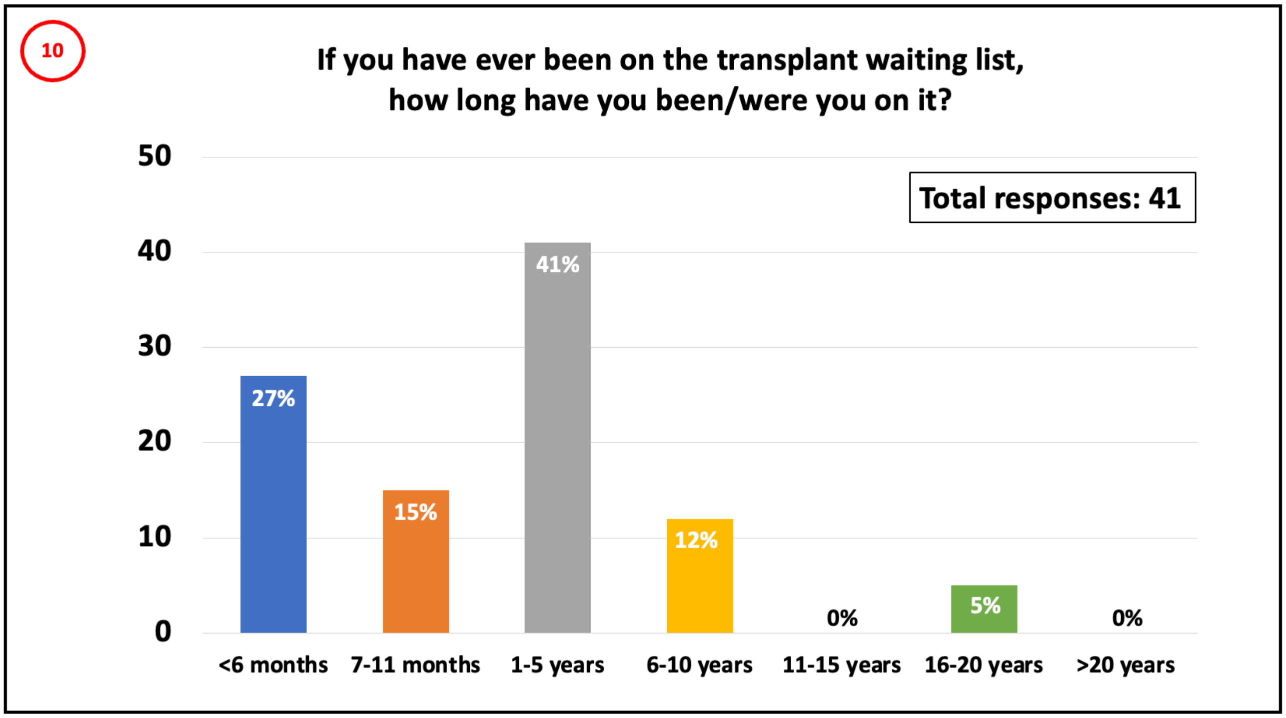
APPENDIX 6: Continued

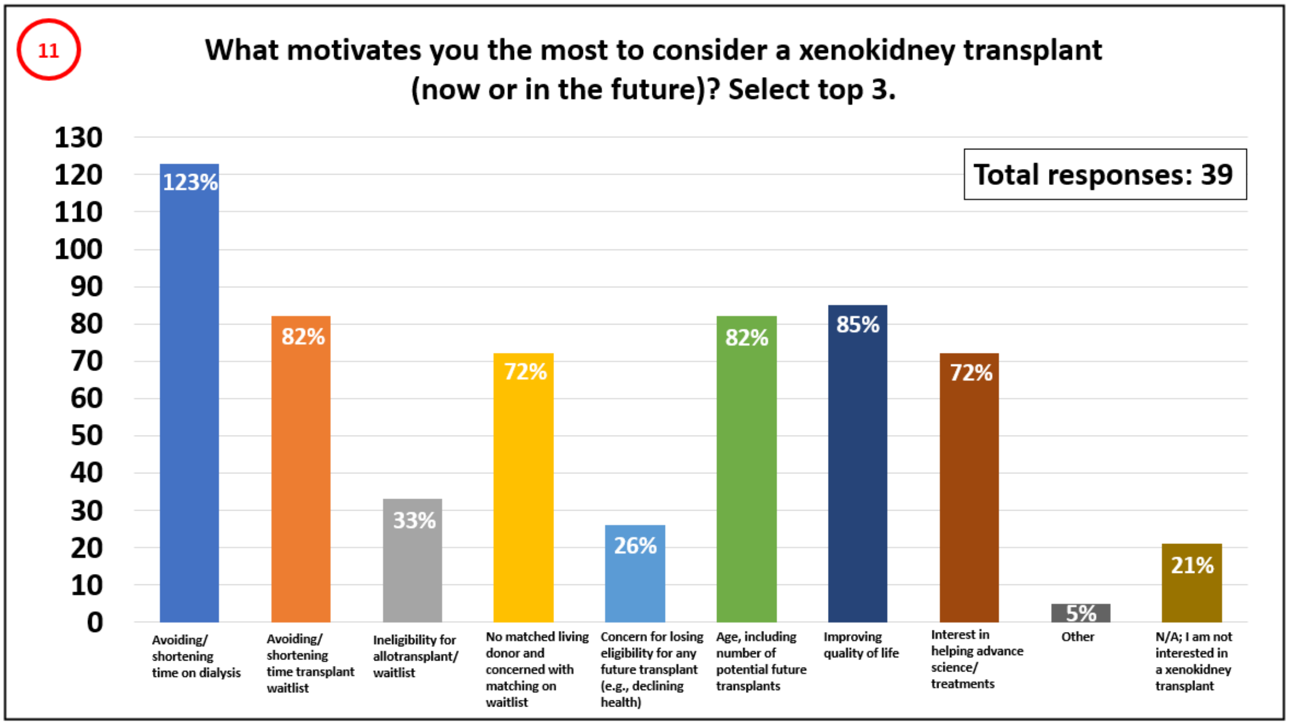
Discussion A: Patient Experiences with Kidney Disease: Why Patients May Consider Kidney Xenotransplantation (Expectations & Outcomes)


What is your or your loved one's current level of kidney function (stage of disease)?


Which best describes you or your loved one's experience?


9
If you have ever been or are currently on dialysis, how long have/were you on it?
Total responses: 32
50
40
30
20
10
0
13%
22%
47%
16%
3%
0%
0%
<6 months
7-11 months
1-5 years
6-10 years
11-15 years
16-20 years
>20 years

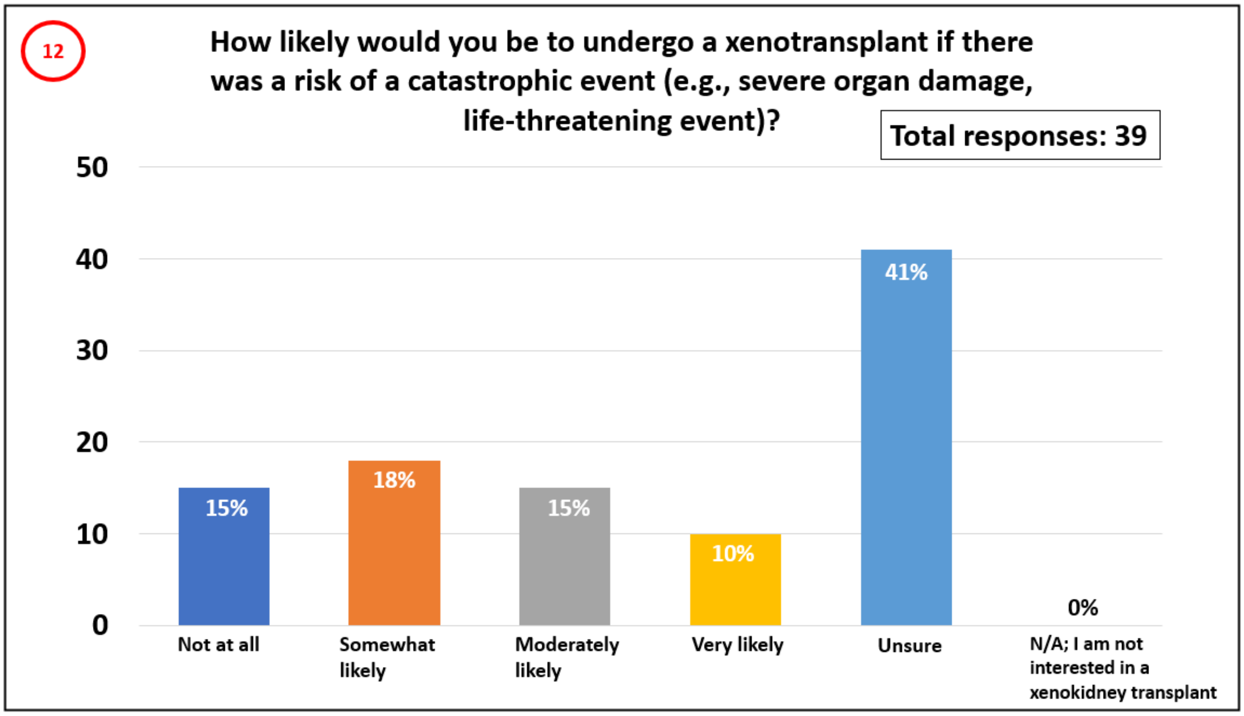

10
If you have ever been on the transplant waiting list, how long have you been/were you on it?
Total responses: 41
50
40
30
20
10
0
27%
15%
41%
12%
0%
5%
0%
<6 months
7-11 months
1-5 years
6-10 years
11-15 years
16-20 years
>20 years



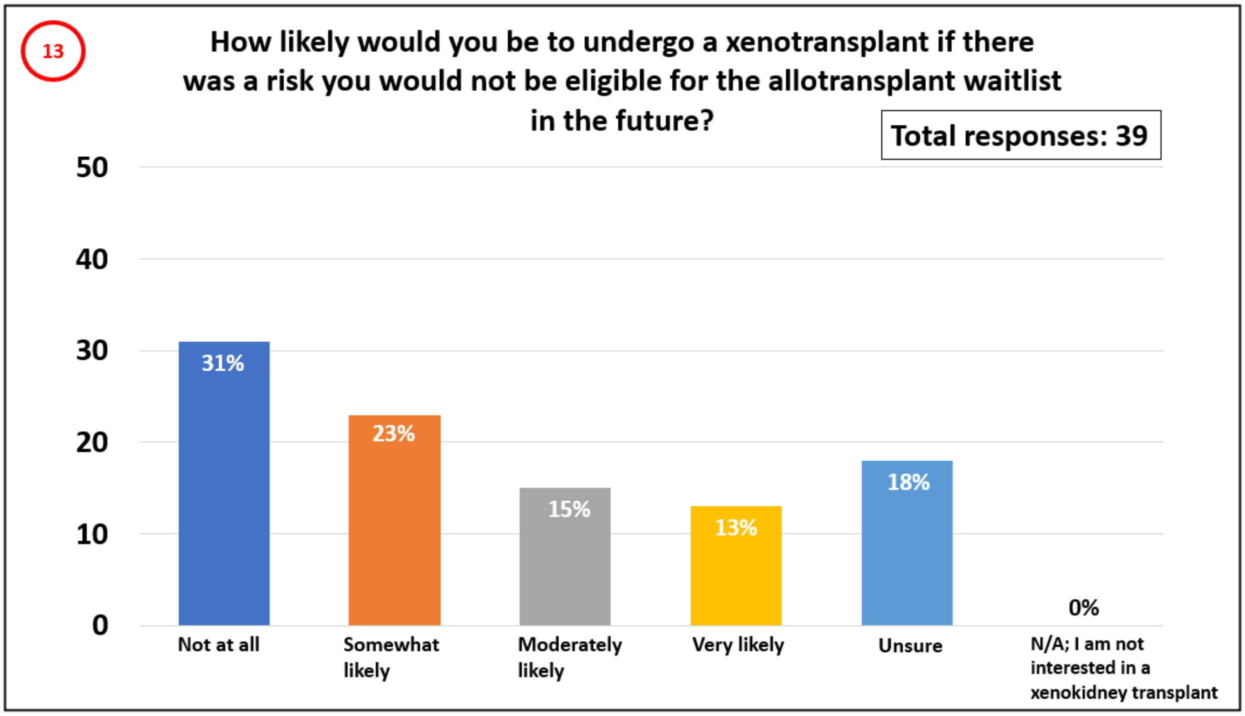
Participants were asked to select their top 3 motivators to consider a xenokidney transplant, thus the graph displays numbers over 100%

APPENDIX 6: Continued

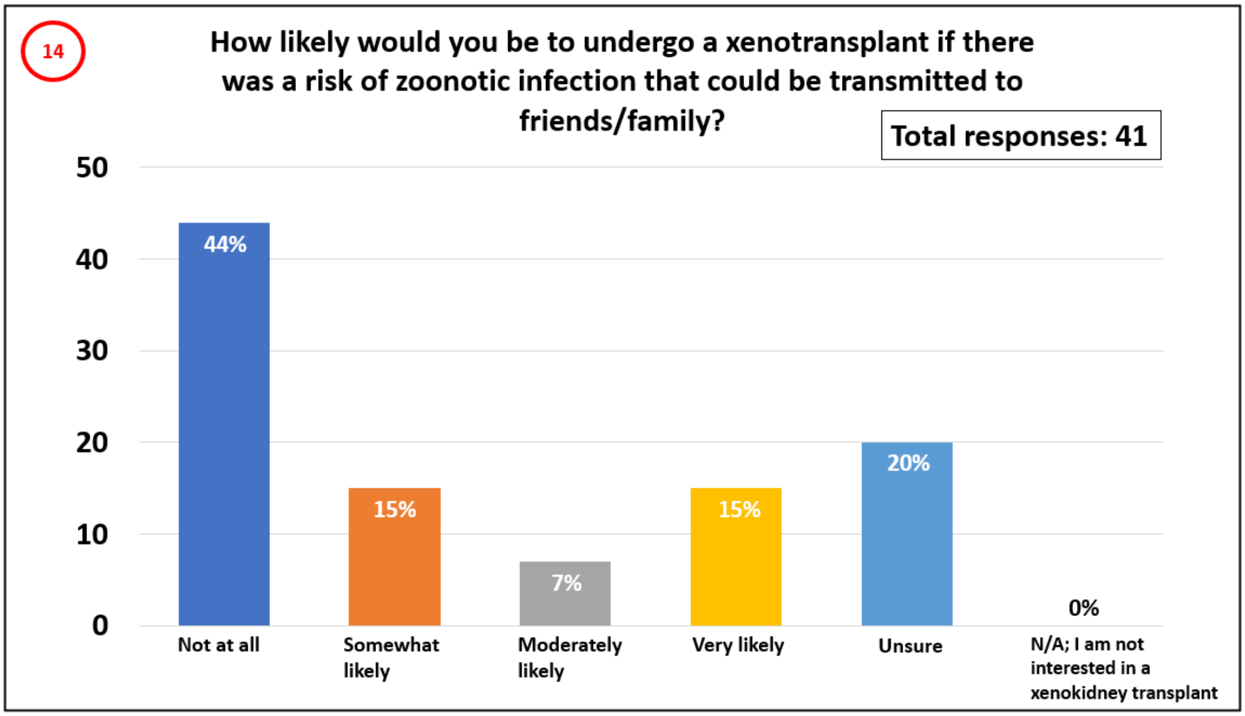
Discussion B: Patient Considerations of Risk & Other Downsides of Kidney Xenotransplantation


⑫ How likely would you be to undergo a xenotransplant if there was a risk of a catastrophic event (e.g., severe organ damage, life-threatening event)?

Total responses: 39

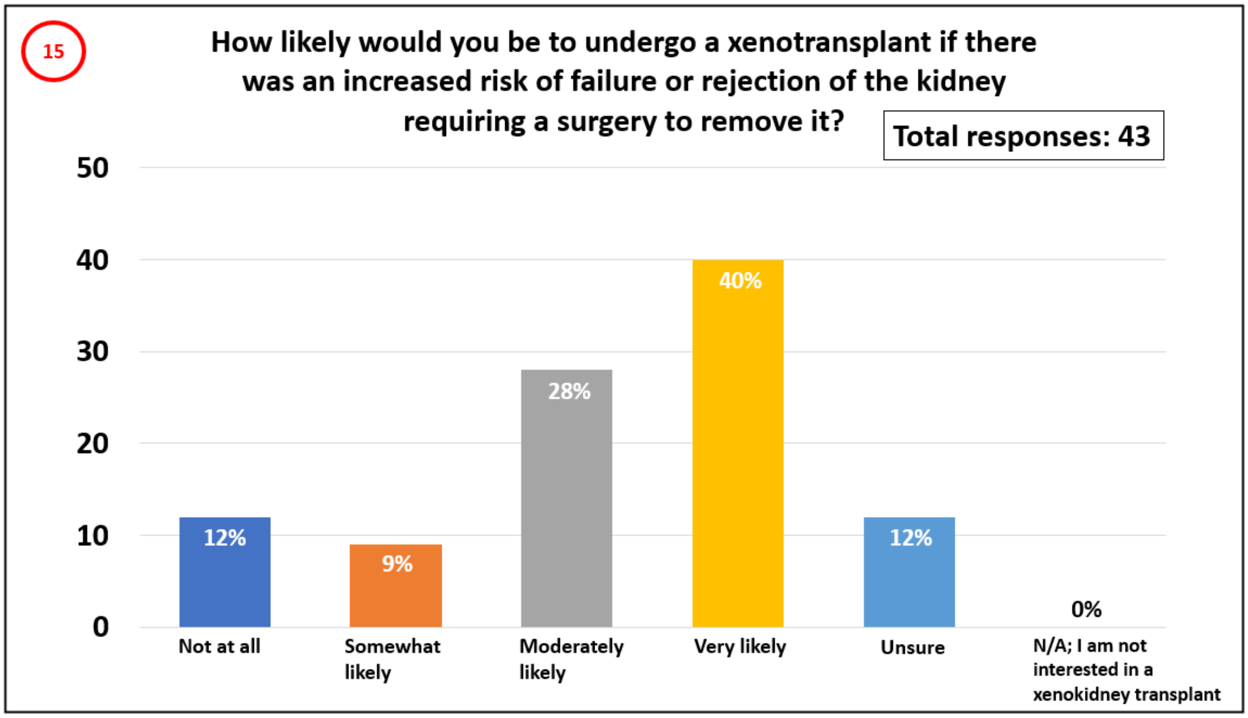

⑬ How likely would you be to undergo a xenotransplant if there was a risk you would not be eligible for the allotransplant waitlist in the future?

Total responses: 39


14

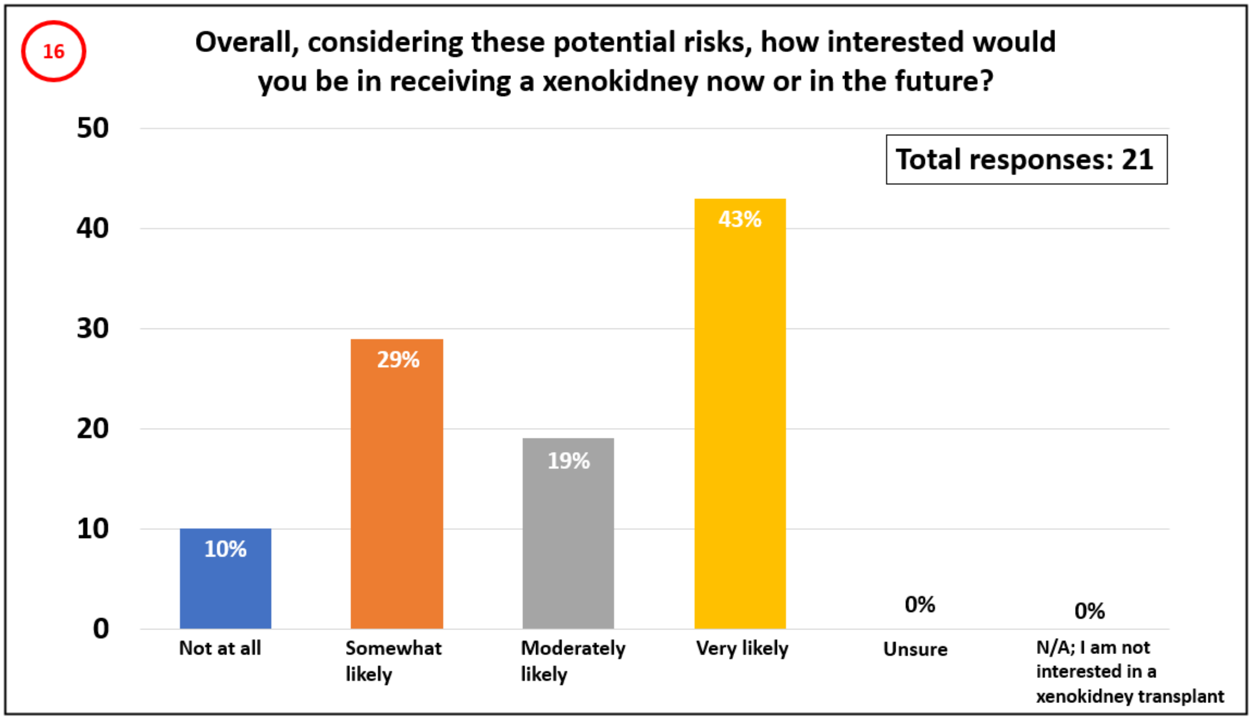
How likely would you be to undergo a xenotransplant if there was a risk of zoonotic infection that could be transmitted to friends/family?

Total responses: 41


15

How likely would you be to undergo a xenotransplant if there was an increased risk of failure or rejection of the kidney requiring a surgery to remove it?

Total responses: 43

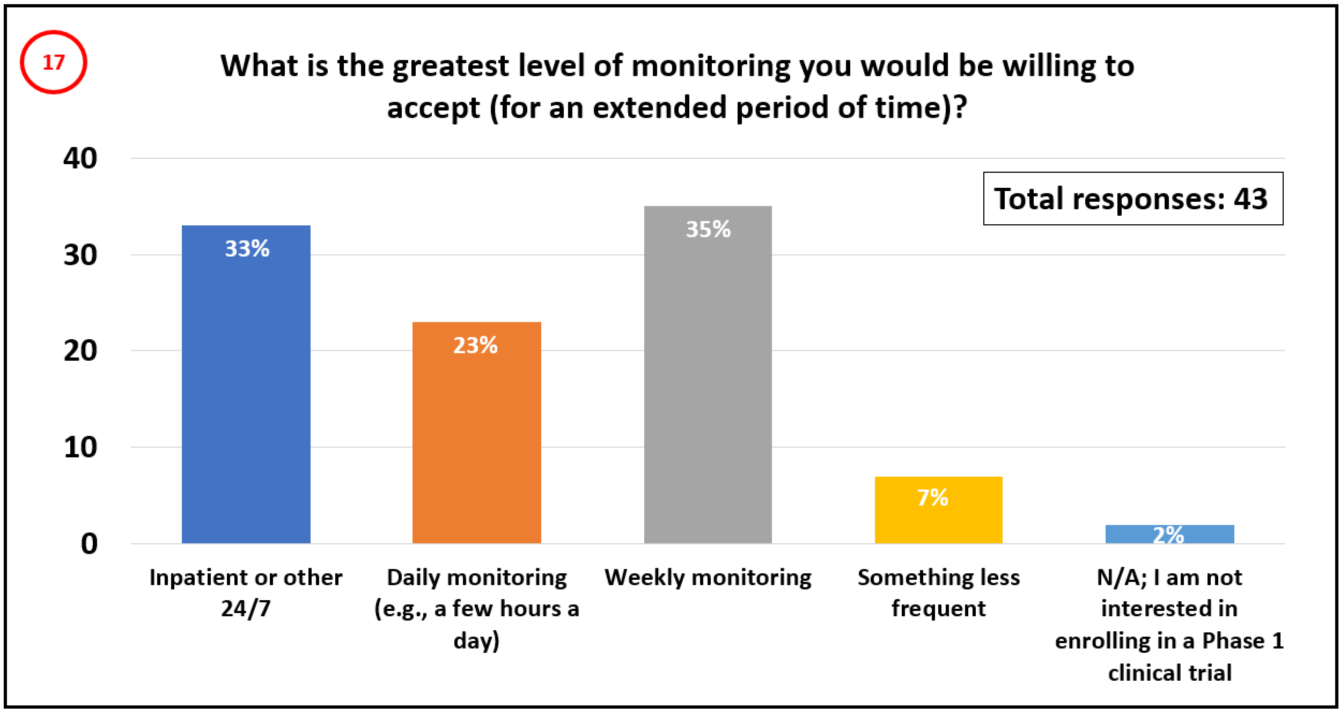


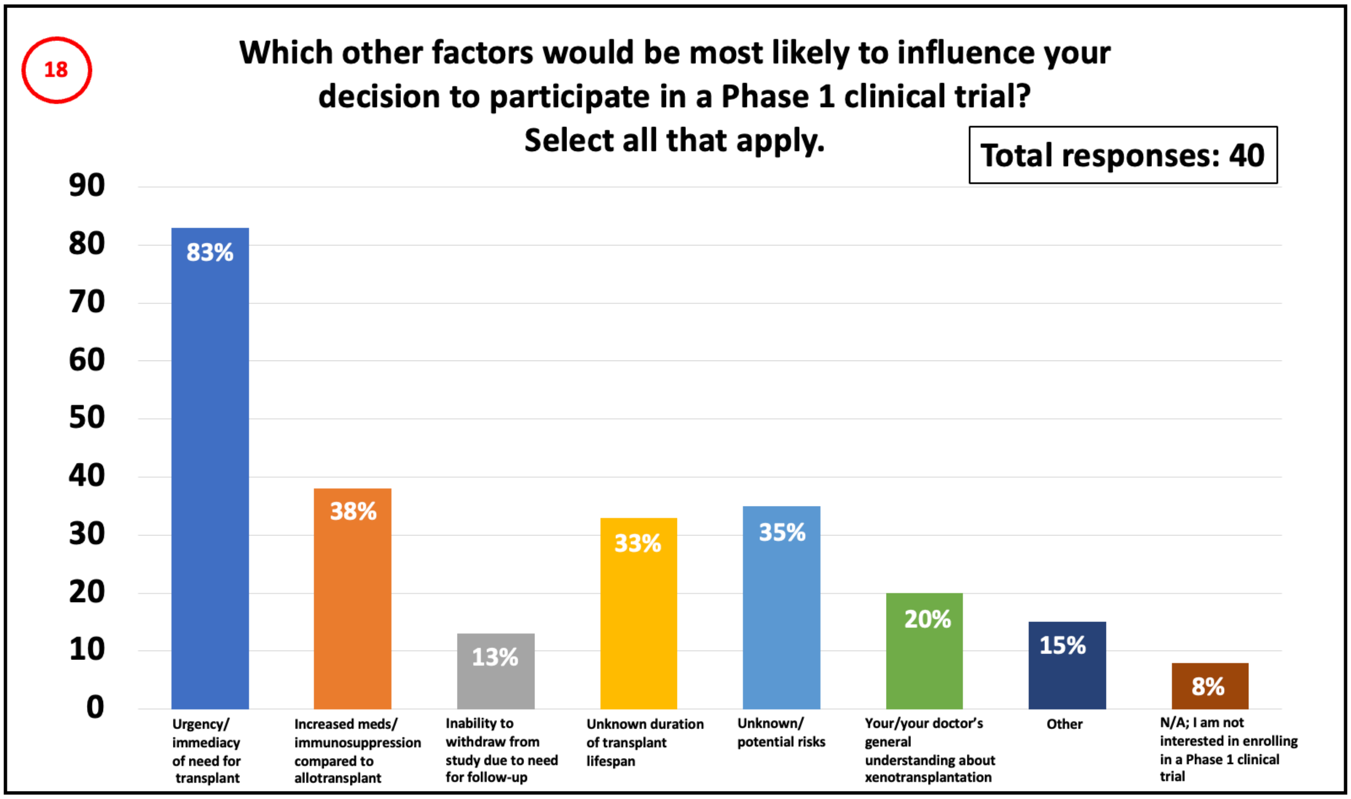
⑯ Overall, considering these potential risks, how interested would you be in receiving a xenokidney now or in the future?

Total responses: 21

APPENDIX 6: Continued

Discussion C: Considerations for Participating in Kidney Xenotransplantation Clinical Trials





APPENDIX 7: ACKNOWLEDGEMENTS

The National Kidney Foundation gratefully acknowledges the generous support of this meeting by:

- eGenesis
- Makana Therapeutics™ Holdings, Inc.
- United Therapeutics Corporation