VOICE OF THE PATIENT REPORT

Post-Transplant Lymphoproliferative Disorder

Externally-Led Patient-Focused
Drug Development Meeting

Meeting Date: May 4, 2022
Report Date: September 1, 2022

NORD®

VOICE OF THE PATIENT REPORT: POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER

This report represents the summary composed by the National Organization for Rare Disorders (NORD®) as a result of an Externally-Led Patient-Focused Drug Development meeting held virtually on May 4, 2022 This report reflects the host organization's account of the perspectives of patients and caregivers who participated in the public meeting.

Submission: This report is submitted as patient experience data for consideration pursuant to section 69C of the Federal Food, Drug, and Cosmetic Act to:

- Center for Drug Evaluation and Research (CDER)
- Center for Biologics Evaluation and Research (CBER)
- US Food and Drug Administration (FDA)

Funding received: Support for this Externally-Led Patient Focused Drug Development meeting was provided by: Atara Biotherapeutics, Inc.

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Version date: September 1, 2022.

Revision statement: This document has not been revised and/or modified after the version date listed above.

Point of contact: Debbie Drell, Director of Membership, NORD; ddrell@rarediseases.org

A MESSAGE OF THANKS

Welcome to this Externally-Led Patient-Focused Drug Development Meeting for PTLD. We're glad you could join us today from wherever you are in the world. NORD is delighted to host this important event with the FDA and for the PTLD community. The goal FDA has defined for these PFDD meetings is to provide key stakeholders including FDA, patient advocates, researchers, drug developers, healthcare providers, and others with an opportunity to hear the patient's voice. The lessons learned include, but are not limited to specific experiences that matter most to the patients, patient perspectives on meaningful treatment benefits, and how patients want to be engaged in the drug development process.

Today is an opportunity to share your thoughts on PTLD. We hope that you find the discussions beneficial and there will be opportunities to participate in polling questions and opportunities to call in from home to share your thoughts as well. We look forward to a very robust discussion today.

Before we start, I would like to thank our sponsor for this meeting, Atara Bio. Without their support, these types of meetings would not be possible.

Thank you and thank you for sharing your stories and perspectives.

Sincerely,

Peter L. Saltonstall
President and CEO, NORD

BIOS

Peter Saltonstall, President & CEO, NORD

Peter joined NORD in 2008 after having served for more than 30 years as a senior executive in both for-profit and not-for-profit health care environments. Under his leadership, NORD has maintained the integrity of the Orphan Drug Act while forging new relationships between the patient community and the executive branch, Congress, HHS, FDA, NIH, Social Security Administration and CMS, as well as with drug and device companies and with the medical, academic and investment communities. His efforts to build collaborations stem from his view that advances for the rare disease patient can be achieved best through joint efforts. Today he continues to be one of the country's leading voices on rare disease issues to industry, FDA, Congress and the federal government. Peter is also committed to globalization of the rare disease patient community, as diseases do not recognize geographical boundaries and research can be expedited when patients from many countries are involved. He has helped established collaborative programs with patient communities throughout Europe, Australia, Japan, Asia and South America. Under Peter's leadership, NORD has grown to be the global reference site for the rare disease community, with NORD's website now receiving more than one million requests a month for information. He has also overseen the expansion of NORD's US-based Patient Assistance Network, which works with manufacturers and patients to provide assistance to patients in need of medications they cannot afford. He has also played a major role in building the NORD Longitudinal Natural History System, which is recognized by the FDA as one of the tools of choice for Patient Organizations collecting data on their disease.

Debbie Drell, Director of Membership, NORD

Debbie serves as the Director of Membership at NORD. In this role, she oversees NORD's membership programs, which support the collective and individual needs of rare disease patient organizations, patients and advocates through education, research, advocacy and mentorship. She brings to the organization over 22 years of leadership in nonprofit public health education, awareness and advocacy. Prior to joining NORD, Debbie spent 13 years with the Pulmonary Hypertension Association, a NORD member organization. During that time, she led the growth of the organization's network of support groups from 80 to nearly 300, developed new services personalized to the diversity of patients and caregivers, and convened the largest gathering of pulmonary hypertension patients in history. Debbie has represented the patient perspective on several national platforms, including as a guest on National Public Radio's Kojo Nnamdi Show. She has served as a member of the board of trustees of the American Thoracic Society, a 115-year-old medical society with a global membership of 16,000 pulmonologists, critical care and sleep disorder researchers, clinicians and other medical professionals. An accomplished public speaker, she has presented extensively at colleges and universities on women's health issues, delivered speeches on caregiving across the country, including at Johns Hopkins University events, and moderated panels at the World Orphan Drug Congress European and American meetings. A graduate of the University of California, Irvine, and the University of Kent, Debbie's dedication to the rare disease community is rooted in a deeply personal connection. She was inspired to enter the field after her older sister, Alex, was diagnosed with pulmonary hypertension.

Ariel Markowitz-Shulman, Associate Director of Strategic Planning, NORD

Ariel Markowitz-Shulman is the Associate Director of Strategic Planning at NORD. She has a varied background based in scientific research and science and health policy. After receiving her MS in Physiology and Biophysics from Georgetown, Ariel has worked in both the public and non-profit sectors on health and science policy, research administration, data analysis and data science strategy, and program evaluation. She came to NORD from a consulting position with the National Heart Lung and Blood Institute, where she planned and implemented a Data Analytics and Portfolio Analysis Program to support the NHLBI in adopting and employing data analysis to facilitate evidence-based decision making and conduct evaluations of their grants funding programs. Prior to NHLBI, Ariel worked at the National Academies of Sciences, Engineering, and Medicine supporting the Forum on Regenerative Medicine, a group dedicated to exploring and advancing regulatory and policy issues related to research, development, and access to new regenerative medicine therapies.

Nicole Gormley, MD, Director, Division of Hematology Malignancies II, FDA

Nicole Gormley, MD, is the Acting Division Director for the Division of Hematologic Malignancies II at the U.S. Food and Drug Administration. Dr. Gormley joined the FDA in 2011 and previously served as a clinical reviewer and the Multiple Myeloma Clinical Team Lead. While in these roles, she has actively engaged with the multiple myeloma community on the development of novel endpoints, including minimal residual disease, and methods to address racial disparities. Dr. Gormley completed fellowship training in hematology and critical care at the National Institutes of Health and served as the Deputy Clinical Director at the National Heart, Lung and Blood Institute prior to joining the Food and Drug Administration.

Thomas M. Habermann, MD, Division of Hematology, Department of Medicine, Mayo Clinic

Dr. Thomas M. Habermann is a hematologist and professor of medicine in Rochester, Minnesota and is affiliated with Mayo Clinic. He received his BS degree in a biology and his medical degree from Creighton University School of Medicine and has been in practice for more than 20 years.

WHAT'S INSIDE

Swapna with family 3 days after transplant

POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER (PTLD) EXTERNALLY-LED PATIENT-FOCUSED DRUG DEVELOPMENT (EL-PFDD) MEETING: EXECUTIVE SUMMARY

Post-transplant lymphoproliferative disorder (PTLD) is a rare complication of solid organ transplants and hematopoietic stem cell transplantation. PTLD is related to immunosuppression therapy and the Epstein-Barr virus. Immunosuppressive therapy leaves patients at a greater risk of developing infections and, in some people, of developing post-transplant lymphoproliferative disease. Early diagnosis and prompt treatment of these disorders are extremely important.

The specific symptoms and severity of PTLD can vary greatly from one person to another. Some affected individuals develop a mild, noncancerous overgrowth of affected tissue. Other people can develop a cancerous, life-threatening form of lymphoma. Individuals affected by PTLD face an elevated risk of complications as compared to other transplant patients and an increased risk of transplant rejection. In addition, individuals with PTLD have a higher mortality rate compared to other forms of lymphoma. The primary goal of treatment is to cure the PTLD while preserving the function and health of the transplant. Because the transplants that necessitate immunosuppression vary, there is no uniform approach to treatment. Current standard of care includes some combination of immunosuppression reduction, with or without single agent rituximab in early B-cell PTLD, and then R-CHOP chemotherapy.

The Externally-Led Patient-Focused Drug Development (EL-PFDD) initiative was developed in response to FDA's interest in more systematically obtaining patients' perspectives on the burden of disease and impact of current treatments. EL-PFDD meetings are traditionally organized, led, and paid for by patient organizations. In this case, because no national nonprofit organization exists that is solely focused on people living with PTLD, The National Organization for Rare Disorders (NORD) applied to the FDA and was granted approval to host an EL-PFDD meeting focused on this disease. For the safety of the community, a fully virtual meeting was held on May 4th, 2022.

The objective of the meeting was to increase our understanding of how patients, families, and caregivers experience and manage PTLD, the factors that are considered when treatments are chosen, and side effects and complications of current available treatments. This may, in turn, help researchers and the FDA understand patient preferences when developing new therapies and evaluating the benefit-risk for new treatment options.

The voices of people living with PTLD and caregivers were heard through courageous patient and caregiver testimonies, live polling of the broader audience, and post-meeting commentary. The meeting was attended via live webcast by 69 participants.

Testimony and facilitated discussion resulted in a rich portrait of the experiences of people living with PTLD and yielded a number of key insights:

- PTLD is often diagnosed after a difficult medical transplant journey, which leads to unique challenges:
    - All people living with PTLD have some sort of comorbidity. Most patients have many.
    - Communication about PTLD is often confusing and unclear, with many patients unsure if they are undergoing treatment for cancer.

- The combination of medications needed to treat patients' PTLD and underlying conditions frequently produce serious side effects.
- Many patients face financial hardships and barriers to coverage of their PTLD-related health care, including insurance providers that are hesitant to cover treatments.
- Treatment, hospital visits, and diagnostic scans for PTLD can lead to significant psychological and emotional trauma, anxiety, and financial stress for already overburdened patients and families.
- Immunosuppression can necessitate long periods of isolation which increases anxiety and depression.

- The few treatment options available for PTLD are further limited by complications with patients' underlying conditions and unique comorbidities:
    - Immunosuppression reduction, an effective approach to treat PTLD, increases the risk of transplant rejection.
    - Existing treatments often lead to life-threatening complications due to an already weakened immune system.
    - The complexity of PTLD and its treatment can exacerbate existing disparities in access to care and clinical trials.
    - Finding other patients with the same combination of diagnoses is extremely difficult.
    - PTLD lacks a national nonprofit solely focused on these patients.

- Most people living with PTLD continue to experience long-term effects related to the disease or its treatment:
    - Ongoing psychological issues, fatigue, and pain have a significant negative impact on daily life.
    - Self-confidence can be negatively impacted by changes in energy level, cognition, physical appearance, as well as delayed school or career milestones.
    - "Invisible symptoms" such as fatigue and cognitive issues lead to isolation, judgement and discrimination.
    - Post-traumatic stress disorder is common and often triggered leading up to and during medical visits and scans.
    - COVID presents additional risks for people living with PTLD who are immunocompromised and medically vulnerable.

Polling of patients and caregivers helped elucidate the weight of symptoms of PTLD and the importance of treatments for this complex disease:

- People living with PTLD and their caregivers report a wide range of symptoms:
    - Fatigue
    - Psychological/emotional (e.g., PTSD, anxiety)
    - Loss of appetite
    - Headaches
    - Pain in area where PTLD was found
    - Painful lymph nodes
    - Bone pain

    - Pain at tumor site
    - "Ghost pain"
    - Shortness of breath (dyspnea)
    - Swelling and fluid at incisions

- People living with PTLD and their caregivers ranked the following symptoms as those that most negatively impact their daily life:
    - Fatigue
    - Psychological issues
    - Pain

- People living with PTLD experience a high level of emotional and social stress including:
    - Anxiety
    - Hopelessness
    - Low self-esteem
    - Social isolation
    - Depression
    - Unwanted attention based on appearance
    - Difficulty with relationships
    - Bullying from others

- People living with PTLD face difficult challenges in daily life including:
    - Limited daily function
    - Lack of understanding by others related to life with PTLD
    - Modified school or career goals
    - Missed school
    - Employment negatively impacted
    - Family stress
    - Difficulty exercising or participating in sports

- People living with PTLD and their caregivers ranked the following as their biggest concerns about living with PTLD:
    - Infection
    - Rejection and relapse
    - Immunosuppression
    - Access to medical care

- People living with PTLD use or have used a wide range of medications or supportive treatments:
    - Benadryl (intravenous, oral, or other)
    - Rituximab
    - Steroids
    - Pain relievers (prescribed, OTC, or other)
    - Chemotherapy
    - Neupogen
    - Neulasta
    - Claritin (for drug-related bone pain)
    - Radiation

- Most people living with PTLD and their caregivers report not knowing about or not being eligible for clinical trials.
- People living with PTLD and their caregivers ranked the following as most important to their decision about participating in clinical trials:
    - Whether I need to stop my current disease management or treatment regimen
    - Potential side effects from the new drug
    - Whether the drug is supposed to treat symptoms or the underlying cause of my disease
    - Distance to trial site

- People living with PTLD and their caregivers ranked the following as most important when deciding on a new treatment or drug:
    - Severity of side effects known for the drug
    - Whether the drug will improve my PTLD
    - Evidence that the drug improves specific symptoms most bothersome to you

- When looking at future treatments, without considering side effects, 70% of poll respondents favored evidence that the drug would extend lifespan versus evidence that it would reduce complications of PTLD, though both were cited as important factors.

Because PTLD is a rare, severe, and highly variable condition, this EL-PFDD meeting played an important role by improving the understanding of the disease and associated treatments. The perspectives collected within this report provide a unique window into the experiences of individuals affected by this condition and their caregivers, and may help direct the FDA, academic researchers, and pharmaceutical companies to develop critical therapies and interventions for this underserved and isolated patient community. In addition, these insights may now be used to help develop a benefit-risk framework that the FDA can utilize in its regulatory decision-making. Some preliminary recommendations for this benefit-risk framework can be found in this report.

"Meetings such as this externally led Patient-Focused Drug Development meeting really strengthen our understanding of a disease and treatment burden and what we call the therapeutic context. And so, input from these meetings can really support FDA staff in a lot of different ways as we conduct the benefit risk assessment for individual products or as we advise drug sponsors on their development programs throughout the entire life cycle."

Nicole Gormley, MD, Director, Division of Hematology Malignancies II, FDA

POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER EXTERNALLY-LED PFDD DESIGN

The patient perspective is critical in helping the US Food and Drug Administration (FDA) understand the context in which regulatory decisions are made for new drugs. Externally-Led Patient-Focused Drug Development (EL-PFDD) meetings provide an opportunity for patients, their families, and caregivers to share critical information about the impact of the disease on their daily lives and their experiences with currently available treatments. Patients' experiences provide valuable insight for the FDA and other key stakeholders, including researchers, medical product developers and healthcare providers.

EL-PFDD meetings are traditionally organized, led, and paid for by patient organizations, and FDA personnel attend on a case-by-case basis. In this case, because no national nonprofit organization exists that is solely focused on people living with PTLD, The National Organization for Rare Disorders (NORD) applied to the FDA and was granted approval to host an EL-PFDD meeting focused on this disease. For the safety of the community, the meeting was fully virtual and featured live, engaging, interactive components, including polling, patient remarks, and engagement with federal decisionmakers and researchers.

This meeting was a year in the making. NORD released a call for stories and worked with an informal patient and caregiver advisory group to review the patient and family stories that were submitted. Presenters were carefully chosen to ensure diverse experiences, comorbidities, diagnosis, and severity. In addition, age, gender, ethnicity and geographical location were considered.

As new drug applications are filed by drug developers, the comprehensive "Voice of the Patient" report generated after the meeting is a critical additional resource for the FDA beyond the mandatory safety and efficacy data. This EL-PFDD meeting enabled the PTLD community to share with key FDA officials and other stakeholders the burdens of the disease and perspectives on future idealized treatments. This, in turn, may inform the FDA regarding the benefit-risk balance of treatment options, the severity of the disease and the urgency of unmet medical needs.

Post-transplant lymphoproliferative disorder is a rare condition with no targeted treatment currently available. Existing medical interventions introduce significant risks and burdens to patients, especially given the serious comorbidities often present. NORD believes PTLD has unmet needs and a severe disease burden.

The goals of this meeting were as follows:

- Collect data and discern key insights for clinical trial design from individuals affected by PTLD and their caregivers, so that the outcomes of potential therapeutics can be measured in ways that are both clinically sound and therapeutically impactful.
- Provide researchers, drug developers, and the FDA with a robust understanding of patients' and caregivers' experiences with PTLD, including how individuals view their quality of life, which aspects of the disease are most problematic for them, and what actions they currently perform to treat and cope with this disease.

The EL-PFDD meeting included panelists that represent a spectrum of perspectives, including adults and children living with PTLD and caregivers.

The voice of the PTLD community was heard through courageous patient/caregiver testimonies, open discussions with the meeting attendees, live polling of the broader audience, and post-meeting commentary.

A recording of the entire EL-PFDD meeting for Post-Transplant Lymphoproliferative Disorder can be viewed at the NORD website: bit.ly/NORD-PFDD-PTLD-Meeting

BACKGROUND ON POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER

What is Post-transplant Lymphoproliferative Disorder?

Post-transplant lymphoproliferative disorder (PTLD) is a rare, but well-known complication of solid organ transplants and hematopoietic stem cell transplantation. PTLD is characterized by the overproduction and spread of too many white blood cells (lymphocytes). This can cause complications ranging from a benign (noncancerous) enlargement of an organ or tissue because of the overproduction of these cells (hyperplasia) to the development of a malignant (cancerous) form of lymphoma. PTLD is the most common malignancy complication of organ transplantation and represents 21% of all malignancies in solid organ transplant versus 4% to 5% in people who are not immunocompromised.

What causes Post-transplant Lymphoproliferative Disorder?

PTLD is highly associated with immunosuppression therapy and the Epstein-Barr virus. People who receive solid organ transplants are treated with drugs that suppress the activity of the immune system. This is done to help the body accept the transplant and avoid rejection. Individuals receive these drugs at the time of the transplant (induction therapy) and must remain on these drugs for the rest of their lives (maintenance therapy). Immunosuppressive therapy leaves patients at a greater risk of developing infections and, in a small number of cases, of developing PTLD.

In many PTLD cases, the transplant recipient becomes infected with the Epstein-Barr virus, either through a primary infection after the transplant or when the dormant virus is reactivated. In the case of reactivation, the virus may have remained latent after a prior infection or been introduced in the transplanted organ. The virus spreads to white blood cells, usually a type of lymphocyte called a B-cell, which then grow out of control. Children are less likely to have had an Epstein-Barr virus infection before immunosuppression and therefore are more likely to develop PTLD.

PTLD only occurs in a small percentage of people who receive a transplant, regardless of whether they have had Epstein-Barr infection. As an example, the long-term risk for developing PTLD after a renal transplantation is 2%. Because of this, researchers believe that there are additional factors necessary for the development of this disorder. Although the Epstein-Barr virus is identified in most affected individuals, some patients do not have any evidence of this infection. Researchers are not sure what causes PTLD in people with the Epstein-Barr-negative version of PTLD.

How is Post-transplant Lymphoproliferative Disorder diagnosed?

Early diagnosis and prompt treatment of this disorder is extremely important. The first sign of PTLD is often elevated Epstein-Barr virus levels in the blood. Follow-up diagnosis is based upon identification of characteristic symptoms, a detailed patient history, a thorough clinical evaluation, and a variety of specialized tests. Tests include a complete blood count (CBC), chemical (metabolic) panel, an evaluation for the Epstein-Barr virus, tissue biopsy, and specialized imaging techniques such as computerized tomography (CT) scanning, PET scanning, and magnetic resonance imaging (MRI). If doctors suspect that the central nervous system is involved, a lumbar puncture (spinal tap) may be ordered. In some cases, the tumor tissue may also be studied for genomic changes that indicate PTLD.

What are the symptoms of Post-transplant Lymphoproliferative Disorder?

The specific symptoms and severity of PTLD can vary greatly from one person to another. Some affected individuals develop a mild, noncancerous overgrowth of affected tissue, while other people can develop a cancerous, life-threatening form of lymphoma. The mild, benign form of PTLD can resemble reactive hyperplasia, the normal process in which lymph nodes become enlarged in response to an infection or inflammation. PTLD can be localized, which means the disease only affects a specific area of the body or widespread (disseminated), which means it affects several different areas of the body. It can also cause severe, life-threatening complications. In addition, PTLD may affect the transplanted organ, and these cases commonly involve extranodal tissue.

Specific signs and symptoms depend on several factors including the areas of the body affected and the type of PTLD. Affected individuals often develop symptoms that are vague and can be nonspecific, which means that the symptoms are common to many different disorders or conditions. These symptoms can include a persistent, chronic fever, unintended weight loss, and excessive sweating, especially at night (night sweats). Some individuals develop abnormal enlargement of the lymph nodes (lymphadenopathy), fatigue, or a general feeling of poor health (malaise).

How is Post-transplant Lymphoproliferative Disorder currently treated and managed?

Because the underlying conditions that necessitate immunosuppression vary, there is no uniform approach to treatment. The primary goal of treatment is to cure the PTLD, while preserving the function and health of the transplant.

While initial treatment strategies vary based on PTLD subtype, current standard of care includes some combination of immunosuppression reduction, with or without single agent rituximab in early B-cell PTLD, and then R-CHOP chemotherapy. Specific treatment options are available for PTLD that are not standard of care for de novo lymphoma, including surgery, immunosuppression reduction, and anti-CD20 monoclonal antibody therapy as a single agent.

In instances where immunosuppression can be safely reduced in early PTLD, rapid and dramatic reduction in PTLD is often observed, remissions can be complete, and no follow-up treatment is needed.

What are the outcomes for individuals living with Post-transplant Lymphoproliferative Disorder?

PTLD is a serious, life-threatening condition. Individuals affected by PTLD face an elevated risk of complications as compared to other transplant patients and an increased risk of transplant rejection. In addition, individuals with PTLD have a higher mortality rate as opposed to de novo diffuse large B cell lymphoma. While extensive outcomes data is not available, a number of retrospective studies have been completed in recent years at major transplant centers and have identified a range of statistically significant prognostic factors.

What research is currently being conducted to develop new therapies for Post-transplant Lymphoproliferative Disorder?

Investigative studies are currently underway for EBV vaccine for EBV-negative patients, EBV specific T-cell infusions, allogeneic cytotoxic T-cell therapies, peptide selected therapy, and virus specific T-cell therapies. These treatments are not on the market at this time and are not FDA approved.

MEETING PARTICIPANT DEMOGRAPHICS

The EL-PFDD meeting was attended via a livestream webcast by 69 participants. Of the meeting participants, 18 were patients or caregivers (26%) and 11 of these participated in the panel discussions. Others in attendance came primarily from industry, advocacy organizations, and government.

The polling was made available to all patients and caregivers, and approximately 83% participated in the polling exercises. In addition, polling was offered on the NORD website for 30 days following the meeting and three additional individuals contributed responses.

Of the polling participants, 55% were PTLD patient caregivers and 45% were individuals living with PTLD. The polling revealed that 100% of the participants were US-based, with 90% identifying as female and 10% identifying as non-binary. The majority of respondents (90%) identified as White (Non-Hispanic) with 10% identifying as Hispanic, Latino/a, Latine, Latinx.

Demographic Polling Questions

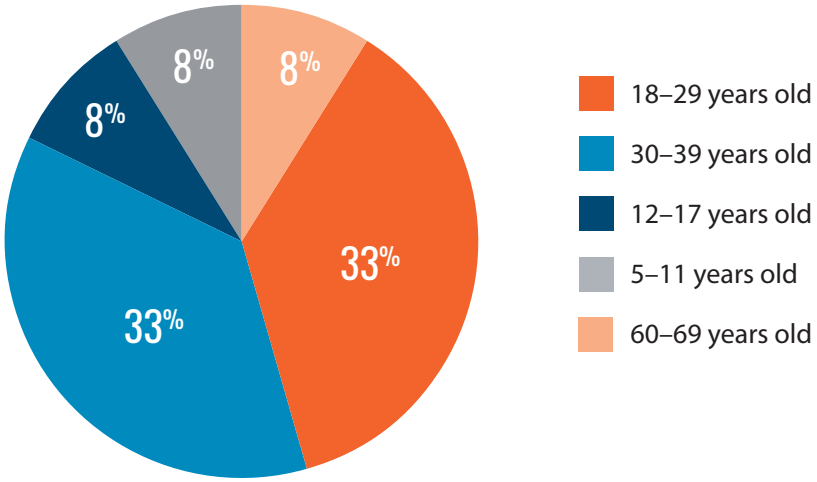
Where do you live?

This poll showed that half of the participants were from the Midwest (50%) with the remaining respondents from varied locations within the US.

What is your age or the age of the person you are caring for?

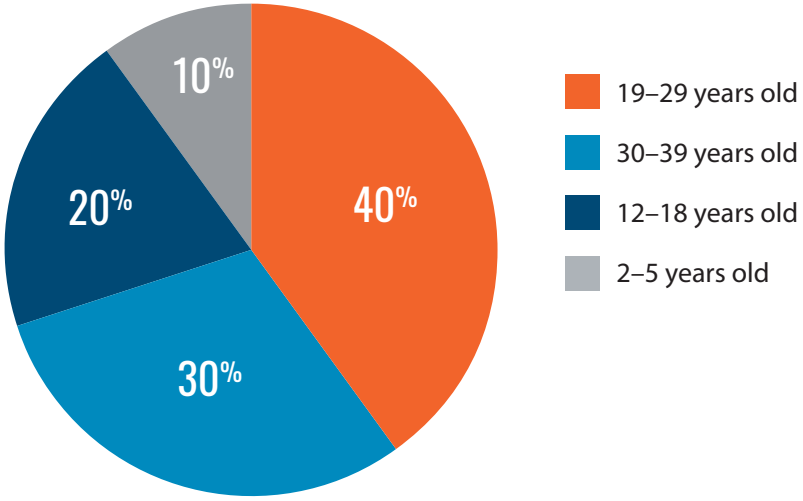
While there was a broad range of ages represented, most were under the age of 40:

33% were 18–29 years old, 33% were 30–39 years old, 8% were 12–17 years old, 8% were 5–11 years old, and 8% were 60–69 years old.



At what age did you or your loved one receive a diagnosis of PTLD?

Diagnosis of PTLD tended to come in early adulthood for respondents. Of the patients represented, 40% were diagnosed with PTLD at 19–29 years of age, 30% at 30–39 years of age, 20% at 12–18 years of age, and 10% 2–5 years of age.



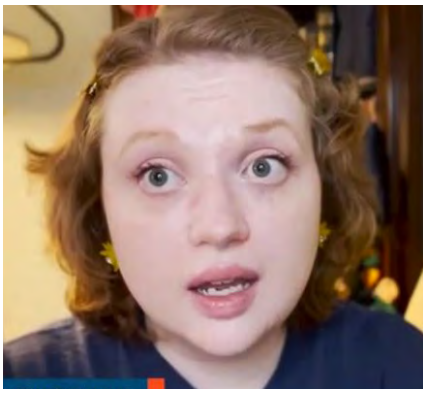
VOICE OF THE PATIENT, TOPIC 1: LIVING WITH POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER - BURDENS AND SYMPTOMS

The first half of the meeting was dedicated to patients and caregiver experience living with PTLD, including its impacts on daily life, health, psychology, relationships, school, and career. Patients and caregivers related the burden of living with PTLD and the symptoms presented by this disease. The session began with stirring personal testimonies from patients and caregivers living with PTLD. This was augmented by in-depth discussion with panelists, comments from the virtual participants, and a poll of the broader audience. Following the meeting, all attendees were able to submit additional comments via email for a period of 30 days.

Session 1: Patient and Caregiver Testimonies

The full testimonies from each patient can be found in Appendix 2. Some of the most impactful comments made by each individual are included below.

Ellen (Patient, 26 years old):



"In the first four days after the EBV initially came back positive, the EBV level in my blood increased 266% and I went from symptomatic of mononucleosis to lymph nodes swollen across my entire body. In another three days I was hospitalized with masses appearing in my lungs on CT and nearly delirious from pain"

"After nearly two years of fighting insurance to cover my transplant, failing and receiving life-saving treatment only via the charity of the hospital, I felt hopeless. I had fought so hard to get access to life-saving treatment, in this case a bone marrow transplant, and I wasn't sure I had the strength to fight all over again. Rare disease meant that I had fallen through the cracks in the system, and I felt like I was poised to slip through yet again."

"At the end seventh week I was admitted to the clinic feeling unwell and my oncologist recognized the warning signs of a thyroid storm, which they now believe was triggered by the rituximab. I spent that night alone in the hospital crying and delirious as nurses filled my bed with ice in an attempt to bring down a fever that ranged up to 106 and failed to respond to any medications. After another week of hospitalization, I was able to return home and begin recovering for the third time."

"I don't have many clear memories of that period in the hospital, I journaled daily but I had violent tremors and the words aren't legible, even to me, in many places. I remember there being a lot of pain and describing my lymph nodes in my head and neck as feeling as if they were marbles made of glowing hot glass. I remember slipping in and out of waking as my mother read aloud to me, trying to distract me from the pain. And I remember being isolated."

**The testimonies in this report was transcribed from the live event. Any omissions or errors are unintended.*

Sarah (Parent/Caregiver):

"Everett was hospitalized for sleep apnea from swollen tonsils and a swollen lymph node in his neck. It was then that he was diagnosed with Epstein-Barr virus with a fear of PTLD. We had never even heard of PTLD before this and that it was something that his transplant medications can cause. This was a very scary moment for us. It was ruled from a CT scan that he did not have PTLD, but we should watch him closely."

"A few weeks had passed and Everett was back in the hospital with rectal bleeding. It was ruled that the bleeding was from ulcers but it was a fear of ours that the EBV had spread to his gut and had now caused PTLD. Everett then began to throw up one to two times a day for about six weeks. It then became so bad that he was hospitalized. Then I noticed that his abdomen had become tender and there was a palpable mass found. The pain became unbearable for Everett pretty quickly."

"We are one-income family, which is already pretty difficult when you have a disabled child involved. And now we are going to have to start adding in expenses for traveling to a hospital 3.5 hours away for his treatment."

"Everett's been cleared from his PTLD and has finished his chemotherapy. We are extremely excited about this. However, there are new fears that come along with having even being diagnosed with PTLD because this was caused by his transplant medications, he's not able to go back on all of them or as strong of doses. So, we have a new fear of rejection. And then there's also the fear that this cancer will return. I don't think those fears will ever go away."

Marianna (Patient, 23 years old):

"…not long after my transplant, I started crying out in pain and knew something was seriously wrong. My pain tolerance is high, but the large painful bumps on my head and neck were too much for me to handle. I'd crawl into bed to try to find some relief only to wake up drenched in sweat with a fever."

"PTLD robbed me of what little energy I had after my bone marrow transplant. I used every last drop of it going between my home and inpatient hospital stays. Moving from bed to bed sounds pretty easy for a healthy person, but sometimes I cried and threw up just from having to move at all. Most 21-year-olds celebrate their independence, but I was holding onto the bar in my shower while my mom washed my hair and my dad drove to pick up my prescriptions."

The combination of medications I was on to combat my reaction caused severe restlessness that led to me feeling

intense anxiety. My heart would pound relentlessly, and I would have panic attacks that required me to need even more medications… I struggle with PTSD from my traumatic experiences related to PTLD and still undergo treatment for it to this day. After I have a panic attack, I'm often so exhausted that I have to lay in bed for the rest of the day. I still feel physically ill when I remember having to sit in ER waiting rooms full of people, coughing and sneezing, while I close my eyes and hoped that I wasn't risking my life by putting my new immune system to the test.

Rebekah (Patient, 34 years old):

"Due to the emotional medical and mental trauma I experienced during my time with PTLD, I still go to a behavioral therapist and a trauma-educated psychiatrist for general anxiety disorder, moderate depression, and posttraumatic stress disorder. I see a long-term cancer doctor annually… for preventative healthcare involving my bladder and heart."

"I realized I needed better care than I received. I deserved more information and preparation for how my body and mind might be impacted after my PTLD diagnosis. It's important to remember how receiving an intense and complex diagnosis like PTLD at a young age can impact a patient's ability to process emotions and even result in medical trauma. This aspect deserves just as much attention and care as our physical diagnosis is. Patients living with PTLD deserve holistic care."

Greg and Cyndi (Parent/Caregiver):

"Less than four months after her heart transplant, Marisa contracted PTLD, which proliferated her body and brain following a valiant battle. Marisa succumbed to her illness in January 2017. Despite being hospitalized for a total of more than two years and maintaining hundreds of doctors' appointments, Marisa lived an inspirational life."

"My wife, Cyndi, and I are eternally grateful for the time God blessed us with Marisa. But we struggle daily to live with the tragic irony that the transplant performed to save her life inevitably claimed it, along with the heart of a donor whose family is also grieving."

Session 1: Polling Questions and Results

The following is a summary of the polling results for Session 1. For a full description of the polling questions, see Appendix 3

Have you experienced any of the following difficulties because of your PTLD? (Select ALL that apply)

- The poll revealed that though underlying conditions vary, there are many similarities in the experiences of patients.
- All participants reported fatigue, loss of appetite, and psychological/emotional difficulties such as PTSD or anxiety.
- All respondents reported some kind of pain, though the location varied. 67% had pain in the lymph nodes or in the area where the PTLD was found, 44% had bone pain, and 33% had pain at the tumor site or "ghost pain".
- 67% experienced headaches.
- 33% had shortness of breath (dyspnea).
- 11% had swelling and fluid at incisions.

Which THREE of the following symptoms of your PTLD most negatively impact your daily life?

The poll showed that 89% of participants reported fatigue, 78% reported psychological issues, and 56% reported pain as the most significant negative impact on their daily life for this question. Both headaches and fatigue were chosen by 22% of respondents. More than one in five participants selected "other," including nutrition/loss of appetite/weight loss, diarrhea/bloating, and thinning of hair/swelling of face.

Which have you experienced while coping with your PTLD? (Select ALL that apply)

Experiences among patients also exhibited a high degree of similarity. The most common responses to this question included anxiety (100%), hopelessness (88%), low self-esteem, social isolation, or depression (75%), difficulty in relationships or unwanted attention based on appearance (50%), and bullying from others (25%).

Which of the following statements is true for you as related to living with PTLD? (Select ALL that apply)

Most respondents (80%) reported that school or work was affected by PTLD, including 60% reporting that they've modified school or career goals because of PTLD, 50% reporting that PTLD has caused them to miss school more than they are comfortable with, and 40% reporting that their job was negatively affected. Participants reported that their general daily function is limited by PTLD (75%) and they often feel that others don't know what it's like to live with PTLD (75%). In addition, family stress is common in 40% of respondents lives and 30% cannot participate in sports or other physical activities they enjoy.

What are your biggest concerns about living with PTLD? (Select ALL that apply)

Most individuals living with PTLD have a wide range of concerns.

- Access was a major concern for respondents. 70% reported access to medical care being an issue, while 50% had financial concerns and 40% had insurance difficulties.

- Most participants were concerned about future exposure: 90% about infection, 80% about immunosuppression, and 40% about risk of infection from COVID.
- 80% were concerned about rejection and relapse and 60% about first-line treatment not working.
- 60% were concerned about recurrence of PTLD and/or the development of lymphoma post-PTLD.
- 50% were concerned about mental health concerns.
- 40% were concerned about malnutrition.

Session 1: Facilitated Discussion

The following is a sampling of insightful comments that were made by panelists or submitted by the broader attendees during the facilitated discussion.

Of all of the symptoms that you experience because of your condition, which one to three symptoms have the most significant impact on your life?)

Marianna: "I think the two symptoms that impacted my life the most were the fatigue and the pain in my lymph nodes. The fatigue obviously kept me from doing a lot of things, not even just high activity activities, but getting out of bed, taking care of myself. And obviously, the pain in my lymph nodes for me was in my neck and in my head. So, it was hard to lay down comfortably."

Rebekah: "The pain and fatigue I still have even [after] 23 years of remission, still are significant factors in my daily life. And another… is the fear of relapse, the worry and the trauma, especially during the pandemic with how my history of the PTLD impacted my risk factors. That definitely was significant."

Ellen: "For me, pain is definitely the most significant. I am about one year out from my first clean scan at this point, and I still have what I call angry head marbles, and it's palpable lymph nodes that are still swollen and painful even a year later and show up on scans as reactive lymph nodes and continue to cause pain, even though the PTLD is not active. I'd say that fatigue is second, and there were points, especially when I was in active treatment, when the exhaustion was so bad that I couldn't stay awake for more than a few hours during the day. And third for me personally, would be appearance and self-confidence. The way my clothing fits, the way I see myself in the mirror, the way others see me, when the lymph nodes were incredibly swollen, I felt like I looked like a chipmunk. When I was on high dose chemo, I felt like I looked like a skeleton. There's a constant changing reflection in the mirror that leads to body dysmorphia and uncertainty with knowing what I'm going to see when I look in the mirror each morning."

Greg: "I think that the encroachment of PTLD on the brain is very rare. And in Marisa's case, it was swift and quick, and it impacted her, she had chronic tonic seizures, eye droop, blurred vision, lost the fine motor skills. She lost her memory to the point where she didn't even recognize her own mother who's her best friend. She lost the ability to swallow properly, essentially became vacant and ultimately was placed on a ventilator one final time. It was really horrific to watch someone so vibrant and expressive and personable just to be reduced to that."

What symptoms are affecting you now, and can you give a real-world example of how it's impacting your daily life?)

Ellen: "I continue to struggle with pain mostly. There are days when I am aware of the swollen lymph nodes in my armpits, behind my knees, in my neck. For me, my PTLD progressed to below the diaphragm, there were nodules in my lungs, that sort of thing. The body remembers and only being this far out, there is echoes of pain and inflammation that I feel every time I wake up in the morning, every time I want to go out and do something with my brother."

Ellen: "…the PTLD treatment left me with no functional immune system. And so, I get IVIG every four weeks. And as I approach needing the replenishing of the IVIG, I experience increased fatigue. I experience increased swelling in my lymph nodes. I increase in almost all of my symptoms, and there is this cycle that I'm bound to, of dropping down to this low point, getting the medication, getting stronger, feeling better, and then dropping back off."

Rebekka: "I'm 23 years in remission and I still have a lot of pain under my armpits, outside of my neck and my head. There is muscle and muscle wasting and bone issues with my rare disease, but upon doing long term preventative healthcare with my long-term cancer doctor, the external pain I'm experiencing is specifically related to the PTLD I had."

Ellen: "…I immediately post diagnosis was like, all right, let's get physical therapy in here. Let's get OT in here. I want to do this and I was so fatigued that it just wasn't possible. And that was really hard for me, especially someone who had used physical exercise to cope, and PTLD was incredibly limiting in that."

Ellen: "…treatment also gave me extreme tremors, which meant that I had to walk with a cane or remain in a wheelchair. And it has been a long slow climb back up. And I still cannot do the physical exercise that I would like to. So, for me, physical exercise has been something that I have had to set aside because of PTLD. It hasn't really been so much a part of my recovery as a goal to reach as a result of recovery."

Marianna: "After I got sick, I gained about 60 pounds, which made me kind of unfamiliar with my body. It kind of made me a little clumsy because it was such a rapid weight gain. So, I needed to start exercising to kind of become more familiar with my body, so I would stop bumping into things"

Marianna: "…the fatigue made it to where I didn't want to get out of bed and obviously, I couldn't stay that way forever once I started to recover. Fatigue, I feel like is going to be long term in my life."

Marianna: "…with all the chemo that I had for my initial diagnosis and also the PTLD has messed with my bones a lot. The calcium is really weak. I don't quite have osteoporosis yet, but I do have osteopenia. So, I am starting to lift weight, nothing crazy, just small weights, because that helps with bone strength."

Marianna: "I had to take quite a bit of time off of school and it did affect my self-esteem because a lot of the people I was supposed to graduate with are graduating right now actually and I'm a sophomore in my bachelor's program. I'm learning to be okay with it, but that's definitely hard for young people to feel like you're behind. I don't currently work full time anywhere because it's hard to find an accommodating job, and that can make me feel bad about myself at times too. Even though I don't currently have PTLD, the disabilities and effects are long lasting or permanent."

Marisa and caregiver

Rebekah: "…the PTLD side effects being in remission definitely does affect my ability to find an accommodating job and accommodating paid work and also legally identifying as disabled… And that includes owning a vehicle for transportation to get to work and things, that…affects low self-esteem and those kind of feelings…finding accommodations and access and transport and housing and in a career definitely has affected my life."

Ellen: "The only thing that has completely thrown me off of my ability to keep up with school and work is PTLD. And it's the reason that I had to watch all of my friends graduate without me... And as someone who has their entire life had to run twice as hard as their peers to go the same speed. And it was really hard to finally meet the disease that threw me off track. And I identify with what my peers have mentioned about self-esteem because I very much put a lot of my self-esteem into my academic performance."

Marianna: "I had a bone marrow transplant before PTLD, so that was what made my hair fall out, what made me thin and look sick. So, when I got PTLD after, and my hair started growing in and I was all healthy looking and glowing and put on weight. People were like, great. So, you can go back to school. Why are you at home? Why are you in bed? And now that I'm back at school with accommodations for PTSD, for cognitive difficulties, for fatigue, it can be almost embarrassing at times to admit that I need these still. People don't afford you the same things when the treatment and the illness don't make you look as sick or the disabilities afterwards."

Ellen: "Shortly after my PTLD diagnosis, I began losing weight rapidly. I had no appetite at all. I honestly found food repulsive at some points and I had been on TPN prior to that and I wanted to do anything not to go back to that. And I immediately began experiencing muscle wasting. I was losing weight so rapidly and it became something for me of a need for my team to work in a more interdisciplinary approach because my doctors very much were like, well, the medical answer is TPN, but I needed a solution that was more holistic to my quality of life."

Rebekah: "The appearance thing in cancer is so varied and so deep. And it hits on culture and religion and us as whole people. And the PTSD is a big part of why I fear getting cancer again because as you can see, going back to that time in my life is very hard."

NORD's Associate Director of Strategic Planning Ariel Markowitz-Shulman (left) and Director of Membership Debbie Drell (right)

VOICE OF THE PATIENT, TOPIC 2: CURRENT & FUTURE TREATMENTS

To understand the perspectives of people living with PTLD and caregivers regarding current and desired future treatments, a panel of patients/caregivers shared their thoughts and experiences. This was augmented by in-depth discussion with the audience members and by a poll of the broader audience on specific questions. Following the meeting, all attendees were able to submit additional comments via email for a period of 30 days. The objective of the session was to gain a better understanding of the pros and cons of current treatments, and then to develop patient-focused insights on what the community values most in the development of new therapies. The results of the patient voice activities from Session 2 are summarized below.

Session 2: Patient and Caregiver Testimonies

The full testimonies from each patient can be found in Appendix 2. Here are some of the most impactful comments made by each.

Erin (Parent/Caregiver):

"And it took a lot of tests and a lot of different teams coming in until they finally were able to diagnose him with PTLD. He had to undergo a bone marrow biopsy and a PET scan, both with anesthesia. These were really hard on him and his body and his mental health at the time as he wasn't feeling well. And he had gone through all of these procedures and surgeries or related to transplant. We were really at a time where he thought he would be healing and he just wasn't getting better and he wasn't feeling well."


Erin and Beau

"It also took Beau, I think, a longer time to heal mentally and physically from his transplant experience because of the compounded effects of the PTLD and all the medical interventions that went with it. And well, I was hoping he was going to be back in school and healing and starting his new life, he just had a major setback, which was hard on him, and also hard on me as his caregiver emotionally to see my kiddo go through such hurting and pain and unexpected medical procedures."

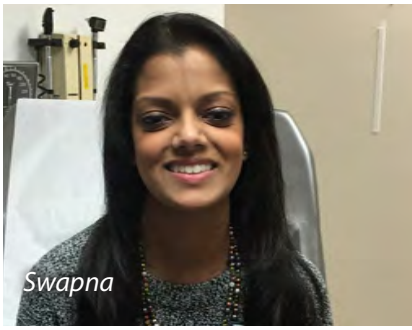
Swapna (Parent, 32 years old):

"I received 50 mg of IV Benadryl and IV rituximab was started. I received a rituximab infusion weekly for four consecutive weeks and one extra dose one month later. I was hospitalized for a week for the first two infusions."

"No one explained anything to me. During those days, I went to Dr. Google because the doctors were in and out of my room quickly with little details and I did not know what questions to ask. At that time, in 2014, there were no resources on PTLD catered to the patient and family community like there are today. I was desperate for information."

"I was consumed by the regimen. During the five weeks of infusions on Tuesday of every week, we would spend the day at the outpatient infusion center getting the rituximab and pre-medication of Benadryl. I would feel exhausted for the rest of the week. On good days, I started my day at 3:00 PM. I was

depressed. My caregiver, my dad, helped me to find at least one fun thing to do every day to get me out of the house. Always making sure to go to a place at nonpeak hours. If it wasn't for him, I would've never left my bed."


Swapna

"Before the PTLD diagnosis, I had to get multiple injections of Neupogen twice a week in clinic with no real boost in the count. Once I was diagnosed with PTLD however, my oncologist made an appeal to my insurance provider to cover Neulasta for my case. I received two Neulasta injections and my white blood cell count finally bounced back. The Neupogen and Neulasta injections caused scream worthy bone pain, where it felt like ice picks were stabbing me in the core of my bone. Despite the severe acute pain, receiving Neulasta saved me from multiple trips to clinic every week and constant chronic pain from repeated Neupogen injections that were not working well enough. It was a small win in this journey."

"Since my diagnosis of PTLD and regimen of rituximab infusions eight years ago, I have not had another encounter with the disorder. However, three months later due to immunosuppression, I was diagnosed with aspergillosis requiring voriconazole for six months and one year later with avascular necrosis in my hips and shoulders requiring joint replacements."

"Now, almost eight years out for my transplant, I do regularly think about the recurrence of PTLD and feel the heavy responsibility of being vigilant of finding it on my shoulders; because since one year post diagnosis, I have not had any screenings for PTLD. I actually had no idea PTLD could reoccur until I met other solid organ transplant recipients who have had it. I have a fear. What if it does come back? And what if it is not an early visible diagnosis like last time?"

"I hope treatments moving forward and their side effects allow me to keep on living outside of the hospital rather than consuming me, halting my life and energy for weeks and forcing me to be inpatient."

Brad (Patient, 51 years old):


Brad

"My oncologist told me that my PTLD could be treated for a time with an antibody called Rituxan, but the likelihood was that I would die in about a year. Needless to say, I was deeply distressed by this news and so was my wife. I had to take an early retirement also for my job as a college professor or risk losing my medical benefits, which were in danger of running out. However, my prognosis changed dramatically a month or so later when my oncologist at a conference learned about a new possible treatment, a clinical trial at Memorial Sloan Kettering sounded extremely promising. It was set up for people with my exact prognosis and boasted a remarkable cure rate of 66%. The side effects were said to be minimal and I met all the criteria."

"The logistics of being treated, however, were formidable, given my blindness and ongoing illness. I needed to fly from California to New York, live for nearly four weeks in an apartment and find my way to the hospital for weekly infusions. We were fortunate enough that we could afford the travel and the accommodations… We paid for the entire trip on our own, an expense many families would not have been able to cover."

"Today, I feel no ill effects from my PTLD and I've been able to resume my photophoresis in order to manage my chronic GDHD. I am still amazed at how rapidly I went from a terminal diagnosis to being declared cancer free. However, I know that I was very fortunate to have a family who could afford to travel to New York, rent an expensive apartment and put their lives on hold to help me through a third life threatening medical crisis. Others facing my predicament with fewer resources might not have been so lucky.

Michele (Parent/Caregiver):

"Kayla was looking forward to speaking to you, but unfortunately, at 29 years old, her life journey ended this past February 5th, 2022 due to complications from chronic rejection of multiple organ transplants."

"In Kayla's own words, in an email to her physician, when I receive the infusion, it makes me very sick. I have an intense amount of abdominal and back pain, itching, flushing, and overall feel very sick. I was premed with IV Benadryl, another dose in the middle of the infusion, and one last dose at the end of the infusion. Also, at the start of the infusion, until the end, I received IV pain meds, every two hours to help alleviate the pain. This all barely took the edge off, but helped."

"The evening of each subsequent infusion and into that next day, her back pain was excruciating, which left her curled up in a ball. The back pain, nausea and fatigue made it so that she was unable to sleep or function for that treatment day or the next. Kayla's symptoms gradually improved over the course of the next week or so from the infusion. This created anxiety as the upcoming treatments got closer because Kayla knew she would feel miserable and there was another uphill battle to conquer. How could you not have anticipatory anxiety knowing that you are going to walk into an eight-hour medical visit full of horrible pain, fatigue, and nausea that was unbearable?"

"When most transplant patients receive the diagnosis of PTLD, they are at their most vulnerable, the most sick, the lowest of reserves. Understanding the side effects that can occur, even though the medication does help, is daunting to say the least. Kayla told myself and others that she hoped new treatments would have much less side effects as it's difficult to wrap your head around how much more sick you will become before you get better."

Kayla

Ola Ojewumi (Patient, 30 years old):

"I met with oncologists and even got a second opinion at another hospital. Surprisingly, my oncologist chose to wait several years to treat my PTLD with immunotherapy. Apparently my PTLD was not advanced enough to treat yet. I was required to have yearly scans at Johns Hopkins Kimmel Cancer Center to monitor the expansion of my cancer with growth."

"The doctors did not provide any support or resources like information about potential clinical trials. They treated my cancer diagnosis completely cavalierly. It wasn't until I reached age 25, that my Hopkins medical team decided to pursue treatment with a drug called Rituxan. This was perplexing because I believe that in most cases, doctors prefer to start cancer treatment the moment cancer is detected."

"During cancer treatment, my clinicians never spoke with me about treatment outcomes for African Americans or provide research to learn more about the drug. I was hesitant to ask about race and ethnicity, because discussions about race is seen as taboo in society. I was afraid my concerns would be dismissed or seen as insignificant. Representation matters when it comes to clinical trials for cancer treatment. For example, during my treatment, I wondered how I would respond to it and if it would be effective for people who looked like me.

Sarah (Parent/Caregiver):

"The first rituximab infusion sent him into anaphylactic shock, his airways swelled up. This was a very scary moment for my husband and I, and what made it worse was knowing that they were going to have to try again."

"Everett was also on prednisone, which brought about the worst symptoms. There was insomnia, there was agitation, there was hair growth everywhere, he had weight gain, he had fatigue. Because this PTLD was caused from his transplant medications, he was no longer able to take those anymore, and prednisone was given daily. Therefore, all these symptoms were even worse."

Greg and Cyndi (Parents/Caregivers):

"Chemotherapy can't safely be administered fast enough in cases such as Marisa's where PTLD rapidly advances and encroaches upon the brain. US FDA approval of immunotherapy would eliminate the required screening period for patients such as Marisa who desperately need an alternative approach to conventional treatment."

Ellen (Patient, 26 years old):

"The high doses of rituximab immediately post-transplant left me with hypocellular bone marrow that has to regenerated properly. With the assistance of intravenous immunoglobulin, or IVIG, dosed every four weeks I still can't maintain an IgG level over 500, and my oncologists and immunologists don't know if I will ever be able to get off of the IVIG or if we have permanently broken that part of my immune system, because of how they had to treat the PTLD."

Session 2: Polling Results

The following is a summary of the polling results from Session 2. For a full description of the polling questions, see Appendix 3.

Select the medications or supportive treatments you use or have used for PTLD. (Select ALL that apply)

The most common answers to this question included Benadryl, steroids, or Rituximab (80%), pain relievers (67%), chemotherapy (50%), Neupogen (42%), and Claritin for drug-related bone pain or Neulasta (33%). Only 8% reported having received treatment with radiation.Discussion Question from FDA: If you were told you ineligible for a trial, what was the reason? And was expanded access ever considered or presented as an option to you?

How well does your current treatment regimen reduce the most significant symptoms of your PTLD?

While 11% of participants reported that their current regimen reduced their symptoms very well or moderately well, the majority of respondents (78%) do not currently receive any treatments.

What is your experience in, and perception of, clinical trials for a new PTLD drug?

Most respondents had not participated in clinical trials. Overall, 67% answered that they didn't know about clinical trial opportunities and 25% reported that they were not eligible. Only 8% had participated in a trial and would do so again.

Of the following factors related to a test drug in a clinical trial, select UP TO FIVE that you rank as most important to your decision about participating in a clinical trial.

The most common responses to this polling question included whether current disease management and treatment regimens would need to be stopped (91%), potential side effects from a new drug (91%), whether the drug is supposed to treat symptoms or the underlying cause of the disease (64%), distance to trial site (55%), and whether there is a chance of receiving a placebo (36%).

Which factors are the most important to you when deciding to select a new treatment or drug for your PTLD? (Select top THREE)

Respondents ranked the following as most important to be addressed by a new drug treatment: severity of side effects known for the drug (89%), whether the drug will improve my PTLD (78%), and evidence that the drug improves specific symptoms most bothersome to you (67%).

Without considering side effects of a drug, which ONE of the following would be most important to you in a future therapy for your PTLD?

In response to this polling question, 70% of respondents chose evidence that the drug will significantly extend lifespan as the most important aspect of a future therapy and 30% chose evidence that the drug will significantly decrease the complications of PTLD.

Session 2: Facilitated Discussion

The following is a sampling of insightful comments that were made by panelists or submitted by the broader attendees during the facilitated discussion.

How well did your treatment regimen impact the most significant symptoms of your disease?

Sarah: "The first rituximab infusion sent him into anaphylactic shock, his airways swelled up. This was a very scary moment for my husband and I, and what made it worse was knowing that they were going to have to try again."

Sarah: "Everett was also on prednisone, which brought about the worst symptoms. There was insomnia, there was agitation, there was hair growth everywhere, he had weight gain, he had fatigue. Because this PTLD was caused from his transplant medications, he was no longer able to take those anymore, and prednisone was given daily. Therefore, all these symptoms were even worse."

Cyndi: "Chemotherapy can't safely be administered fast enough in cases such as Marisa's where PTLD rapidly advances and encroaches upon the brain. US FDA approval of immunotherapy would eliminate the required screening period for patients such as Marisa who desperately need an alternative approach to conventional treatment."

What are you currently doing to treat your condition or its symptoms?

Swapna: "I've been in remission. But if you want to say, I take regular immunosuppression to protect my organ, that includes immunosuppression medication, as well as prednisone. I take that daily."

Ola: "I actually get my yearly scans done at Johns Hopkins Kimmel Cancer Center to monitor the growth. And it seems to be decreasing in size every year. So, that's how I'm managing my condition."

Erin: "My son also takes immunosuppressant medication every day, and then we monitor monthly for the EBV virus. And it's just always on my mind how I can keep him the safest and the healthiest, and we're always hand washing and mask wearing and just being super careful out and about in the world. So really we focus on the prevention and make sure he eats really well."

Brad: "I don't currently take any treatments for my PTLD. I'm considered to be in remission, if not cured. They do monitor all my blood levels. And occasionally, I have high levels of EBV, which is the sign that my PTLD might be coming back. But honestly, I'm far more concerned with not getting sick from whatever virus is handy or a pandemic, or I'm managing my chronic graft-versus-host disease symptoms, which are much more present in my mind."

Ellen: "The high doses of rituximab immediately post-transplant left me with hypocellular bone marrow that has to regenerated properly. With the assistance of intravenous immunoglobulin, or IVIG, dosed every four weeks I still can't maintain an IgG level over 500, and my oncologists and immunologists don't know if I will ever be able to get off of the IVIG or if we have permanently broken that part of my immune system, because of how they had to treat the PTLD."

Did you or your family experience any barriers when accessing treatment?

Ola: "It was only up until interacting with other people in the PTLD community that I learned how severe PTLD was. My team treated it so cavalierly and I don't know ... I would say the barrier to treatment is having oncologists and doctors who don't treat it as a pertinent issue and not seeing the seriousness and the emergent, and to be honest, how deadly the disease was."

Michele: "…you have so many different doctors and then they have their own particular ideas of how you should or shouldn't be treated, even though it seems like there's pretty much a standard of care. One doctor wanted to do this treatment this many times and another one wanted to do it at different amount of times. One doctor said, "Yes, you could have pain medications because it is painful." The other doctor said, "Oh no, you can't have pain meds because it's not painful." So, there was some of that kind of back and forth, which wasn't necessarily an obstacle to care, but it was an obstacle in the getting of the care. And when you're super sick, that's disheartening to say the least."

Erin: "I do feel like it took a while to get a diagnosis… I kept kind of calling in and everyone was saying, "Yeah, that's pretty normal." And it felt like it took a long time to really be kind of taken seriously that he wasn't getting better. And then once we were admitted to even properly diagnose him and I bring this up because I did hear at that point that EBV can be kind of a silent disease or it's hard to diagnose. It's hard to find sometimes. And I think that's an important point when talking about PTLD is this, if you're not kind of lucky enough to have some really overt symptoms or even if you do, it's difficult to catch it. And so, I feel like it took a longer than it should to find it."

Swapna: "I also had difficulty in getting access to one treatment, which was Neulasta. After the PTLD diagnosis, my white blood cell count dropped. After transplant, my white blood cell count dropped and then it dropped even more after the PTLD diagnosis. And we were continuing to give Neupogen injections regularly in clinic, two to three times a week, multiple injections. And it wasn't doing anything to the white blood cell count. It was only after the oncologist appealed to the insurance provider to cover Neulasta did it really bounce back. And I only needed two injections and thankfully, only needed two injections because the insurance provider wouldn't cover anymore."


Brad

Brad: "I'm still very surprised that I went from hearing from my primary trusted oncologist that I had about a year to live to a matter of a couple of weeks later him saying, "Well, I went to this conference, you see. And gee, they have this clinical trial that's absolutely perfect for you. And you stand an excellent chance of being cured. I mean, I wonder what would've happened if he hadn't gone to that conference. And it seems from people's responses that this is not an unusual state of affairs, that people don't seem to be aware of clinical trials that are going on."

Brad: "I think this actually touches into a much bigger issue in the transplant community in general, which is that, compared to the European model, as I understand it, where there are fewer transplant centers, but they are all full-service transplant centers… And they would have, then, ideally, a specialist in PTLDs as well, who would be up on the research. But in this country, there are a ton of places doing transplants that, honestly, maybe shouldn't be because they don't have the infrastructure and they don't have the expertise in all of the transplant complications."

How has your treatment regimen changed over time and why?

Ola: "I will say that because my doctors weren't particularly concerned with my PTLD, I stopped getting my scans, and I ended up hospitalized. And they did a CT scan or whatever and they're like, "Your cancer is worsening. You have to get treatment." So, I actually go for my yearly scans now… I actually care more."

Swapna: "I think in the cancer community, there's something called scan anxiety, 'scanxiety'. I can relate, and I think it's applicable to this community as well. In terms of my treatments, I got the rituximab for four weeks consecutively, and then, another week a few weeks later. And then, I got a PET/MRI one year later to make sure it was still in remission. And in that PET/MRI, I got an incidental finding of avascular necrosis in another joint. So, I don't love... I don't have good memories of doing whole body scans, because when you go looking, you may find something. I was a complex case, I am a complex case, I will be a complex case is what I always say."

Swapna: "I didn't even know it was a cancer or terms like remission could be used… and had no idea of the severity of it… If you search PTLD in our support group, it's quite remarkable, the spectrum of treatments and experiences that I was pretty naive to in just my own journey."

PRELIMINARY BENEFIT-RISK FRAMEWORK PROPOSAL FOR PTLD

Benefit-risk assessment is the foundation for the FDA's regulatory review of human drugs and biologics. These assessments capture the agency's evidence, uncertainties, and reasoning used to arrive at its final determination for specific regulatory decisions. Additionally, they serve as a tool for communicating this information to those who wish to better understand the FDA's thinking. Background and guidance on benefit-risk assessments can be found at the following link:

https://bit.ly/Risk-Assessment-FDA

The input provided by people with PTLD and their caregivers at the EL-PFDD meeting was used to prepare the preliminary benefit-risk table on the next page. This is a sample framework that is intended to provide an understanding of the benefit-risk aspects for two of the key decision factors, analysis of condition and current treatment options, that factor into the benefit-risk assessment. This sample framework is likely to evolve over time and could be incorporated into a benefit-risk assessment framework for a drug under review.

Sample Benefit-Risk Framework for Post-Transplant Lymphoproliferative Disorder

DIMENSION	EVIDENCE AND UNCERTAINTIES	CONCLUSIONS AND REASONS
Analysis of Condition	Post-transplant lymphoproliferative disorder (PTLD) is a rare complication of solid organ transplants and hematopoietic stem cell transplantation that is highly associated with immunosuppression therapy and the Epstein-Barr virus. Some affected individuals develop a mild, noncancerous overgrowth of affected tissue while others develop a cancerous, life-threatening form of lymphoma The specific symptoms and severity of PTLD can vary greatly from one person to another, but often include: • Extreme fatigue • Psychological/emotional issues (e.g., PTSD, anxiety) • Loss of appetite • Headaches • Pain at multiple sites PTLD patients and their caregivers are most concerned about: • Infection • Rejection and relapse • Immunosuppression • Access to medical care • Development of post-PTLD lymphoma or recurrence • Failure of first-line treatment PTLD patients experience a ve ry high level of anxiety and depression and social stresses such as isolation and low self-esteem.	PTLD is a complex condition associated with a wide variety of serious symptoms. • Initial signs of PTLD are often confused for symptoms of underlying conditions, complications of transplant surgery, or side effects of medications. • The complexity of PTLD and its treatment can exacerbate existing disparities in access to care and clinical trials. • The pain and fatigue caused by PTLD and its treatment are severely debilitating and often accompanied by myriad other symptoms and side effects. • Most people living with PTLD continue to experience long-term effects related to the disease and its treatment. PTLD is often diagnosed after a difficult medical transplant journey, which leads to unique challenges and a variable benefit-risk profile. • Diagnosis of PTLD can lead to significant trauma, anxiety, and financial stress for already overburdened patients and families. • All people living with PTLD have some sort of comorbidity. Most patients have many. • Communication about PTLD is often confusing and unclear, with many patients unsure if they are undergoing treatment for cancer. • Finding other patients with the same combination of diagnoses is extremely difficult.

Sample Benefit-Risk Framework for Post-Transplant Lymphoproliferative Disorder

DIMENSION	EVIDENCE AND UNCERTAINTIES	CONCLUSIONS AND REASONS
Current Treatment Options	The primary goal of treatment is to cure PTLD, while preserving the function and health of the transplant. While initial treatment strategies vary based on PTLD subtype, current standard of care includes some combination of immunosuppression reduction, with or without single agent rituximab in early B-cell PTLD, and then R-CHOP chemotherapy. The most common medications and supportive treatments for PTLD include: • Benadryl (intravenous, oral, or other) • Rituximab • Steroids • Pain relievers (prescribed, OTC or other) • Chemotherapy • Neupogen • Neulasta • Claritin (for drug-related bone pain) • Radiation	The few treatment options for PTLD are further limited by complications with patients' underlying conditions and unique comorbidities. • Immunosuppression reduction, an effective approach to treat PTLD, increases risk of transplant rejection. • Existing treatments often lead to life-threatening complications due to an already weakened immune system. New treatment or drugs should: • Improve survivability of people living with PTLD • Reduce side effects • Ensure continued function and health of transplants • Improve specific symptoms, including those that present long-term Access to care and coverage are critical since PTLD presents after an already costly medical odyssey.

CONCLUSIONS

On May 4th, 2022, NORD hosted a virtual Externally-Led Patient-Focused Drug Development (EL-PFDD) meeting. In attendance were patients, caregivers, government officials, health care providers, industry representatives, patient advocates, and others. The EL-PFDD meeting was an opportunity for patients and families to inform the FDA, drug developers, and other key stakeholders on the true burdens of living with post-transplant lymphoproliferative disorder and how patients view the benefits and risks of treatments.

The meeting was successful in bringing the voices of patients and caregivers to the FDA and other stakeholders who are critical in ensuring that this diverse patient population receives effective treatment and holistic care. At the conclusion of the meeting, Rebekah Palmer summarized the impact of the meeting:

In addition, Debbie Drell, Director of Membership at NORD, shared these parting words:

> "There have been some tears. There have been some moments of joy and a lot of honest storytelling. This disease is brutal, but our families and our community are strong and courageous. We're so grateful for what you shared. For those living with the disease and for future generations, we know this meeting will help bring better treatments, better options, and more hope to change our lives."

"I realized I needed better care than I received. I deserved more information and preparation for how my body and mind might be impacted after my PTLD diagnosis. It's important to remember how receiving an intense and complex diagnosis like PTLD at a young age can impact a patient's ability to process emotions and even result in medical trauma."

Rebekah Palmer

APPENDIX 1: REFERENCES AND RESOURCE MATERIALS

The full recording of the PTLD Externally-Led Patient-Focused Drug Development meeting can be found at the following link to the NORD website:

bit.ly/NORD-PFDD-PTLD-Meeting

This site also contains the meeting agenda and the following slide presentations:

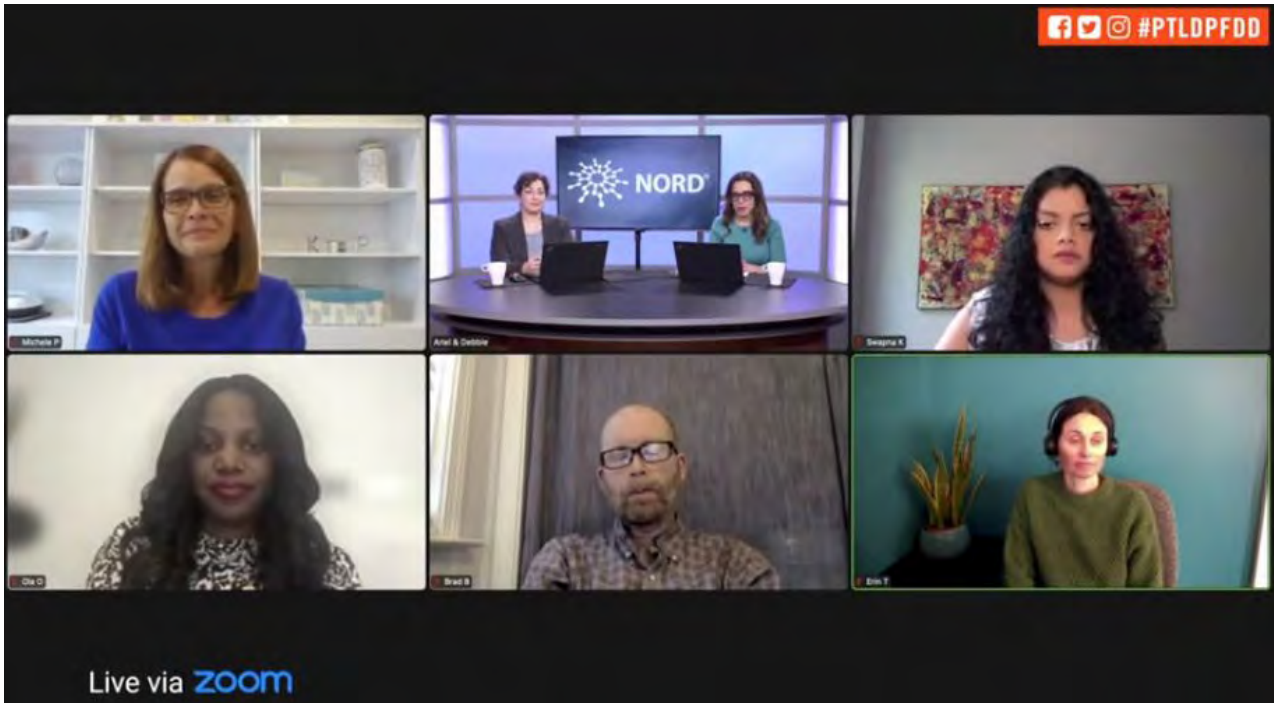
bit.ly/NORD-PFDD-PTLD-Agenda

Clinical Overview of Post- Transplant Lymphoproliferative Disorder (Thomas M. Habermann, MD, Division of Hematology, Department of Medicine, Mayo Clinic)

https://bit.ly/FDA-PTLD-Habermann

For more information on post-transplant lymphoproliferative disorder, please see the information posted in the Rare Disease Database on the NORD website:

bit.ly/NORD-PTLD-Video



APPENDIX 2: FULL PATIENT AND CAREGIVER TESTIMONIES

Session 1: Living with Post-Transplant Lymphoproliferative Disorder—Burdens and Symptoms

Ellen, patient:


Ellen

"My name is Ellen Louise Keyser, and I currently live in Sun Prairie, Wisconsin with my husband and our two cats. I've lived in the rural Midwest my whole life, I was born in Missouri and raised in Iowa. I'm 26 years old and I have lived 26 of those year with a primary immune deficiency and refractory systemic autoinflammatory diseases, not to mention all of the iatrogenic side effects from nearly a decade of steroids and chemotherapy to treat said diseases, and ovarian tumor at 23 and a bone marrow transplant at 25.

In January of last year, I was one week shy of being six months post bone marrow transplant when I was told that I had Epstein-Barr virus positive PTLD. I'd have a rough transplant and hit a lot of speed bumps along the way. After transplant the biggest of them had been facing delayed immune reconstitution. To make matter worse, my insurance had refused to cover a donor lymphocyte infusion, which meant that I hadn't gotten one despite my oncologist's best attempts.

All that being said, to tell that I wasn't in really a great place to go into more chemotherapy at that time. There wasn't much to obliterate to begin with, and only six months out from transplant this felt more like driving off a cliff that hitting yet another speed bump. At that point in time lymphoma hadn't even been on my radar. I was worried about GVHD, graft failure, infections, the normal things, so to speak. However, a whole cancer hadn't even crossed my mind.

At the six-month mark I was just starting to look forward to things like removing a few medications, eating some new foods, or seeing my husband again, as he was working in an emergency room at the time and with no COVID vaccine at that point I had to be isolated from him. Suddenly all of these hopes were thrown out of the window and I was thrown back into survival mode.

The first sign that something was amiss was the fact that my EBV level came back positive. It came with symptoms of mono, exhaustion, sore throat, fever. In the first four days after the EBV initially came back positive, the EBV level in my blood increased 266% and I went from symptomatic of mononucleosis to lymph nodes swollen across my entire body. In another three days I was hospitalized with masses appearing in my lungs on CT and nearly delirious from pain.

When all was said and done I was diagnosed with EBV positive high grade B-cell lymphoma with plasmacytic differentiation. Radiation was off the table due to the fact that it would likely kill the new donor cells completely. It was decided that the only viable option that insurance would cover at that time was high dose rituximab. If that failed, I would have to find another clinical trial and hope to undergo T-cell therapy.

After nearly two years of fighting insurance to cover my transplant, failing and receiving life-saving treatment only via the charity of the hospital, I felt hopeless. I had fought so hard to get access to life-saving treatment, in this case a bone marrow transplant, and I wasn't I had the strength to fight all over again. Rare disease meant that I had fallen through the cracks in the system, and I felt like I was poised to slip through yet again.

In the end I received six weeks of high dose rituxan. I thought I would start to recover but there were more complications. At the end seventh week I was admitted to the clinic feeling unwell and my oncologist recognized the warning signs of a thyroid storm, which they now believe was triggered by the rituximab. I spent that night alone in the hospital crying and delirious as nurses filled my bed with ice in attempt to bring down a fever that ranged up to 106, and failed to respond to any medications. After another week of hospitalization, I was able to return home and begin recovering for the third time.

I don't have many clear memories of that period in the hospital, I journaled daily but I had violent tremors and the words aren't legible, even to me, in many places. I remember there being a lot of pain and describing my lymph nodes in my head and neck as feeling as if they were marbles made of glowing hot glass. I remember slipping in and out of waking as my mother read aloud to me, trying to distract me from the pain. And I remember being isolated.

There were times when there no visitors allowed and I remember begging a nurse not to leave me alone, telling her that I was scared even as she left the room because she had to care for her next patient. I had my first clean scan at the end of April last year, and I celebrated my one-year post-transplant anniversary, and by the time you're watching this video I will have just passed my one-year anniversary of that first clean scan post Rituxan.

The high doses of rituximab immediately post-transplant left me with hypocellular bone marrow that has to regenerated properly. With the assistance of intravenous immunoglobulin, or IVIG, dosed every four weeks I still can't maintain an IgG level over 500, and my oncologists and immunologists don't know if I will ever be able to get off of the IVIG or if we have permanently broken that part of my immune system, because of how they had to treat the PTLD.

The future is unknown and if this is the rest of life so be it, but I can still hope to fully recover some day. For now, all I can do is wait and keep getting my infusions, and keep my fingers crossed. Going into transplant I had a primary encase cell deficiency, and now I have a secondary immune deficiency. For me, PTLD and the lack of treatment options directly post-transplant means that I've traded one form of a disease for another form of the same disease, and the disease that I went through the hell of transplant to try and escape.

My hope for PTLD patients in the future is that treatment doesn't mean sacrificing a full recovery from whatever the primary disease was. Thank you."

Marianna, patient:

"Hi, my name is Marianna De León and I live in Dallas, Texas. Two days after I turned 21, I found out that I needed a bone marrow transplant. I thought that this would be the worst thing to ever happen to me, but I had no idea what I was about to go through beyond my worst nightmares. Later that year, not long after my transplant, I started crying out in pain and knew something was seriously wrong. My pain tolerance is high, but the large painful bumps on my head and neck were too much for me to handle. I'd crawl into bed to try to find some relief only to wake up drenched in sweat with a fever. We rushed to the hospital where I was quickly given my life-changing diagnosis. I was diagnosed with stage three, PTLD. My transplant journey went from cautiously optimistic to unstable and uncertain.

I didn't know how to go home and tell my loved ones. We had such high hopes for my recovery from bone marrow transplant. And now I had this crushing news to share. What little independence I had started to gain back, I lost it in an instant with this diagnosis. I was no longer just recovering from a bone marrow transplant. I was now fighting off this rare little-known cancer with a new weak immune system. PTLD robbed me of what little energy I had after my bone marrow transplant. I used every last drop of it going between my home and inpatient hospital stays. Moving from bed to bed sounds pretty easy for a healthy person, but sometimes I cried and threw up just from having to move at all. Most 21-year-olds celebrate their independence, but I was holding onto the bar in my shower while my mom washed my hair and my dad drove to pick up my prescriptions.

It felt like I was the only person in the world moving backwards, completely uncertain of the future. I had only planned to take one semester off when I had found out I needed my bone marrow transplant, but I ended up taking off three. I actually missed being worried about graduating college and finding a job because it seemed so much easier than worrying about what to do if chemo didn't work. The one type of chemotherapy that my doctor approved for my case was difficult to get prescribed to me because my insurance provider was not sure that it would be successful. There is not a standardized treatment for PTLD, which also made my insurance provider hesitant to approve any risky treatments. This chemo treatment required me to be inpatient for over a week at times, making my life outside of PTLD, take a backseat.

I often had to get my outpatient infusions without my mom who was also my caregiver. The only way they would let her be with me when I was inpatient was if she got a negative result on a COVID test and promised not to leave the unit I was in until I was discharged. I couldn't see my dad or brother at all in person until I got home. And even at home, they couldn't be in the same room as I was unless they were masked and being very cautious. Being in and out of the hospital meant not seeing my dog very much either. I cried thinking about how I couldn't pet him or even see him while my fragile immune system endure treatment. I did not have the strength to stay awake very long, meaning that even online school was off the table for me. And I couldn't see my friends in person, but I also didn't have much energy to call or text him regularly. So I was very isolated.

What's more as the chemo cause an allergic reaction that was so unbearable. I needed more treatments just to get through my treatment. My skin broke out in rashes, so itchy and painful. I felt like I was on fire for days. My skin was bright red on my torso and extremities. And the only thing that brought me relief was a combination of Benadryl, steroids, anti-itch medications, and bags of ice all over my body constantly. The combination of medications I was on to combat my reaction caused severe restlessness that led to me

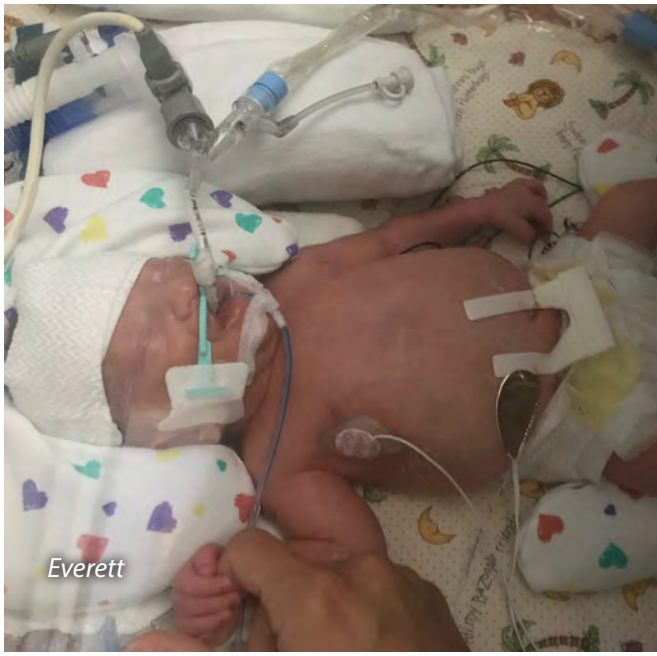
feeling intense anxiety. My heart would pound relentlessly, and I would have panic attacks that required me to need even more medications. I received a pet scan a few weeks after my last rituximab infusion, and to everyone's surprise, there was no signs of PTLD on the scan. I continued to get scans every few months for about one year and when all the results were negative, I finally felt comfortable saying that I'm in remission. Cancer treatment is never fun, but going through it during a pandemic where I was alone in pain and with no one to hold my hand and comfort me most of the time has permanently altered me. I still have panic attacks and nightmares about having to endure it without my loved ones next to me. I struggle with PTSD from my traumatic experiences related to PTLD and still undergo treatment for it to this day. After I have a panic attack, I'm often so exhausted that I have to lay in bed for the rest of the day. I still feel physically ill when I remember having to sit in ER waiting rooms full of people, coughing and sneezing while I close my eyes and hoped that I wasn't risking my life by putting my new immune system to the test.

There wasn't a day where I didn't think about my PTLD and wonder if I was going to survive or pass away and leave nothing behind but a stack of bills. When I go to my cancer center for my routine check-ins, I still burst into tears on my way home. And I don't know that will ever stop. I often see people carefree without a mask on, but I'm so terrified of getting sick and needing to go back to the hospital. So, I'm very cautious. I finally went back to school, but I fear for my health every time I have to sit in a classroom. I still wonder if my PTLD may return someday or if my body will suffer more complications from the treatment. I still have to monitor my calcium because my bones are very weak after treatment. I experience a lot of weakness because I spent a lot of time unable to exercise much.

It took me a long time to get back into shape and I still don't have the fitness level I had before PTLD. My fatigue has improved, but not very much. And I often feel as exhausted as I did when I was sick and getting chemo. I am beyond happy to have had the amazing and unexpected gift of going into remission, but I will always bear the scars of not only my PTLD but the harsh, traumatic treatments I needed to survive it. Thank you for listening."

Sarah, caregiver:

"Hi, I am Sarah O'Connor and I'm mom to Everett, a beautiful 3.5 year old boy. Everett has been battling kidney disease since before he was born. He was born 10 weeks premature and began dialysis at day 3 of life.


Everett

Four months post kidney transplant was the first cancer scare. Everett was diagnosed with Epstein-Barre Virus (also known as EBV), and the fear was that he had developed PTLD. That was the first time we had even heard of this cancer and that it was something caused by the transplant medications. At the time, Everett had a swollen lymph node in his neck and swollen tonsils which was causing sleep apnea. A CT scan was performed and determined that the nodes were small enough to rule out PTLD. A few months later, Everett was back in the hospital with rectal bleeding. While ruled it was from an ulcer, it was a fear of ours that the EBV spread to his gut, and turned into cancer

A few weeks passed and Everett began to throw up 1-2 times a day which lasted 6 weeks. He was hospitalized again and at this point I noticed a tender spot on Everett's abdomen which became unbearable for him.

Everett had to be transferred to the hospital that sees him for his transplant care. There he ended up undergoing his 31st surgery at only three years of age. During this surgery, Everett lost parts of his intestines when they removed several masses. We were just glad that he did not have to have a colostomy AGAIN. When the surgeon came to speak to us, he told us they would be sending the masses off to be biopsied but that he was certain it was PTLD. CANCER. At that point it was basically clarified that our child, who has already been fighting for his life his entire 3 years, was now going to have to battle this devastating disease.

Everett began chemotherapy and weekly rituximab infusions, the first of which sent him into anaphylactic shock and his airways swelled up. It was a very scary moment for my husband and I, especially knowing they would have to try again.

Everett was also on prednisone which brought the worst symptoms of insomnia, increased agitation, hair growth (everywhere), weight gain, and fatigue. Because this cancer was caused by Everett's immune suppression drugs, he had to be taken off both of those and placed on a daily prednisone dose as well making his side effects a little worse.

Receiving this diagnosis affected so many other aspects of our lives-financially, economically, emotionally.

We are a one income family which is already difficult when a disabled child involved and now we are having to add more travel expenses for Everett's treatment.

At the time of diagnosis, Everett was beginning school for the first time. This was already scary due to him being immunocompromised from his transplant, a pandemic going on and this would be the first time he was in someone else's care and around children who most likely don't understand why he is different. Now he would also be missing lots of school for treatment.

Everett's diagnosis brought on a whole new level of fear and anxiety for me. Will I ever be able to return to work to help pay the bills? Will our son ever have a chance to find out what life outside of the hospital is like? Is anyone going to be able to assist me with the next trip to Chicago? Is Everett's older brother, Declan, beginning to resent me for having to spend so much time away and for having to focus more on his brother? Will I ever get to connect with friends again? Is my family going to start resenting me for always asking for help? When is Everett going to catch his break?

We are extremely grateful for our family and support system. They are always willing to help us out but sometimes that means that not only do our lives get put on hold once again, but their lives are placed on hold as well in order to help us. There is so much guilt that comes with needed to ask for all the help and knowing we are not able to return to favor at this time. We just pray that they know how much it means to us.

Everett has finished his chemotherapy and has been cleared as of his last CT scan. While we are extremely excited about this news, the effects of his diagnosis still linger. Because of PTLD, he will be on less immunosuppressants than before which means we must watch his kidney function with a new fear of rejection and that his cancer may return. These fears will never go away.

Thank you for letting me share our family's experience with PTLD.

Rebekah, patient:

"My name is Rebekah Palmer and I am from Boyceville, WI and am in my mid-thirties. I'd like to take you back to my twelfth year of life. I already have a diagnosis of cystinosis since kindergarten, a rare metabolic disease that has affected my kidneys most severely in my body first. I struggle with gastric reflux as well, which is common with my condition. My kidney transplant takes place June 24, 1999 the summer between my 6th and 7th grade academic years. It is a success with a few bumps of reversing mild rejection and this continuing fatigue that should have been resolved with a now working kidney. As my 7th grade year in a fundamentalist Baptist school heads into October and November, I am experiencing many missed school days again along with aching in my throat and left ear soreness.

An ear, nose, and throat doctor tells my mother I have behavioral problems as I shouldn't be this whiny and tearful at my age and starts inquiring into her relationship with my father. By December, my mother is wrung emotionally as I keep her awake with audible sounds of pain as well as my nine-month-old brother who isn't sleeping through the night just yet. She feels like too much is on her plate as primary caregiver for her three children. We go to a chiropractor who says my lymph nodes "feel like hamburger", as in the ground beef meat. My mom calls the transplant center and relays the behavioral analysis of the ENT and what the chiropractor says. My coordinator gets us to the hospital where my kidney transplant took place within three days and they complete a biopsy.

I have B Cell Lymphoma cancer. In the transplant handbook we were given in the summer it said one out of ten kidney transplant patients get some sort of cancer. I end up being the one out of those ten transplant patients. I am diagnosed with PTLD on December 17, 1999. I hear the doctors discuss the 3 months to 3 years life expectancy but I also heard my parents in discussion when I was diagnosed with cystinosis that I would die between ages 9 and 12 and I am 12. Life only exists in now and never later in my mind. Much is left unclear about how PTLD might impact me.

Emotionally, I feel numb. I watch the Nanny and Little House on the Prairie. My hair falls out and I focus on these shows in reruns. I am being given chemotherapy. Little to no effort is made to prepare me for the painful effects of chemotherapy, especially gastrointestinal. I stay at the hospital for a week at a time when I receive the drug through a Hickman.

My mom and my youngest brother are the most frequent visitors as my father works two jobs now to cover medical expenses and my middle brother is involved with wrestling and school and friends of the family and relatives look after him.

There is a psychologist who comes and visits me periodically but I don't know what to say to him. He typically comes and just sits in my room when I'm sleeping. I know this because the nurses tell me he was there.

He doesn't talk much to me when he is there. And I don't want to talk about my treatment and my cancer. I don't know how to start but I want to talk to the psychologist about the sex abuse I went through as a five-year-old. The father of the teenage male who sexually abused me is the stand-in youth pastor until my church and school hires someone else. And his son is in the youth group. Which they keep coming to sing to me in my hospital room and I can't even focus on songs meant to encourage me when their all in the room.

At this time, I am also struggling with figuring out my identity as a gay Christian. This, along with trying to process my abuse, impacts my ability to process and heal from PTLD. My hair has all fallen out and I feel so good in a body with a short haircut. I go into remission in May of 2000. The stress and effects of chemotherapy continue to impact me. I am diagnosed with irritable bowel syndrome (IBS) at 20 years old, and then gastroparesis at 25 years.

Almost 20 years later after PTLD, I attend an ad-hoc PTLD group in Texas, where I meet Debbie Drell, from NORD. This is the first time I acknowledge all my intersections and can better understand the full impact of PTLD on my life. Due to the emotional, medical, and mental trauma I experienced during my time with PTLD, I still go to a behavioral therapist and a trauma educated psychiatrist for general anxiety disorder, moderate depression, and post-traumatic stress disorder. I see a long-term cancer doctor annually for preventative healthcare involving my bladder and heart. I realize I needed better care than I received. I deserved more information and preparation for how my body and mind might be impacted after my PTLD diagnosis. It's important to remember how receiving an intense and complex diagnosis like PTLD at a young age can impact a patient's ability to process emotions and even result in medical trauma. This aspect deserves just as much attention and care as our physical diagnoses. Patients living with PTLD deserve holistic care. Thank you for your time.

Greg and Cyndi, caregivers:

"Good afternoon. My name is Greg Tufaro. I live in Edison, New Jersey.

My beautiful daughter, Marisa Rose Tufaro, whose life PTLD claimed when she was just 13 years old, had unlimited potential. She was an honor roll student, student council vice president and served on the Youth Advisory Council at Children's Hospital of Philadelphia. Involved in myriad extra-curricular activities, Marisa took dance classes, received vocal lessons, performed in school plays, and was a gifted artist. After a fire destroyed her elementary school, Marisa spoke on camera to reporters from major New York City television stations. As the daughter of a sportswriter, she conducted an extensive video interview on Bring Your Child to Work Day for USA TODAY NETWORK New Jersey with Karl-Anthony Towns, the NBA's 2015 No. 1 overall draft pick.

Marisa was intelligent, articulate, funny, charismatic, obstinate, sympathetic, feisty, determined, creative beyond words and, most importantly, loved. Despite mounting medical issues, she approached life with unjaded innocence and a positive outlook. Born with a complex cardiac defect that required six open-heart surgeries, Marisa developed two life-threatening conditions – protein-losing enteropathy and plastic bronchitis – that necessitated a heart transplant. Marisa was 12 years old when she underwent a complicated 19-hour transplant. Her bypass run is believed to be the longest in the history of a pioneering children's hospital, which conducted the nation's first successful pediatric heart transplant nearly four decades ago. With precocious strength and courage, she navigated a 73-day long postoperative recovery, which commenced with more than a week of ECMO and included well over a month in the cardiac intensive

care unit. Watching Marisa fight for life while on a ventilator and tethered to cardiac wires and intravenous lines amid the sporadic beeping of monitors breaking an otherwise eerie silence in a cramped hospital room was emotionally disturbing.

Miraculously nursed back to health following a grueling journey, Marisa was discharged in September 2016 with the promise of a new life on which an insidious disease cruelly reneged. Less than four months after her heart transplant, Marisa contracted PTLD, which proliferated her body and brain. Following a valiant battle, Marisa succumbed to her illness in January 2017.

Despite being hospitalized for a total of more than two years and maintaining hundreds of doctor's appointments, Marisa lived an inspirational life. My wife, Cyndi, and I are eternally grateful for the time God blessed us with Marisa. But we struggle daily to live with the tragic irony that the transplant performed to save her life inevitably claimed it, along with the heart of a donor whose family is also grieving.

Marisa's PTLD has been described as a grave form that occurred early after transplant and was widespread, making it difficult to treat. When infusions of high-dose intravenous methotrexate, intended to penetrate the blood-brain barrier, failed, dangerous whole-brain radiation therapy was administered in a last-ditch effort to save Marisa's life. It, too, was unsuccessful.

Marisa was eligible to be part of a clinical study to receive potentially life-saving immunotherapy because she was unresponsive to standard treatment protocols for patients with PTLD, including Rituxan and chemotherapy. Marisa died on the exact same day the three-week screening period to receive the immunotherapy ended. Had Marisa been able to receive and respond to the immunotherapy upon her Stage 3 diagnosis, I believe without equivocation she would have had an excellent chance of survival. Chemotherapy can't safely be administered fast enough in cases such as Marisa's, where PTLD rapidly advances and encroaches upon the brain. US FDA approval of immunotherapy would eliminate the required screening period for patients such as Marisa, who desperately need an alternative approach to conventional treatment.

Marisa spent 161 of the last 214 days of her life as a patient at a nationally renowned children's hospital, where dozens of doctors and nurses, profoundly impacted by her remarkable courage and will to survive, were reduced to tears upon her untimely passing.

Marisa

As a way to keep alive Marisa's indomitable spirit and ensure her legacy can be one of helping others, Greg and I established a nonprofit in her loving memory. Since its inception less than five years ago, The Marisa Tufaro Foundation has donated a quarter of a million dollars to help pediatric patients and other children in need throughout the greater Middlesex County, New Jersey area. The nonprofit also provides resources for PTLD patients and their caregivers.

Our hope is that medical advances – and all the prayers the hands of a certain angel in heaven above can make – will lead to life-saving treatments for PTLD patients.

Thank you."

Session 2: Current and Future Treatments

Erin, caregiver


Erin and Beau

'Hi, my name is Erin Tansey and I live in Seattle, Washington. I have a nine-year-old son. His name is Beau, and he was diagnosed at birth with autosomal recessive polycystic kidney disease, also known as ARPKD and it affects his kidneys and his liver, primarily his kidneys. And so when Beau was born, he was seen very closely by his nephrology team. They managed his kidney function through a very strict diet and a lot of medication. So Beau was on 13 different medications a day and had to take them all throughout the day. And then also couldn't eat a lot of phosphorous, protein, potassium, and sodium, which is pretty much all food. So it was really difficult to feed a little baby and then a growing little boy. And so he also didn't feel great because he had such low kidney function.

And then when Beau turned six, his kidney function declined from his baseline, which was about 50% to over the course of a year to about 10%. And so we knew he was ready for transplant. And so to be ready for transplant, Beau needed one of his kidneys removed to make room for a new kidney, and then also to go on dialysis, to heal up and get strong enough to receive a new kidney through transplant. So Beau underwent the pretty major surgery of having a kidney removed and having a dialysis catheter placed. And then we went to the hospital for dialysis three times a week, and all these procedures were really hard on Beau mentally. He kind of went from being a fun loving kid to really quiet and not very happy most of the time. He never wanted to go to the hospital, which used to be his favorite place with all his friends. And now it became this scary place he was trying to avoid. And in general, he just didn't feel great.

He also was missing a lot of school through this time, too, because of recovering from procedures, going to dialysis and just in general, feeling weak and unwell. So finally, Beau healed up after some dialysis and right when he turned seven, he actually received my kidney as a transplant. So he got a new kidney from me as his mama. And this was a really optimistic time. We had heard how well people did after kidney transplant, how much more energy they had. They wanted to eat more. There was less meds. And so we we're really ready for a new quality of life for Beau.

Well, after Beau was transplanted, he started to recover for the first month and then he kind of went downhill. He had pretty severe GI symptoms, fever, just really tired and didn't feel well. And we were very in close contact with our team and ultimately they referred us to the emergency room, and we were admitted shortly after for several weeks. And during this time, the teams couldn't quite figure out why Beau wasn't recovering. And it took a lot of tests and a lot of different teams coming in until they finally were able to diagnose him with PTLD. He had to undergo a bone marrow biopsy and a PET scan, both with anesthesia. These were really hard on him and his body and his mental health at the time as he wasn't feeling well. And he had gone through all of these procedures and surgeries or related to transplant. We were really at a time where he thought he would be healing and he just wasn't getting better and he wasn't feeling well.

And so once we were able to determine Beau had PTLD in his tonsil tissue, he underwent another surgery to have his tonsils removed. We were lucky. We were lucky that we caught it. We were lucky that it was

removed, and we have been lucky so far, and that we just test for the EBV virus that causes the PTLD and Beau has always come back negative since, but we do worry that it might crop up again and cause issues for Beau again. So it's always in the back of our minds and we're always worried.

It also took Beau, I think, a longer time to heal mentally and physically from his transplant experience because of the compounded effects of the PTLD and all the medical interventions that went with it. And well, I was hoping he was going to be back in school and healing and starting his new life, he just had a major setback, which was hard on him, and also hard on me as his caregiver emotionally to see my kiddo go through such hurting and pain and unexpected medical procedures.

So my takeaway from this is just for all the people who go through organ transplant and go through that difficult process, for the unfortunate few who do get PTLD, I just wish that there was an easier solution or remedy or way to treat it that wasn't so hard on people's bodies, and that it was something that was easily cured and easily remedied. Thank you so much for listening to today and thank you for your time."

Swapna, patient


Swapna

"Hi my name is Swapna Kakani and I am from Huntsville, AL. I was diagnosed with post-transplant lymphoproliferative disorder, specifically EBV positive diffuse large B Cell lymphoma, monomorphic PTLD, in September 2014, soon after my 25th birthday.

three months prior I had an isolated small intestine organ transplant at the Cleveland Clinic, in Cleveland, OH. I was born with the rare disease Short Bowel Syndrome due to the congenital defect of the small intestine, atresia. From day two of life to now 32 years and counting, I have been living with total parenteral nutrition through a central venous catheter and/or enteral nutrition through a gastrostomy tube. After 31 central lines, 25 central line infections, dozens of bowel surgeries, fistulas, no food by mouth for three years, and finally the removal of my remaining intestine, I decided to go forward with the transplant, however, with full knowledge that a transplant is not a cure but rather it can be an exchange of hardships.

When we got the call, I was instructed to go immediately to the hospital. It was there we were told I had PTLD type B-Cell, and B-cell was more treatable, but no other details were told, like what is PTLD. What does it stand for? The weekend was a blur of constant infusions and doctors trying to move fast.

72 hours after diagnosis, the kitchen sink was thrown at me. After morning rounds, I went for a new central line placement, after just having reached the milestone of no more IVs and tubes for the first time in my life. I also received, an Endoscopy of the GI tract, and a PET MRI. Waiting in my room when I got back was the Oncologist. He said, you will be receiving rituximab but if this doesn't work, then you will get the quote "real" chemo. No other information was provided. Tuesday morning, I received 50 mg of IV Benadryl and IV rituximab was started. I received a rituximab infusion weekly for four consecutive weeks and one extra dose 1 month later. I was hospitalized for a week for the first two infusions.

No one explained anything to me! During those days, I went to dr. google, because the doctors were in and out of my room quickly with little details and I did not know what questions to ask. At that time in 2014, there were no resources on PTLD catered to the patient and family community like there are today. I was desperate for information. Online, I saw the words pop up: EBV, chemo, cancer, in the midst of journal articles. There was no information dedicated to PTLD's association with small intestine transplant. I had to stop reading – it was terrifying.

I had the transplant in June, I came home in August after a chyle leak. Here I was end of September back in the hospital for what may be cancer and I had no other choice but to follow my clinicians blindly! I was only 25 years old, and I had just finished college 6 months prior to the transplant. I pushed myself to see hope, and to focus on what I did have control over. I walked the halls every day to see the art to try to escape from the pain in my heart and the disappointment and grief in not seeing my vision post-transplant, simply the overwhelming feeling of going through another complication and suffering one more time. My dad and I had moved to Cleveland for a year for the transplant and the subsequent recovery that it required while my mom, stayed at home in Alabama, to continue to work. My mom came once a month on the weekends. I know this was as hard on my Dad as it was on me. We were both away from our family, friends, and regular routine. I was desperate to begin living!


Swapna with her father

Instead, I was consumed by the regimen during the five weeks of infusions. On Tuesdays of every week, we would spend the day at the outpatient infusion center getting the rituximab and premedication of Benadryl. I would feel exhausted for the rest of the week. On good days, I started my day at 3:00pm. I was depressed. My caregiver, my dad, helped me find at least one fun thing to do every day to get me out of the house always making sure to go to a place at non-peak hours. If it wasn't for him, I would have never left my bed. By Sunday, I would start to somewhat feel like myself again, I would bring my computer out, talk to friends, live vicariously through them, but Tuesday "infusion day" was around the corner. In addition, because of infusions, my blood pressure increased requiring medications, and I started having headaches. Other indirect effects that took a toll on my body included my nutrition.

I was already struggling to learn how to eat on my own without IVs and tubes for the first time in my life post-transplant. With the addition of the rituximab infusions and PTLD diagnosis, I lost my appetite and thus little motivation to eat. We decided to restart the total parenteral nutrition. In addition, my white blood cell count dropped. Before the PTLD diagnosis, I had to get multiple injections of Neupogen twice a week in clinic with no real boost in the count. Once I was diagnosed with PTLD, however, my oncologist made an appeal to my insurance provider to cover Neulasta for my case. I received two Neulasta injections and my white blood cell count finally bounced back. The Neupogen and Neulasta injections caused scream worthy bone pain where it felt like ice picks were stabbing me in the core of my bone. Despite the severe acute pain, receiving Neulasta saved me from multiple trips to clinic every week and constant chronic pain from repeated Neupogen injections that were not working well enough. It was a small win in this journey.

I consider myself lucky. Even though there is hardly anything lucky about a rare disease diagnosis. The tumor that ended up being PTLD and what was biopsied, was in a very visible spot, on my stoma in the bottom right quadrant of my abdomen and on the half of the stoma that is visible to my naked eye. That spot became our informal marker to indicate if the rituximab was working. With every infusion it got smaller until it completely disappeared. Since my diagnosis of PTLD and regimen of rituximab infusions, I have not had another encounter with the disorder. However, three months later, due to immunosuppression, I was diagnosed with aspergillosis requiring voriconazole for six months, and one year later with avascular necrosis in my hips and shoulders requiring joint replacements.

Now almost eight years out from my transplant, I do regularly think about the reoccurrence of PTLD and feel the heavy responsibility of being vigilant of finding it on my shoulders because since one year post diagnosis, I have not had any screenings for PTLD. I actually had no idea PTLD could reoccur until I met other solid organ transplant recipients who have had PTLD. I have a fear – what if it does come back, and what if it is not an early and visible diagnosis like last time?

I hope treatments moving forward and their side effects allow me to keep on living outside of the hospital rather than consuming me, halting my life and energy for weeks, and forcing me to be inpatient. It is truly this peer community I have met since transplant, and the creation of resources and knowledge sharing events for PTLD that do give me hope and confidence in my own disease journey whatever the future may bring."

Brad, patient

"Hi, I'm Brad Buchanan and I live in Sacramento, California. I was diagnosed with my PTLD, which is a B-cell lymphoma triggered by the Epstein-Barr virus, in October of 2016. I was 46 years old.

The immediate effect of this diagnosis was that I was forced to suspend my regular 4-hour treatments of extra-corporeal photopheresis (ECP), which were designed to reduce my graft-versus-host disease symptoms. After a difficult stem cell transplant in early 2016, I still had many troublesome GvHD symptoms, including stomach pain, diarrhea, itching skin, and chronic fatigue, and so I knew I needed more photopheresis. However, it appeared that the T-cells that would normally keep the virus at bay had been killed off by the very same treatments that saved my life when my transplant left me with an acute case of GvHD. So, I had no choice but to suspend my ECP in order to maximize my chances of survival.

My oncologist told me that my PTLD could be treated for a time with an antibody called Rituxan, but that the likeliest scenario was that I would die of my PTLD in around one year. Needless to say, I was deeply distressed by this news, as was my wife, and I took early retirement from my job as a college professor. My father, mother and brother were also devastated: each of them had played a major role in helping me survive my very rocky transplant experience, and now it seemed that all their efforts had been in vain. We chose not to share this dire scenario with our two daughters, who were aged 11 and 7 at the time.

However, my prognosis changed dramatically a month or so later when my oncologist learned about a new possibility at a conference: a clinical trial at Memorial Sloan Kettering. The trial was extremely promising: amazingly enough, it was set up for people with my exact prognosis, and boasted a remarkable cure rate of 66%. The side effects of the treatment were said to be minimal, and I met all the criteria. The logistics of being treated, however, were formidable, especially given my blindness and ongoing illness: I needed to fly

from California to New York, live for nearly four weeks in an apartment, and find my way to the hospital for weekly infusions. We were fortunate enough to be able to afford the travel expenses and accommodations; my only concern was that, being blind and still very sick, there was no way I could negotiate the journey and the logistics of living in New York City on my own.

Fortunately, my parents agreed to drop everything and meet me at La Guardia Airport, take me to Manhattan, and live with me for the duration of my treatment. My wife, unable to leave our two children to come with me, enrolled me in the clinical trial, and then rented a suitable apartment in Manhattan. (There was no room in the residential spaces the hospital usually reserved for its patients.) We paid for the entire trip on our own, an expense many families might not have been able to cover.

I flew to New York in December 2016, and two months later, a PET scan showed that my PTLD had been treated successfully. The Rituxan I had been given before the trial proved surprisingly effective in degrading the B-cell lymphoma, and the allogeneic T-cells provided in New York had cleared up any vestiges of cancer that remained. The clinical trial itself ended soon afterwards, and the T-cell treatment I received is far more widely available.

Today, I feel no ill effects from my brief time with a PTLD, and I have been able to resume my photopheresis in order to manage my chronic GvHD. I am still amazed at how rapidly I went from a terminal diagnosis to being cancer-free. However, I know that I was very fortunate to have a family who could afford to travel to New York, rent an expensive apartment, and put their lives on hold to help me through a third life-threatening medical crisis. Others facing my predicament with fewer resources would not have been so lucky. "

Michele, caregiver

"Hello, my name is Michele Pfab and I'm here representing my daughter, Kayla Pfab for whom I was a caregiver. Kayla was looking forward to speaking to you, but unfortunately, at 29 years old, her life journey ended this past February 5th, 2022 due to complications from chronic rejection of multiple organ transplants. After many years of being ill, Kayla is finally diagnosed with intestinal failure at the age of 21. She received two transplants, including an isolated small intestinal transplant in November 2015 and a modified multivisceral transplant in February 2019.

Immediately after the second transplant, Kayla's body was working hard to heal, but she then had to endure four additional major surgeries over the following three weeks in addition to two bouts of acute rejection. Her body's reserves were nearly nonexistent, but she was a fighter who fiercely hoped to get better. Worsening pain, nausea, fatigue, distention, and night sweats that she began experiencing were attributed to the recovery from the transplant and many complications. Large amounts of fluid leaking from the incision forming puddles when she stood up were concerning.

Rising EBV levels raised some concerns. But when those numbers went sky high, a PET scan was ordered, which revealed swollen lymph nodes in both the upper and lower abdominal cavity and PTLD was diagnosed. Since Kayla was inpatient at the time of her diagnosis, treatment could begin very quickly. The oncologist and transplant team worked together to create an aggressive treatment plan, which included one weekly infusion of rituximab for a total of four doses taking her off of the antirejection meds for a short time and a significant increase of her usual steroid dosage to help stave off rejection.

The oncologist immediately began looking for clinical trials and other treatments in case the plan they came up with did not work. Thankfully for Kayla the plan began to work and the PTLD began to get better. In Kayla's own words, in an email to her physician, when I receive the infusion, it makes me very sick. I have an intense amount of abdominal and back pain, itching, flushing, and overall feel very sick. I was premed with IV Benadryl, another dose in the middle of the infusion, and one last dose at the end of the infusion. Also, at the start of the infusion, until the end, I received IV pain meds, every two hours to help alleviate the pain. This all barely took the edge off, but helped.

After four weeks of treatment and a PET scan that showed the PTLD was significantly improved, Kayla was finally released from the hospital and was scheduled for four additional doses of rituximab at an outpatient infusion center. The evening of each subsequent infusion and into that next day, her back pain was excruciating, which left her curled up in a ball. The back pain, nausea and fatigue made it so that she was unable to sleep or function for that treatment day or the next. Kayla's symptoms gradually improved over the course of the next week or so from the infusion.

This created anxiety as the upcoming treatments got closer because Kayla knew she would feel miserable and there was another uphill battle to conquer. How could you not have anticipatory anxiety knowing that you are going to walk into an eight-hour medical visit full of horrible pain, fatigue, and nausea that was unbearable?

As time went on, the PTLD stayed in remission. Kayla had weekly EBV levels drawn and PET scans periodically. The worry that it could come back was ever present. Knowing that the past treatment worked was a comfort, but the knowledge of the side effects made it feel almost unendurable again.

When most transplant patients receive the diagnosis of PTLD, they are at their most vulnerable, the most sick, the lowest of reserves. Understanding the side effects that can occur, even though the medication does help, is daunting to say the least. Kayla told myself and others that she hoped new treatments would have much less side effects as it's difficult to wrap your head around how much more sick you will become before you get better. Thank you for continuing to find treatments that make very sick patients not have to become more ill before hopefully healing.

Ola, patient

"My name is Ola Ojewumi, and I live in the Washington DC metropolitan area. I'm the founder and director of a small education nonprofit called Project Ascend. We provide college scholarships to disabled youth and grants to youth led community initiatives. My journey into rare disease started at age nine with a blind-siding diagnosis of a rare heart condition called hypertrophic cardiomyopathy. In less than two years, my

heart and kidneys failed. Soon I was put on the organ transplant waiting list. And at age 12, I became the recipient of a lifesaving heart and kidney transplant.

Prior to my transplant, I was warned of various complications that could arise from organ rejection and even potential death. However, I wasn't informed of other dangers that laid lurking around the corner. The potential of developing a rare form of cancer called post-transplant lymphoproliferative disorder, otherwise known as PTLD. Not too long after my surgeries, my transplant doctors informed me that I acquired Epstein-Barr virus transmitted from my donor. EBV and PTLD are closely related.

Soon after my transplants, my lymph nodes would swell. When I was a teenager, my nephrologist noticed the lymph nodes in my neck were swollen. She informed me that there was a possibility that I could have developed this post-transplant cancer. I stood there stunned at my new reality. I already survived a near death experience with hypertrophic cardiomyopathy and organ transplants. And now a fatal form of cancer could be my final undoing.

I was formally diagnosed with PTLD when I was a freshman at Howard University at age 19. I met with oncologists and even got a second opinion at another hospital. Surprisingly, my oncologist chose to wait several years to treat my PTLD with immunotherapy. Apparently my PTLD was not advanced enough to treat yet. I was required to have yearly scans at Johns Hopkins Kimmel Cancer Center to monitor the expansion of my cancer with growth.

The doctors did not provide any support or resources like information about potential clinical trials. They treated my cancer diagnosis completely cavalierly. It wasn't until I reached age 25, that my Hopkins medical team decided to pursue treatment with a drug called Rituxan. This was perplexing because I believe that in most cases, doctors prefer to start cancer treatment the moment cancer is detected.

Despite the long wait, I've responded well to six weeks of intravenous treatment. And I've been in remission ever since. In my life as a chronically ill adult living with multiple disabilities, I've noticed something really unique. I'm usually the only person of color in these spaces. As I share my story with you, I've recognized the privilege of having a seat at the table in this important discussion. Considering African Americans are severely underrepresented in cancer treatment research, I'm going to use this opportunity to speak about the importance of diversity and inclusion in drug development.

During cancer treatment, my clinicians never spoke with me about treatment outcomes for African Americans or provide research to learn more about the drug. I was hesitant to ask about race and ethnicity, because discussions about race is seen as taboo in society. I was afraid my concerns would be dismissed or seen as insignificant. Representation matters when it comes to clinical trials for cancer treatment. For example, during my treatment, I wondered how I would respond to it and if it would be effective for people who looked like me. I say this from my very own personal experience.

As a child, I had asthma and my doctors prescribed albuterol for treatment. Whenever I would take the drug, my asthma would become worse. It was later noted in a research study that albuterol was not effective in children like me because there weren't any black children included in the clinical trials. Our lives literally depend on inclusion and destroying racial bias in medicine.

Thank you for giving me the space to share my story."

In memory of Kayla Pfab, and all of those who have lost their lives to PTLD, and in honor of those who are living with PTLD.

APPENDIX 3: POLLING QUESTIONS

Demographic Polling Questions:

1. I am:
    a. An individual with PTLD
    b. A caregiver of someone with PTLD
2. Where do you live?
    a. East coast (Eastern time zone)
    b. Midwest (Central time zone)
    c. West (Mountain time zone)
    d. West coast (Pacific time zone)
    e. Canada
    f. Mexico, Caribbean Islands
    g. Outside of North America
3. Do you identify as:
    a. Male
    b. Female
    c. Non-Binary
    d. Other
4. Please select the response that best reflects your race and/or ethnicity:
    a. American Indian or Alaska Native
    b. Arab/Middle Eastern/North African
    c. Asian or Asian American
    d. Bi- or Multi-Racial
    e. Black or African American
    f. Hispanic, Latino/a, Latine, Latinx
    g. Native Hawaiian or Other Pacific Islander
    h. White (Non-Hispanic)
    i. Not listed
    j. Prefer not to answer

5. What is your age or the age of the person you are caring for?
    a. Less than 5 years
    b. 5-11 years
    c. 12-17 years
    d. 18-29 years
    e. 30-39 years
    f. 40-49 years
    g. 50-59 years
    h. 60-69 years
    i. 70 or greater

6. At what age did you or your loved one receive a diagnosis of PTLD?
    a. 0-1 year
    b. 2-5 years
    c. 6-11 years
    d. 12-18 years
    e. 19-29 years
    f. 30-39 years
    g. 40-49 years
    h. 50-59 years
    i. 60-69 years
    j. 70 or greater

Topic 1 Polling Questions: Living with PTLD — Burdens and Symptoms

1. Have you experienced any of the following difficulties because of your PTLD? (Select ALL that apply)
    a. Headaches
    b. Bone pain
    c. Painful lymph nodes
    d. Pain at tumor site
    e. Pain in area where PTLD was found
    f. "Ghost pain"
    g. Fatigue
    h. Loss of appetite
    i. Swelling and fluid at incisions
    j. hortness of breath (dyspnea)
    k. Psychological/emotional (e.g., PTSD, anxiety)

2. Which THREE of the following symptoms of your PTLD most negatively impact your daily life?
    a. Fatigue
    b. Fever
    c. Headaches
    d. Pain

e. Psychological
f. Sweating
g. Swelling
h. Other

3. Which have you experienced while coping with your PTLD? (Select ALL that apply)

a. Anxiety
b. Bullying from others
c. Depression
d. Difficulty with relationships
e. Hopelessness
f. Low self-esteem
g. Social isolation
h. Unwanted attention based on appearance
i. None of the above

4. Which of the following statements is true for you as related to living with PTLD? (Select ALL that apply)

a. miss school more than I'm comfortable with
b. I've modified my school or career goals because of PTLD
c. PTLD negatively affected my job
d. Family stress is common in my life
e. Others don't know what it's like to live with PTLD
f. I cannot participate in sports or other physical activities I enjoy
g. My general daily function is limited by PTLD
h. None of the above

5. What are your biggest concerns about living with PTLD? (Select ALL that apply)

a. Access to medical care (e.g., coordinating care, relocation to hospitals)
b. Development of lymphoma post-PTLD
c. Financial concerns
d. First-line treatment not working
e. Immunosuppression
f. Inability to be a caregiver, spouse, parent, friend, etc.
g. Infection
h. Insurance difficulties
i. Malnutrition
j. Mental health concerns
k. Recurrence of PTLD
l. Rejection and relapse
m. Risk of infection from COVID
n. Other

Topic 2 Polling Questions: Current and Future Treatments

1. Select the medications or supportive treatments you use or have used for PTLD. (Select ALL that apply)
    a. Benadryl (intravenous, oral, or other)
    b. Chemotherapy
    c. Claritin (for drug-related bone pain)
    d. Neulasta
    e. Neupogen
    f. Pain relievers (prescribed, OTC or other)
    g. Radiation
    h. Rituximab
    i. Steroids (hydrocortisone, prednisone, etc.)

2. How well does your current treatment regimen reduce the most significant symptoms of your PTLD?
    a. Very well
    b. Moderately well
    c. Poorly
    d. Not at all
    e. I do not currently take any treatments

3. What is your experience in, and perception of, clinical trials for a new PTLD drug?
    a. I am currently participating in a trial
    b. I have participated in a trial, and I would do so again
    c. I have participated in a trial, and I would not do so again
    d. I have not participated in a trial because I didn't know about the opportunity
    e. I have not participated in a trial because I was not eligible
    f. I have not participated in a trial, although I was aware of the opportunity & eligible
    g. I would never enroll in a clinical trial
    h. Not sure
    i.

4. Of the following factors related to a test drug in a clinical trial, select UP TO FIVE that you rank as most important to your decision about participating in a clinical trial:
    a. Whether I might get placebo ("sugar pill")
    b. Whether I need to stop my current disease management and treatment regimen
    c. Potential side effects from a new drug
    d. How the drug is taken (by mouth, IV, injection in muscle)
    e. Whether the drug is supposed to treat symptoms or the underlying cause of my disease
    f. Unsure if I can make the commitment to participate in a clinical trial
    g. Frequency of exam appointments
    h. Distance to trial site
    i. Length of trial

j. Negative things I have heard about clinical trials
k. Other

5. Which factors are the most important to you when deciding to select a new treatment or drug for your PTLD? (Select top THREE)
    a. Whether drug is taken by mouth, by IV, or injections in muscle
    b. How often you have to take the drug
    c. Evidence that the drug improves specific symptoms most bothersome to you
    d. Whether the drug will improve my PTLD
    e. Number of side effects known for the drug
    f. Severity of side effects known for the drug
    g. Cost and/or whether covered by insurance
    h. What your physician recommends

6. Without considering side effects of a drug, which ONE of the following would be most important to you in a future therapy for your PTLD?
    a. Evidence that the drug will significantly decrease the complications of PTLD
    b. Evidence that the drug will significantly extend lifespan

APPENDIX 4: MEETING MATERIALS

Agenda

Post-Transplant Lymphoproliferative Disorder Externally led Patient Focused Drug Development Meeting
May 4, 2022

12:30pm	**Opening Remarks** Peter Saltonstall, President & CEO, NORD Swapna Kakani, patient
12:35pm	**Clinical Overview of Post- transplant lymphoproliferative disorder** Thomas M. Habermann, MD, Division of Hematology, Department of Medicine, Mayo Clinic
12:50pm	**Welcome Remarks** Nicole Gormley, MD, Director, Division of Hematology Malignancies II, FDA
1:10pm	**Introduction and Meeting Overview** Debbie Drell, Director of Membership, NORD Ariel Markowitz-Shulman - Associate Director of Strategic Planning, NORD
1:20pm	**Overview of Discussion Format & Demographic Polling Questions**

1:25pm	**Topic 1: Living with PTLD—Burdens and Symptoms** Marianna DeLeon, patient Rebekah Palmer, patient Ellen Keyser Endelman, patient Greg & Cyndi Tufaro, caregivers Sarah O'Connor, caregiver
1:50pm	**Polling Questions and Facilitated Audience Discussion on Topic 1** Debbie Drell, Director of Membership, NORD Ariel Markowitz-Shulman - Associate Director of Strategic Planning, NORD
2:50pm	**Break and Discussion Questions:** 1. Of all the symptoms that you experience because of your condition, which 1-3 symptoms have the most significant impact on your life? 2. Which symptoms affect you now and which symptoms were most significant in other times of your life? 3. How do your symptoms and their impacts affect your daily life? Can you give a real-world example of how PTLD affects your daily life?
3:00pm	**Topic 2: Current and Future Treatments** Erin Tansey, caregiver Michele Pfab, caregiver Swapna Kakani, patient Ola Ojewumi, patient Brad Buchanan, patient
3:25pm	**Polling Questions and Facilitated Audience Discussion on Topic 2** Debbie Drell, Director of Membership, NORD Ariel Markowitz-Shulman - Associate Director of Strategic Planning, NORD Questions: 1. What are you currently doing to help treat your condition or its symptoms? 2. How has your treatment regimen changed over time and why? 3. How well does your current treatment regimen treat the most significant symptoms of your disease?
4:25pm	**Closing Remarks** Rebekah Palmer, patient
4:30pm	**Wrap Up and Next Steps** Debbie Drell, Director of Membership, NORD Ariel Markowitz-Shulman - Associate Director of Strategic Planning NORD
4:45pm	**Adjourn**

About this Meeting:

The patient perspective is critical in helping the US Food and Drug Administration (FDA) understand the context in which regulatory decisions are made for new drugs. Externally-Led Patient-Focused Drug Development (EL-PFDD) meetings provide an opportunity for patients, their families, and caregivers to share critical information about the impact of their disease on their daily lives and their experiences with currently available treatments. Patients' experiences provide valuable insight for FDA and other key stakeholders, including researchers, medical product developers, and health care providers.

The National Organization for Rare Disorders® (NORD) has organized this EL-PFDD meeting on post-transplant lymphoproliferative disorder (PTLD). PTLD is a rare cancer related to organ and stem cell transplants, as well as Epstein-Barr virus. There is no nonprofit organization dedicated to this community and the last known gathering involved less than a dozen patients and caregivers, pre-pandemic. NORD believes this rare disease is one with an unmet need and a severe disease burden.

The goal of this EL-PFDD meeting is to provide researchers, drug developers and FDA with a robust understanding of patients' and caregivers' experiences with PTLD, including how individuals with PTLD view their quality of life, which aspects of the disease are most problematic for them and what actions they currently perform to treat and cope with this disease. The results of this meeting will be shared publicly in a "Voice of the Patient" report in an effort to inform the development of potential therapeutics that can improve the lives of patients living with PTLD

Speakers

Marianna De Leon is 23 years old and lives in Dallas, Texas. She was diagnosed with PTLD after receiving a bone marrow transplant at 21. She is currently in remission, and is back at school, hoping to complete her degree while enjoying time with family, friends and her dog.

Rebekah Palmer is 34 years old and lives in Superior, Wisconsin. She was diagnosed with PTLD after a kidney transplant at the age of 12 to treat cystinosis, a rare metabolic condition. She currently serves as the Vice President at Next Generation of Cystinosis and a Rare News Curator at the Cystinosis Society. She is a dedicated rare disease advocate and a published author.

Ellen Keyser Edelman is 26 years old and was diagnosed with PTLD at 25 6 months after a bone marrow transplant. She is a Master of Divinity student at Chicago Theological Seminary and a Candidate in the PC (USA). She currently lives with her husband and their two cats in Wisconsin. Ellen is involved in patient advocacy, runs a doll hospital, and enjoys making art and music in her spare time.

Sarah O'Connor is mom to 2 boys, 3-year-old Everett & 5-year-old Declan. Everett was diagnosed with PTLD after a kidney transplant at the age of 2.5 after being diagnosed with kidney failure before he was born. She lives in Galesburg, Illinois with her husband and children.

Greg and Cyndi Tufaro live in Edison New Jersey. They are the proud parents of Marisa Rose, who lost her life due to complications from PTLD in January 2017 after receiving a heart transplant at only 13 years old. Marisa was a gifted student and artist. Greg & Cyndi started the Marisa Tufaro Foundation in her memory to assist pediatric patients and other children in need throughout the greater Middlesex County NJ area.

Brad Buchanan is a retired English professor living in Sacramento CA. In 2015 he was diagnosed with a rare form of T-cell lymphoma, which defied diagnosis for months, produced an undetected lung tumor, and required a life-saving stem cell transplant in 2016. He contracted PTLD after transplant for which he was successfully treated through a clinical trial at Memorial Sloan Kettering in New York City. When not hanging out with his two daughters, he writes poetry, academic prose, and creative nonfiction about his recovery from multiple rare diseases. He also facilitates online writing workshops through the UC Davis Cancer Center and the Sacramento Society for the Blind.

Swapna Kakani is a passionate patient advocate and professional speaker on the Short Bowel Syndrome, rare, and chronic, disease patient experience. Having been diagnosed with Short Bowel Syndrome at birth, she underwent a small intestine transplant when she was 24 years old and after her transplant was diagnosed with PTLD. Swapna was born and raised in Huntsville, AL and graduated from the University of Alabama at Birmingham with a bachelor's degree in Psychology and a Master's of Public Health.

Ola Ojewumi is the founder and director of Project ASCEND, an education nonprofit that provides college scholarships to disabled youth. Her journey into rare disease started at the age of 9 when she was diagnosed with hypertrophic cardiomyopathy. At age 12 she received both a heart and kidney transplant and soon after was diagnosed with Epstein Barr Virus and later PTLD. Ola graduated from the University of Maryland, College Park with a bachelor's degree in government and politics. She is a passionate advocate, and public speaker who lends her expertise in the areas of gender, race and disability. She currently lives in the Washington DC area.

Michele Pfab is the mother of Kayla, who received the gift of transplant twice in the form of an intestinal transplant and then a modified multivisceral transplant. Michele was at Kayla's side every step of her journey as her mom, advocate, caregiver, sounding board, assistant, and all-around cheerleader. Kayla's journey led her to the founding of Transplant Unwrapped, whose mission is to educate and support patients in their journey with intestinal failure, intestinal rehabilitation and intestinal and multi visceral transplantation. Michele wants to continue on with Kayla's passion to give others the support she and Kayla felt from so many and access to knowledge that was not always easy to find.

Erin Tansey is the mother of Beau, who was diagnosed at birth with autosomal recessive polycystic kidney disease (ARPKD). After Erin donated her kidney to Beau when he was 7 years old, he developed symptoms of PTLD. Today Beau is a healthy 9 years old and he and his mom live in Seattle, Washington where Erin serves on the Family Advisory Council of Seattle Children's Hospital.

APPENDIX 5: ACKNOWLEDGEMENTS

Sponsors

Many thanks to our generous sponsor, Atara Biotherapeutics, Inc.

Authors

This "Voice of the Patient" report was written by James O'Leary, Independent Consultant and Patient Advocate.

About the National Organization for Rare Disorders (NORD®)

The National Organization for Rare Disorders, a 501(c)(3) organization, is a patient advocacy organization dedicated to individuals with rare diseases and the organizations that serve them. NORD, along with its more than 330 patient organization members, is committed to the identification, treatment and cure of rare disorders through programs of education, advocacy, research and patient services

Many thanks to
the many individuals who helped
to make this meeting a success
and who participated in person and
on the webcast.

Your voices
were HEARD!

Mission Statement

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