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ORIGINAL RESEARCH ARTICLE

Determining Commonalities in the Experiences of Patients with Rare Diseases: A Qualitative Analysis of US Food and Drug Administration Patient Engagement Sessions

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Abstract

Background Rare diseases are estimated to affect more than one in ten Americans. However, most patients with a rare disease face significant emotional, physical, and social challenges. To better understand the burden of disease and unmet needs, the US Food and Drug Administration (FDA) conducts and supports multiple patient engagement platforms. We analyzed summaries from these discussions to identify commonalities among patients with disparate rare diseases, the results of which could inform priorities for cross-disease policies and medical product development.

Methods We conducted a qualitative analysis of patient engagement session summaries to investigate shared experiences across rare diseases. Cross-disease similarities were identified within four dimensions: product development/regulatory, clinical/physical, social/psychological, and economic/financial. Summaries from 29 rare diseases were included in our analyses.

Results Within the product development/regulatory dimension, we observed that patients and caregivers across rare diseases shared the desire for development of medical products that cured their disease or improved their overall quality of life. In the clinical/physical dimension, we found that patients had numerous common symptoms, including pain and fatigue. In the social/psychological dimension, we observed significant negative impact on mental health. Within the economic/financial dimension, patients and caregivers shared that disease burden caused significant financial hardships.

Conclusion We found remarkable similarities among patients with rare diseases across all four dimensions. Our results indicate that, even among rare diseases with diverse etiologies, patients share numerous commonalties due to their diseases: a lack of effective treatment options, certain physical symptoms, mental health challenges, and financial concerns.

1 Introduction

Listening to patients' concerns and preferences is foundational for both healthcare delivery and medical product development. The patient perspective brings ideas and the potential for innovation that can assist healthcare providers and medical product developers in designing guidelines and creating drugs, biologics, and devices that can provide a meaningful difference to patients' lives.

This is especially true for rare diseases. In the USA, a rare disease is defined as a disease with a prevalence of fewer than 200,000 people [1]. It is estimated that there are 7000–10,000 rare diseases, yet only approximately 5% have an approved treatment [2, 3]. Additionally, for many rare diseases, little is known about the underlying pathophysiology or natural history, which is problematic for medical product development of drugs, biologics, and devices and establishing standards of care [4–7].

Given these challenges, determining similarities in patient experiences among disparate rare diseases could assist in establishing priorities for development of medical products and the development of treatment guidelines [8, 9]. To determine these commonalities, we analyzed summaries from two US Food and Drug Administration (FDA) patient engagement platforms designed to capture patient perspectives and amplify the patient voice directly to FDA and other stakeholders: (1) Patient-Focused Drug

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Key Points for Decision Makers

Patients with different kinds of rare diseases shared significant burdens due to pain, fatigue, mental health concerns, and financial difficulties.

Common issues voiced by patients suffering from various rare diseases suggest there are potential opportunities for medical product development and care management strategies to address these shared concerns in rare diseases.

Development (PFDD) meetings (created as part of the fifth reauthorization of the Prescription Drug User Fee Act in 2012) and (2) Patient Listening Sessions (PLS) (created as part of ongoing FDA initiatives to incorporate the patient voice into the work of the agency in 2018) [10–12].

Topics addressed in patient engagement sessions include the symptoms, impacts of the disease on daily life (including employment, socializing, and hobbies), treatment experiences, benefit-risk assessment of therapies, and ideals for future drug development. Additionally, caregivers also shared their experiences in some sessions. While PFDD and PLS meetings are held for both rare and common diseases, this research focuses solely on those for rare diseases.

PFDD meetings function specifically to provide a platform for both patients and caregivers to share the most significant symptoms impacting their daily lives, as well as their opinions of current approaches to treatment. The primary goal is to ensure the incorporation of the patient experience into drug development and evaluation. The target audience for these sessions includes medical product developers, researchers, as well as FDA staff [13]. PFDD meetings are led either by FDA ("FDA-led") or by patient advocacy groups ("externally led"). After the PFDD meeting, a "Voice of the Patient" report is available online containing a summary of the dialog. There have been approximately 100 PFDD meetings held between 2013 and 2022 [14].

PLS meetings focus on patients and caregivers rather than on specific medical products and aim to provide patients with a platform to share their experiences and needs related to their health, disease, symptoms, and treatment preferences. The target audience is FDA staff members involved in medical product evaluation and review [15]. PLS meetings are hosted by the FDA Patient Affairs Staff and are considered either "patient-requested" or "FDA-requested," depending on which group initiated the meeting. After PLS meetings, Patient Listening Session summaries are posted online. There have been approximately 50 PLS meetings held between 2018 and 2022 [14].

While both the PFDD and PLS sessions follow similar formats, dialogs may be framed differently. The FDA-led PFDD and FDA-requested PLS sessions may contain more FDA-specific questions (e.g., regulatory, product specific, etc.) for patients to answer. The externally led PFDD and patient-led PLS meetings are generally conducted by patient groups and include more general questions about lived experiences with a rare disease.

In this research, we used qualitative analyses of patient engagement sessions to determine commonalities among patients with different rare diseases [8]. Patient engagement sessions provide a unique opportunity to use qualitative research to identify similarities due to the in-depth dialogues of patients' experiences and perspectives that they contain.

2 Methods

For our analysis, we used the most recently published PFDD and PLS rare disease session summaries as of 1 December 2021. Selecting these session summaries provided a sample that included a variety of diseases and patient populations, while maintaining a manageable volume of material to analyze.

Our final sample included patient engagement session summaries focused on 29 different diseases (Table 1). There were five externally led PFDD meetings, five FDA-led PFDD meetings, ten patient-led PLS, and nine FDA-requested PLS. For a given disease, we included both adult and pediatric sessions if they were separately split. Both meeting types could include patients and caregivers. The PFDD summaries ranged from 23 to 93 pages in length. The PLS summaries ranged from 2 to 13 pages in length. The session summaries provided us with over 620 pages of data to analyze.

A qualitative analysis was performed using a series of iterative steps. First, four dimensions were predetermined for analysis: product development/regulatory, clinical/physical, social/psychological, and economic/financial. These were based on the authors' prior knowledge of the themes present in these meetings, as well as the areas of interest for this research study [8].

The coding process was conducted using the qualitative analysis software ATLAS.ti 9. Keywords within the sessions were identified and coded into one of the four dimensions. Keywords were defined holistically and included any word related to one of the four dimensions. Symptoms that frequently recurred in a session were only coded once to ensure that longer summaries did not bias the results. Lists of the keywords for each dimension were then analyzed to

Table 1 Description of FDA patient engagement sessions and rare diseases used in analysis ($n = 29$)

Disease	Disease description	Meeting type	Date	Pages
Acromegaly	Endocrine disorder related to excessive growth hormone resulting in overgrowth and large facial features	Externally led PFDD	21/01/2021	93 p
Adrenomyeloneuropathy	Metabolic disorder related to damage to brain and spinal cord membranes resulting in spinal cord dysfunction	Patient-led PLS	07/05/2021	6 p
Alpha-1-antitrypsin deficiency	Pulmonary disorder related to low levels of alpha-1-antitrypsin resulting in emphysema and liver disease	FDA-led PFDD	29/09/2015	33 p
Childhood cerebral adrenal leukodystrophy	Neurologic disorder related to the accumulation of fatty acids in the brain resulting in difficulty walking and learning disabilities	FDA-requested PLS	13/11/2019	3 p
Cystic fibrosis (nonsense mutations only)	Pulmonary disorder related to the body's ability to clear mucus resulting in blocked airways and lung damage. This session focused on the 10% of patients with cystic fibrosis that do not benefit from currently approved therapies	Patient-led PLS	15/07/2021	13 p
Fabry disease	Metabolic disorder related to the body's ability to metabolize fat resulting in issues for the kidneys and heart	FDA-requested PLS	04/12/2018	2 p
Focal segmental glomerulosclerosis	Nephrology disorder related to impaired kidney filtration resulting in kidney damage	Externally led PFDD	28/08/2020	81 p
Frontotemporal degeneration	Neurologic disorder related to the progressive damage to nerve cells in the brain resulting in changes in behavior, mood, and memory	Externally-led PFDD	05/03/2021	75 p
Gastroparesis	Gastroenterology disorder related to slowed emptying of food in the stomach that results in digestive symptoms such as nausea and feeling full	FDA-requested PLS	02/12/2019	3 p
Glycogen storage disease type 1	Metabolic disorder related to the inability to breakdown glycogen resulting in enlarged liver and kidneys	FDA-requested PLS	18/03/2021, 25/03/2021	5 p and 6 p[a]
Guillain–Barré syndrome	Neurologic disorder related to the inflammation of nerves resulting in muscle weakness and sometimes paralysis	Patient-led PLS	29/09/2020	12 p
Hemophilia A and B	Hematologic disorder that slows down the blood clotting process resulting in uncontrolled bleeding	FDA-requested PLS	22/09/2014	2 p
Hereditary angioedema	Immunologic disorder related to the accumulation of fluid outside of blood vessels resulting in recurrent attacks of severe swelling usually involving the face, hands, and feet	FDA-led PFDD	25/09/2017	31 p
Homocystinuria	Metabolic disorder related to the body's inability to break down certain proteins resulting in vision issues, skeletal abnormalities, and blood clots	Patient-led PLS	26/06/2020	7 p
Hunter syndrome (mucopolysaccharidosis type II)	Metabolic disorder related to the body's inability to break down complex sugar molecules resulting in heart disease, joint problems, and enlarged internal organs	FDA-requested PLS	04/02/2020	4 p
Huntington's disease	Neurologic disorder related to the progressive breakdown of nerve cells the resulting in movement issues and dementia	FDA-led PFDD	22/09/2015	23 p

Table 1 (continued)

Disease	Disease description	Meeting type	Date	Pages
Hypothalamic obesity	Metabolic disorder related to damage in the hypothalamus resulting in extreme hunger and weight gain	Patient-led PLS	22/10/2021	8 p
Krabbe disease (globoid cell leukodystrophy)	Neurologic disease related to the breakdown of the myelin sheath resulting in respiratory failure, loss of muscle control, feeding issues	Externally led PFDD	29/10/2020	67 p
Late onset GM2 gangliosidoses (e.g., Tay–Sachs and Sandhoff diseases)	Metabolic disorder related to the accumulation of gangliosides resulting in muscle weakness	Patient-led PLS	15/01/2021	8 p
Mastocytosis	Hematologic disorder related to the abnormal accumulation of mast cells resulting in allergic reaction-type symptoms	Patient-led PLS	28/09/2021	7 p
Neuronopathic Gaucher disease	Metabolic disorder related to a deficiency in an enzyme that breaks down fats resulting in enlarged liver and spleen and anemia	Patient-led PLS	09/09/2021	5 p
Organ transplant	Post-transplant management including preventing organ rejection, treating their underlying condition, and complications of immunosuppression	FDA-led PFDD	27/09/2016	27 p
Pemphigus pemphigoid	Dermatologic disorder related to an overactive immune system resulting in lesions and blisters	Patient-led PLS	08/02/2021	6 p
Polyglutamine spinocerebellar ataxias and dentatorubal-pallidoluysian atrophy	Neurologic disorder related to impaired nerve fibers resulting in movement and speech issues and epilepsy	Externally led PFDD	25/09/2020	50 p
Progressive multifocal leukoencephalopathy (PML)	Neurologic disorder related to a virus destroying nerve cells in the brain resulting in movement and speech issues	FDA-requested PLS	22/07/2020, 11/09/2020	5 p and 5 p[b]
Sanfilippo syndrome (mucopolysaccharidosis type III)	Metabolic disorder related to a deficiency in an enzyme that breaks down complex sugar molecules resulting in behavioral symptoms and dementia	FDA-requested PLS	13/05/2019, 17/10/2019	3 p and 3 p[a]
Smith–Magenis syndrome	Neurologic disorder related to the body's ability to produce proteins resulting in unique facial features, cognitive and sleep issues	FDA-requested PLS	12/08/2020	6 p
Systemic sclerosis	Rheumatologic disorder related to the growth of connective tissue resulting in thickening of the skin, but may also cause problems in the blood vessels, internal organs, and digestive tract	FDA-led PFDD	13/10/2020	24 p
Vascular Ehlers–Danlos syndrome	Rheumatologic disorder related to the production and quality of collagen resulting in arterial, intestinal, and/or uterine fragility	Patient-led PLS	07/10/2020	3 p

PFDD patient-focused drug development meeting, *PLS* patient listening session

[a]Two sessions occurred because the adult and pediatric sessions were split

[b]Split into two sessions to account for different FDA questions

observe common themes. The most frequently coded words, or groups of words, were interpreted into key themes via an iterative process between two of the authors (C.M. and K.L.M.) (Supplementary File) [16]. The key themes were compared with the original summary text that the words were pulled from to ensure accurate context [17]. The two authors also confirmed that the coded words were drawn from the summaries of multiple patients with rare disease engagement sessions, to ensure that each key theme was based on commonalities between numerous rare diseases. However, the key themes should not necessarily be interpreted to represent themes that were observed in all sessions, but rather themes that were common across multiple sessions.

3 Results

We analyzed the summaries from 29 patient with rare disease engagement sessions to determine the key themes in similarities among each of the 29 groups of patients with rare diseases who participated in these sessions across the four predetermined dimensions: product development/regulatory, clinical/physical, social/psychological, and economic/financial. We found numerous unifying commonalties between patients across the 29 rare diseases within all four dimensions, despite the wide range of diseases studied. The full list of key themes within these four dimensions is listed in Table 2.

Table 2 Key themes: similarities in experience across rare disease patients

Dimensions	Key themes Patients and caregivers across rare diseases voiced:
Product development/regulatory	The primary goal of therapy development is to find a cure
	Secondary to finding a cure, delaying disease progression or symptom management were equally important to patients
	For new therapies, wanting to know if their quality of life will be improved on the new therapy; a primary concern is the side-effect profile
	Frustration with the lack of treatment options available for their disease
	Reluctancy to participate in a trial where they had the potential of receiving placebo (especially if they had to go off their current therapy regimen)
	Frustration with access to clinical trials due to eligibility criteria limiting enrollment and the burdens of time commitment such as travel to trial sites
	The inability to administer medication orally versus parenteral routes (e.g., injections) that are uncomfortable, painful, and risky
Clinical/physical	Maintaining control of the disease symptoms is challenging
	The most commonly reported symptoms were pain and fatigue/low energy
	Secondary but frequently reported common disease symptoms included sleep disturbances, feeding issues (weight gain/loss, swallowing, and diet modifications), gastrointestinal (nausea, diarrhea, and constipation), movement/mobility (walking, balance, and dexterity), and neurologic (cognitive, speech, and headache)
	A correct and timely diagnosis is important to appropriately manage symptoms and receive treatments; a misdiagnosis or a lack of diagnosis prevents patients from controlling their symptoms and disease
	Surgery is a frequent treatment modality (for some diseases) but not always successful
Social/psychological	The physical and psychological toll of disease is a daily constant stressor
	This toll leads to strained relationships with family, along with feelings of dependency
	This toll also leads to diminished relationships with friends, along with feelings of isolation
	Their mental health is also negatively impacted by the daily stress, worry, frustration, and fear due to disease burden and uncertainty
Economic/financial	The ability to work is greatly impacted by disease burden
	Losing the ability to work leads to challenges in financing treatments and care
	Losing the ability to work leads to the loss of both health insurance and the ability to pay for care
	Losing the ability to work also leads to patients or caregivers being forced into early retirement regardless of whether they are financially (and emotionally) ready to retire
	The ability to gain timely and appropriate access to treatments is delayed due to insurance coverage limitations and prohibitive prices for treatments

3.1 Product Development/Regulatory

3.1.1 Concerns for Quality of Life Pertaining to New Product Development

Patients primary goal with therapy development was to find a cure. They shared:

> "He said he hopes and prays for a cure in his lifetime and would do anything for science so that maybe no one will have to endure what he has." [Adrenomyeloneuropathy PLS]
> "Some participants were more likely to prefer gene therapy because it gives them more hope for a cure as opposed to management of the disease." [Childhood cerebral adrenal leukodystrophy PLS]

Besides finding a cure, managing disease progression and controlling symptoms were key goals. A caregiver explained:

> "I would say minimize symptoms. Obviously we would want her to live a long, productive life as anyone expects to, but we've seen our daughter suffer and we've seen the other side of Krabbe and definitely to reduce those symptoms, reduce the side effects [of the disease] would be huge because I think that improves their quality of life." [Krabbe disease PFDD]

We found that across all sessions, the improvement of quality of life was central to patients' product development goals. A key issue patients shared was the negative impact that treatment side effects can have on their quality of life. As patients shared:

> "Several participants expressed frustration with the extent of the side effects they experienced, including one participant who stated that her treatment regimen 'does not manage my symptoms, just causes them.'" [Organ transplant PFDD]

The development of more convenient routes of administration, such as oral, was also a commonly expressed perspective. They shared:

> "Family hopes for a better treatment without needles." [Neuronopathic Gaucher disease PLS]

3.1.2 Views on Clinical Trial Participation

Patients across all rare diseases emphasized the importance of continued research and development for their condition. However, some patients were reluctant to participate in placebo-controlled clinical trials, citing concerns with not receiving treatment during the study period. A common refrain heard was:

> "More than half of caregivers and patients expressed uneasiness with placebo-controlled trials for PML. Some caregivers and patients believed placebo would waste valuable time and would defeat the purpose of treatment…" [Progressive multifocal leukoencephalopathy PLS]

Others discussed the importance of selecting medical product clinical trial endpoints that are meaningful to patients. As patients shared:

> "Many participants shared their concern about the endpoints that are selected for clinical trials. As parents, they often see progress not measured in the clinical trials, including progress beyond cognitive function." [Sanfilippo syndrome PLS]

Many felt that the trial design did not take their daily lives into consideration. A patient stated:

> "…I don't know that people putting together these trials understand what a pain that is to do [24-hour urine tests] if you're working or in and out of the house throughout the day." [Focal segmental glomerulosclerosis PFDD]

Similarly, a commonality among patients with rare diseases was the significant burden imposed by travel to trial sites. Caregivers and patients shared:

> "He had to travel from Dallas to Boston twelve times in two years to participate in a clinical trial, which was difficult physically and logistically." [Adrenomyeloneuropathy PLS]
> "Distance from where the patient/caregiver lives to the [trial] treatment center also determines how burdensome the visits are." [Hemophilia A and B PLS]

3.2 Clinical/Physical

3.2.1 Controlling Disease

Managing numerous symptoms to help improve daily life is a key issue for patients with a rare disease. Despite the many medications required to control their disease, patients still feel that their symptoms are not effectively managed. Patients shared:

> "Together, I am on over 30 medications. While they do provide some help and relief, I am nowhere close to where I was before acromegaly." [Acromegaly PFDD]
> "Patients indicated that their current medications sometimes make their symptoms manageable, but that

some of the current medications generally seem to lose effect after weeks to months of use." [Gastroparesis PLS]

The inability to effectively control disease symptoms is a common experience for patients with rare diseases. Maintaining control of disease symptoms is a challenging experience for both patients and caregivers. Caregiver perspectives included:

"A majority of caregivers added that although patients' needs may change with development, the level of care remains challenging and complex, requiring constant surveillance." [Smith–Magenis syndrome PLS]
"All caregivers of GSD1a patients agreed that the symptoms were constantly changing, and it was a constant struggle to manage them. One participant described GSD1a as a 'roller coaster ride.' One participant described the burden of raising children with GSD 1a as '24/7.'" [Glycogen storage disease type 1 PLS]

Some caregivers described other challenges, such as disease management in non-verbal patients and learning to use sophisticated medical equipment. A caregiver perspective included:

"[A caregiver] reported that when it became very difficult for her son affected by DRPLA to speak, he started to use an Eye Gaze [communication device], but 'unfortunately because of his epilepsy and myoclonic movements, he can't use that very efficiently.'" [Polyglutamine spinocerebellar ataxias and Dentatorubral-Pallidoluysian atrophy PFDD]

3.2.2 Common Symptoms

The two most commonly reported symptoms by patients are pain and fatigue/low energy. Often patients experience pain and fatigue concomitantly. As patients shared:

"Pain and fatigue after [Guillain–Barré syndrome] recovery remain extremely burdensome to the community." [Guillain–Barré syndrome PLS]

Descriptions of pain symptoms were provided by patients. They shared:

"I wake up every morning in acute pain and until my pain meds kick in, I am unable to function." [Mastocytosis PLS]
"I have birthed two babies without epidurals, and I have actually had a kidney stone, so I do have a high tolerance for pain…and this pain [hereditary angioedema abdominal attack] is above 10 on the pain scale…During these attacks, I can't eat, I can't drink, you basically vomit every little bit that is in you." [Hereditary angioedema PFDD]
"…pain that is indescribable. It is almost like a nerve pain as well as if you got a little blow of air on it, it is excruciating." [Systemic sclerosis PFDD]

Patients described how the fatigue symptoms make them feel. They shared:

"On really bad days, it feels like I'm kind of pushing through mud to get everything done, and I don't often have much energy left by the end of the day." [Focal segmental glomerulosclerosis PFDD]
"Several participants described experiencing constant fatigue, tiring easily, or feeling a general lack of energy. One participant stated that 'on the worst days… I can barely get out of bed.'" [Organ transplant PFDD]

Secondarily, but frequently reported, common rare disease symptoms included food/feeding issues (weight gain/loss, swallowing, and diet modifications), gastrointestinal symptoms (nausea, diarrhea, and constipation), movement/mobility issues (walking, balance, and dexterity), neurologic symptoms (cognitive, speech, and headache), and sleep disturbances. Patients experience many of these symptoms together as they shared:

"Development of treatments that are safe for those with VEDS for other struggles, such as gastrointestinal pain, dysmenorrhea, hormone therapy, menopause, musculoskeletal pain, are also considered vital to the people who spoke during this call to help improve quality of life." [Vascular Ehlers–Danlos syndrome PLS]

Although participants had differing diseases, they shared common symptoms and the desire for greater control over them.

3.2.3 "The Diagnostic Odyssey"

A correct and timely diagnosis is vital to appropriately manage symptoms and receive treatments. A misdiagnosis or a lack of diagnosis prevents patients from controlling their symptoms and may lead to further progression of disease. Patients shared their time-consuming experiences of visiting numerous doctors before obtaining a correct diagnosis, in some instances waiting decades for a correct diagnosis. One patient shared his nearly 30-year diagnostic journey:

"I am 55 years old. I was diagnosed in 2014 at age 48…" [Late onset GM2 gangliosidoses PLS]

Many others shared similar experiences and spoke of delayed treatments due to a diagnosis later in life as well as the impact on patients' quality of life. Caregivers stated:

> "Some caregivers emphasized the importance of early testing for MPS II, reasoning that early diagnosis has a significant impact on patients' quality of life." [Hunter syndrome PLS]

We found that lengthy diagnostic journeys also negatively impacted the relationship between the patient and their care team. As patients stated:

> "The overarching theme here was frustration with medical care, including the feelings of being treated like a hypochondriac, confusion among medical professionals of [Vascular Ehlers–Danlos syndrome] with other non-life-threatening conditions, not being taken seriously in emergencies, and the fear of dying in the emergency department waiting room." [Vascular Ehlers–Danlos syndrome PLS]
> "Some wrote about difficulty getting diagnosed, and one expressed the emotional impact of 'being made out to be a hypochondriac by multiple doctors, nurses, and staff.'" [Systemic sclerosis PFDD]

Constant misdiagnoses resulted in clinical and emotional consequences for patients and caregivers.

3.3 Social/Psychological

3.3.1 Disease Burden on Mental Health

A central commonality was that the burden and uncertainty of their rare disease causes significant stress, worry, frustration, and fear, all of which have severe negative impacts on the mental health of patients. As patients reported:

> "Another speaker shared the crippling anxiety that [cystic fibrosis] has caused him, detailing his fears of not being able to breathe, that his lungs will eventually lose their function, and that he will end up in the hospital." [Cystic fibrosis PLS]
> "Another participant shared that the ongoing worsening of symptoms and feeling 'that I would never get better' led to significant depression." [Huntington's disease PFDD]

We found that patients across the diseases feel that the impact on their mental health is among the worst aspects of the disease. Patients shared:

> "Through all of this [hereditary angioedema symptoms], the other most debilitating symptom is mental health…I suffer with depression; I suffer with anxiety." [Hereditary angioedema PFDD]
> "[Hypothalamic obesity] is described as a "living hell" because the [patient] cannot go unsupervised, it creates toxic family dynamics, puts a strain on marriages and sibling relationships, creates isolation and there is little support available to caregivers or survivors" [Hypothalamic obesity PLS]

Patients shared they felt they were not receiving the mental health resources they need. One patient stated:

> "There's a big mental health component to Acromegaly that needs to be acknowledged…I desperately would have needed access to mental health resources, but no one thought about providing those to me." [Acromegaly PFDD]

3.3.2 Impact on Relationships

The physical and mental toll of their disease often forces patients to depend on their family for help with daily needs. Patients and caregivers explained:

> "What worries me most is the loss of my independence and inability to care for myself and to be an active participant with my family." [Alpha-1-antitrypsin deficiency PFDD]
> "Parents expressed their worry about losing the ability to care for their child at home, either because of the child's condition becoming too severe or because of the parent becoming sick, injured, or aged." [Polyglutamine spinocerebellar ataxias and Dentatorubal-Pallidoluysian atrophy PFDD]

Others elaborated on this theme, sharing that not knowing when the loss of independence would manifest created additional stress. Caregivers also struggle with patients losing their independence. A patient shared:

> "It's very difficult and the spouse, or the mate, or the partner all of a sudden has to take the slack out and it can be a very difficult strain on the relationship or the marriage." [Alpha-1-antitrypsin deficiency PFDD]

Disease burden also affected relationships with friends. The decreased ability to socialize and attend activities with friends due to their disease leads to feelings of isolation. A patient discussed:

> "The isolation of the disease has made my dogs my best friends, and my true friends I had don't call anymore. People just don't know what to do with me." [Frontotemporal degeneration PFDD]

These feelings of isolation are compounded by the rarity of disease, as it is often difficult for others to comprehend what patients are experiencing. For example:

"Homocystinuria is isolating because most people have not heard of it nor do they comprehend the metabolic complexities of the disease. Rarely do others take the time to understand the disease and what it takes to manage it." [Homocystinuria PLS]
"Another caregiver described that many of her daughter's friends have 'faded away. People are uncomfortable seeing her like this. [She's] not the friend they remember.'" [Huntington's disease PFDD]

3.4 Economic/Financial

3.4.1 Losing the Ability to Work

A key issue for patients with rare diseases was the ability to continue working. Symptoms often interfere with the ability to complete a full day of work. For example, a caregiver shared:

"My mother took a job at a local retailer. For the first time in her life, she quit a job when she was unable to retain any of the training. She was humiliated, and her confidence was crushed." [Frontotemporal degeneration PFDD]

The ability of patients to complete their workday is often disrupted not only by the symptoms of their disease, but by the disease treatments as well. As patients shared:

"[Saying infusing my medication has] been disruptive to my work schedule is just about the biggest understatement possible. My infusion from beginning to end [including travel time] takes a pretty hefty time slice out of my day." [Alpha-1-antitrypsin deficiency PFDD]
"Another [patient] described how he could no longer pilot an airplane according to FAA guidelines due to the dose of prednisone he had been prescribed." [Pemphigus pemphigoid PLS]

The disruption to their workday may contribute to loss of employment, which can result in loss of both income and health insurance coverage. Patients and caregivers shared:

"Patients/caregivers shared that they are concerned about the financial burden of treatment. It is especially worrisome to patients who are unable to work, do not have insurance, or are unable to receive disability benefits." [Fabry disease PLS]

Another concern was patients being able to find a job when living with a rare disease. Patients and caregivers shared:

"As I started to look for another job, I wondered what I would tell prospective employers – 'Yes I have 25 years of experience, but on random days I need to completely shut down; at every meeting I will need to get up and walk around for 20 minutes because of swelling and pain, I can't really travel due to my low immune system and risk of stroke, and the commute to the office is too long so I will need to work from home permanently!' This was not going to be easy. But I had to try – I need the health insurance for all the expensive off-label treatments I would need." [Focal segmental glomerulosclerosis PFDD]
"One caregiver talked about how their child(ren) was concerned about not being able to pursue the job or career they are interested in [due to disease burden]." [Glycogen storage disease type 1 PLS]

Due to the need for full-time care at home, many caregivers must leave their jobs as well. A caregiver shared:

"We have forgone possible career opportunities. And many parents ended up quitting their jobs to make sure their child has the care they desperately need. And in our case [he] has spent the last 10 years, essentially out of the paid workforce to provide consistent in-home care." [Krabbe disease PFDD]

Losing the ability to work forces patients into early retirement, regardless of whether they are financially (or emotionally) ready to retire. A caregiver shared:

"He could no longer walk so he retired a second time." [Adrenomyeloneuropathy PLS]

3.4.2 Insurance Limitations

The ability to gain timely and appropriate access to treatments can be delayed due to limitations in insurance coverage and prohibitive prices for treatments. Patients discussed frustration due to denial of coverage for off-label uses of medications. A patient shared:

"At one point I was using more than 10 epi [epinephrine] auto-injectors each month and my insurance would only allow 2." [Mastocytosis PLS]

We found that patients shared similar experiences of delayed treatment due to limits on insurance coverage.

4 Discussion

In this study, we qualitatively analyzed FDA patient engagement sessions for 29 rare diseases and identified numerous commonalities among patients across four study dimensions.

First, we find that patients universally voice that life with a rare disease is overwhelmingly uncertain. This uncertainty

extends to all four dimensions: from concern over whether treatments will be effective to limitations on the patient's ability to engage in socializing and work due to disease burden. This uncertainty translated into a substantial burden on mental health.

Significant anxiety and depression, related to the impact of their disease on daily life, was reported by patients in almost all sessions studied. Additionally, many patients shared that they are not receiving treatment for their mental health. For example, multiple patients across different diseases discussed problems with accessing a therapist, particularly one that understood their unique needs [18].

To alleviate these issues, prioritization of mental health care should be included in treatment plans for patients with rare diseases [17, 19, 20]. While there are multiple ways that this could be implemented, one avenue is to ensure that patient organizations and rare disease Centers of Excellence provide mental health resources [21, 22]. For example, while Centers of Excellence aim to provide patients with multidisciplinary care and determine best practices for treatment and research, a brief review of the websites of many of these centers did not find mental health resources. A first step in addressing this disparity could be adding mental health resources, such as for rare disease therapists or community support groups, onto these websites.

Second, despite the differing etiologies of the rare diseases studied, we found patients reporting many of the same symptoms. Perhaps unsurprisingly, many were related to the nervous system (e.g., pain, fatigue, sleep, headache), which are relatively poorly understood both scientifically and clinically [23–25]. This suggests that there may be opportunities for future medical product development that addresses symptom management in this area irrespective of disease. Additionally, it implies that significant advances in understanding these symptoms in one disease may have larger implications for patients of other, seemingly unrelated, diseases [26]. As a starting point, collaborative rare disease data sharing platforms should consider using these common symptoms as a basis for the initial data fields being collected [27].

Third, we also find that patients with rare diseases want more involvement in the medical product development process. For example, patients want to be involved in clinical trial design, such as the selection of patient-meaningful study outcomes [28, 29]. Patient involvement in endpoint determination is important because patients with rare diseases have unique insights into their most important symptoms [30, 31]. For example, patient input from a PFDD meeting for progressive familial intrahepatic cholestasis (a gastroenterology disorder related to the liver's ability to secrete bile) was used to identify "itch" as a primary endpoint in a drug clinical trial [32].

Considering the patient perspective in the medical product development process may inform more protocols that are more accessible and with more meaningful results [33–35]. In fact, the 21st Century Cures Act ("Cures Act"), signed into law in 2016, requires the FDA to consider the impact of diseases on patients' lives and "patient preferences with respect to treatment of such disease" in the drug development and review process, including the assessment of risk-benefit evaluations that inform regulatory decision making [36, 37]. Internationally, the Council for International Organizations of Medical Sciences (CIOMS) has released a report describing how PFDD-style meetings have helped to incorporate the patient voice in medical product development in the European Union and Japan [38].

The Cures Act also required the FDA to create a Patient-Focused Drug Development Guidance series. In this series of publicly available documents, the FDA provides a roadmap for industry and other stakeholders to recognize the patient voice, including ways to add patient-focused outcome measurements to clinical trials [39]. In addition to the patient engagement sessions utilized in this research, the FDA also provides other avenues for patients to interact with the FDA. This includes a Patient Engagement Collaborative, a Patient and Caregiver Connection program, and a Patient Representative Program [40–42]. Additionally, patient representatives are involved in the review process of rare disease grant applications submitted to FDA's Office of Orphan Products Development.

While the FDA seeks to incorporate the patient voice into product development and review where possible, additional actions can be taken by other stakeholders. For example, medical product developers can seek FDA input early in the medical product development process to discuss the use of patient experience data [43]. In addition, medical product developers may also seek patient input in the early phases of development to identify clinical outcomes for trials [16, 44].

Finally, we find that patients and caregivers reported a significant economic burden due to the costs of living with a rare disease. Patients disclosed significant financial costs of living with a rare disease, including expenses from hospitalizations and medical treatments and equipment [45, 46]. However, the largest reported factor contributing to financial uncertainty for patients and caregivers was the limited ability or inability to work due to disease burden. These difficulties were partly due to the extreme challenges in living with or caring for a patient with a rare disease that have been

previously identified: daily symptom management, time requirements for treatments, and mental health challenges. Losing the ability to work, working less than full-time, or unwanted early retirement causes financial difficulty due to a loss in income, and, in the US, loss of health insurance tied to employment [47].

4.1 Limitations

There are several limitations that restrict the generalizability of our analysis. First, we can only analyze patients who participate in the patient engagement sessions. This limits our analysis to patients who possess the resources (e.g., time, awareness) and ability to engage in these sessions.

Second, patient engagement sessions are public platforms with only limited anonymity for patients when sharing their perspectives. Participants in the patient engagement sessions may not feel comfortable disclosing some topics in a public forum, such as suicidal ideation, reproductive health, or the impact of the disease on sexual intimacy. These types of personal and private topics may not be accurately represented in our results. However, it should be noted that participants are able to make different types of anonymous comment submissions that can be included in the summaries, which could mitigate this limitation.

Third, the FDA does not collect demographic data of participants in the patient engagement sessions, and therefore we cannot provide these data in the manuscript. While efforts are made by the FDA and patient groups to recruit diverse patient perspectives for the engagement sessions, the dearth of quantitative demographic data limits our ability to predict the generalizability of the study.

Finally, the scope of the results of the economic/financial dimension may be limited since these issues were not the focus of the patient engagement sessions, unlike the other dimensions.

5 Conclusion

In this research, we sought to understand whether patients with disparate rare diseases shared any similarities across four dimensions: product development/regulatory, clinical/physical, social/psychological, and economic/financial. A qualitative analysis of summaries from FDA patient engagement sessions for 29 different rare diseases provided key themes for each dimension, and we found significant commonalities. These include similarities in clinical symptoms such as pain and fatigue, as well as significant, unaddressed mental health concerns. Commonalities in the patient perspective can help improve patient care across rare diseases, with implications for the medical product industry, health systems, and health plans.

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Declarations

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Conflict of interest The authors declare that they have no conflicts of interest.

Disclaimer This manuscript reflects the views of the authors and should not be construed to represent FDA's or the Department of Health and Human Services (HHS)'s views or policies.

Availability of data and material Session summaries analyzed in the manuscript can be found on the FDA's website for condition-specific meeting reports and other information related to patients' experience (https://www.fda.gov/industry/prescription-drug-user-fee-amendments/condition-specific-meeting-reports-and-other-information-related-patients-experience).

Ethics approval The FDA institutional research board (IRB) found this study exempt from IRB review.

Consent to participate Not applicable.

Consent for publication Not applicable.

Code availability The codes generated and analyzed for this study are available from the corresponding author.

Author contributions K.L.M. conceived the study. C.M., L.J.F., K.J., S.S., and K.L.M. designed the study. C.M. and K.L.M. collected, analyzed, and interpreted the data. C.M. and K.L.M. drafted the manuscript. L.J.F., K.J., and S.S. provided substantive edits to the manuscript. All authors read and approved the final version of the manuscript.

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