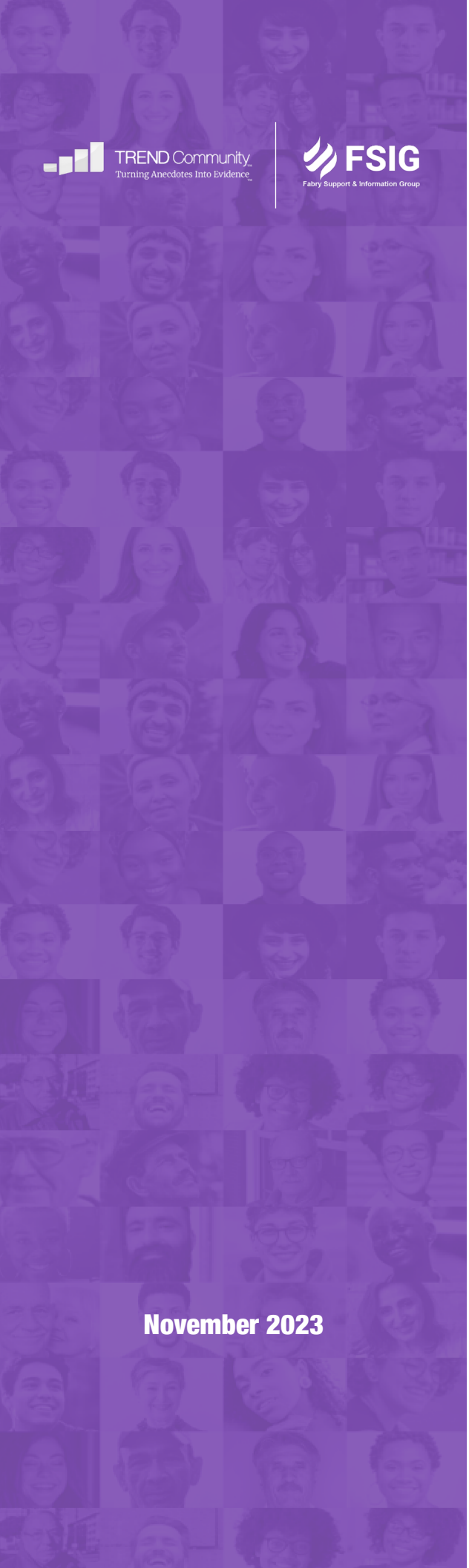

TREND Community
Turning Anecdotes Into Evidence

FSIG
Fabry Support & Information Group

LIVING WITH FABRY DISEASE

Voices From Young Adults

November 2023

TREND Community
Turning Anecdotes Into Evidence

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Fabry disease; rare disease; patient experience; disease awareness; quality of life; patient-reported outcomes

Abstract

Background

Fabry disease (FD) is a chronic, rare genetic disorder that impacts physical, mental, and emotional health. Although a cure remains elusive, FD is treatable. Young adults with FD face a unique set of challenges as they transition from the teenage years into adulthood and take on more responsibilities in managing their disease. To better understand the overall impact of this condition on this patient population and to identify opportunities to create supports tailored to their specific needs, a live Meet Up event was organized to gather their stories while building community and developing actionable solutions.

Methods

The Meet Up event was attended by 9 young adults ages 17 to 30 years with a confirmed diagnosis of FD and 1 significant other who is not living with FD. The event was held in person over 2 days in San Diego, California. A pre-event survey was shared with prospective participants to identify topics for discussion and was completed by 9 respondents. During the event, the contents of topic-based conversations were collected using an anonymous method to extract key insights.

Results

Young adults living with FD identified key issues they face when navigating everyday life, including the need for more assistance with health insurance markets, managing their health, and family planning.

They described challenges in communicating their diagnosis with their social connections, particularly with romantic partners. In addition, participants shared their preferred tools for consuming educational material and receiving support, identified disease knowledge gaps among the broader community, and proposed solutions to bolster awareness about FD and decrease barriers to care while encouraging and supporting patients.

Conclusion

The Fabry Young Adult Meet Up event provided real-world evidence of the challenges experienced by this patient community and highlighted additional opportunities to support this group of patients at a pivotal time in their lives. The results from these proceedings add to the current body of literature about FD and offer an opportunity for caregivers, healthcare providers, researchers, and other allied communities to address these unmet needs and ease the burden experienced by young adults living with this rare, chronic genetic disease.

Background

A Primer on Fabry Disease

Fabry disease (FD) is a rare, inherited genetic disease that belongs to the category of lysosomal storage disorders. It is caused by mutations in the galactosidase alpha (*GLA*) gene on the long arm of the X chromosome, which encodes the lysosomal enzyme alpha-galactosidase A (α-Gal A).[1-3] In healthy cells, this enzyme functions to digest a type of fat molecule called glycolipids, including globotriaosylceramide (Gb3). If it contains a mutation, the α-Gal A enzyme cannot digest Gb3, resulting in a buildup of Gb3 and related glycolipids inside the lysosomes of many cell types, including cells of small and large blood vessels and the kidneys, heart, and nerves.[3,4] This accumulation causes cellular dysfunction, which leads to structural damage and, ultimately, disease manifestations.[5] Although the accumulation of Gb3 begins as early as the fetal period,[6] symptoms typically do not present until later in childhood (see Table 1 below). In addition, this dysfunction triggers a secondary stress response that includes the development of inflammation,[4] ischemia (decreased blood flow), organ hypertrophy (overgrowth of certain organs, such as the heart), and fibrosis (scarring).[1,5] Ultimately, injured cells and secondary stress responses result in multiorgan failure.

The incidence of FD is difficult to estimate due to the wide range of clinical signs and symptoms and the varied age of onset. The reported incidence of FD in women and men is 1 in 40 000 to 117 000 live births.[7] Despite the X-linked nature of this disorder, both males and females can be affected across geographic and ethnic backgrounds.[8] Females develop symptoms due to random inactivation of the normal copy of the X chromosome, a process called *lyonization* that results in the mutated X chromosome being expressed in some cells but not in others.[8] As a result of random X inactivation, symptoms tend to be milder in females than in males. In addition to known pathological mutations, the existence of genetic variants of unknown significance—from *GLA* gene mutations in individuals who do not have the typical findings of FD—further complicate estimates of incidence and prevalence.[9]

Characteristic symptoms of the classic FD phenotype include neuropathic pain, corneal dystrophy, decreased sweating, and skin lesions known as angiokeratomas.[5,10] Due to the X-linked pattern of inheritance, males typically have more severe symptoms than do females.[10,11] The organs most commonly affected are the heart, kidneys, and nerves as well as the cardiovascular, neurovascular, dermatological, and ophthalmological systems.[1,2,5] The accumulation of Gb3 over time in various cell types leads to hypertrophic cardiomyopathy, cardiac arrhythmias, progressive kidney failure, and stroke.[10] Patients with a nonclassic FD phenotype may have fewer organs involved. Regardless of phenotype, as many as 60% of patients with FD have cardiac manifestations.[8,12] The majority of FD-related strokes are ischemic in nature but can also be hemorrhagic.[13] The impact of FD on cognitive function is a concern of patients and healthcare providers and has been evaluated in numerous studies. Some evidence suggests FD-related impairment of executive functioning, particularly information processing speed and attention.[14] However, despite findings of brain structural changes upon imaging, a longitudinal follow-up study of patients living with FD found overall stable cognitive function over 8 years.[15]

As many as 60% of patients with FD will have cardiac manifestations of their disease.

A diagnosis of classic FD can be made clinically based on the constellation of signs and symptoms noted above and then with confirmation by enzymatic and genetic testing.[16] In adults with nonclassic or late-onset FD, a diagnosis can be missed and only reached by screening patients after a stroke, cardiac event, or onset of kidney disease.[17] Given FD's X-linked inheritance and lyonization in female patients, the severity of symptoms can vary widely, and genetic testing is often necessary to make a definitive

diagnosis. With more than 1000 *GLA* variants documented to date in patients with FD,[18] it is also important to note that not all variants have been confirmed to be pathogenic. When the pathogenicity of a given *GLA* mutation is unknown, it is referred to as a genetic variant of unknown significance and may not be causative of disease.[9,18]

Table 1. Phenotypic classification and overview of the clinical spectrum of FD

	CLASSIC	NONCLASSIC
Enzyme activity	None	Some/varying amounts
Age of presentation	Childhood/adolescence	Adulthood – usually between 30 and 70 years old
Symptoms	Neuropathic pain Angiokeratomas Corneal dystrophy Hypohydrosis	Dependent on organ involvement
Organs involved	Multiple, including heart, skin, nervous system, kidneys, eyes	Often 1 organ, with more extensive involvement

In addition to genetic testing, diagnostic evaluation options include biochemical evaluation of α-Gal A enzyme activity, often the first step and most common test used[9]; lysosomal Gb3 levels in the urine[8]; or lysosomal Gb3 levels in the blood.[8] Kidney biopsies, although used less frequently, are diagnostic for FD and can prove particularly useful when molecular and genetic test results are inconclusive for diagnosis.[8] Newborn screening is being implemented in some countries (eg, Italy, Japan, Taiwan).[19] Prenatal testing can be done by chorionic villus sampling or amniocentesis. In families with a known *GLA* mutation, preimplantation genetic screening is now available in embryos created through in vitro fertilization.[20]

Overview of the Current Treatment Landscape

Treatment of FD focuses on disease management, as there is no available cure. Enzyme replacement therapy (ERT) with synthetic α-Gal A enzyme administration via intravenous infusion functions to replace the missing enzyme and enable processing of glycolipids, which in turn prevent accumulation and damaging effects on cells and tissues.[8] Two commercial ERT products, agalsidase beta and pegunigalsidase alfa, are available in the United States, and agalasidase alfa and pegunigalsidase alfa are approved for use in the European Union. An additional treatment option includes the non–ERT-based therapy migalastat. This small molecule functions as a chaperone, binding existing α-Gal A enzyme and preventing its natural turnover, thereby increasing its concentration and activity in lysosomes.[21,22] A major limitation of chaperone therapy is that the chaperone only works for certain types of enzyme variants in the setting of adequate endogenous enzyme production; thus, it is not indicated for all patients with FD.

Two substrate-reduction therapeutic candidates are currently in phase 3 and phase 2 clinical trials.[22] These candidates are small molecules that work upstream of the α-Gal A enzyme by reducing amounts of glycolipids available to the enzyme, thereby decreasing the accumulation of Gb3. Gene therapy approaches designed to increase α-Gal A enzyme activity and enable stable enzyme production are under investigation.[22]

Psychosocial Impact of Living With FD

Pain symptoms, including severe pain crises, are frequent manifestations of FD and negatively impact the quality of life (QoL) and mental health of affected patients.[23,24] An observational study among Italian patients with FD revealed that these patients have a worse QoL than that of healthy adults as well as other patients with certain chronic painful disorders, such as Crohn disease and multiple sclerosis.[25] Patients with FD also experience negative mental health symptoms, including depression, anxiety, and cognitive difficulties.[14,15,26] In the largest study known to date, 46% of patients with FD reported symptoms of clinical depression, with pain identified as the most common correlating factor.[27] Cognitively, patients with FD may have impairments in executive function, information processing speed, and attention,[14] although the extent and clinical impact of these findings remain unclear and continue to be investigated.[28] A study using brain imaging in adults with FD did not reveal a connection with structural brain changes,[28] and although changes in brain white matter have been observed in patients with FD, these structural changes were not found to correlate with depression or anxiety scores.[29] The higher prevalence of depression and anxiety in adults living with FD is consistent with the experience of patients living with other rare diseases. In a survey conducted among adults with rare diseases and

caregivers of children with a rare disease, predictors of anxiety and depression included poor peer relationships, experience of stigma, fatigue, poor sleep, and limited ability to engage in social-cultural activities.[30] Last, emerging data on the psychosocial impact of the COVID-19 pandemic on those living with rare diseases suggest that this patient population experienced increased uncertainty around access to needed health care, social isolation, and adverse mental health consequences. In a recent survey conducted in Spain, adults with a rare chronic condition experienced heightened rates of anxiety and depression compared with those of the general population during the COVID-19 pandemic.[31]

Value of the Patient Experience: Fully Understanding the Burden of FD

Studies on QoL and other factors have established the importance of capturing the many facets of the patient experience, from coping with a new diagnosis to planning for the future and maintaining recommended therapeutic regimens. However, literature on effective interventions to support the young adult (YA) Fabry population during a transitional phase of life—when more freedom and independence are typically desired as well as expected by cultural norms—is lacking. Live events such as the Meet Up described here offer a unique venue for patients living with serious conditions to share their experiences with one another, gain support and resources, and collect critical primary qualitative evidence to inform programs to better support patients along their disease journey. Such events may be particularly impactful for YAs living with FD who may have experienced even greater isolation than the general population during the COVID-19 pandemic and are now navigating a return to “normal” societal activities. The purpose of this listening study was to engage YAs living with FD to understand their communication preferences and areas where programs can offer further support and maximize success in their adult lives.

Methods

The Fabry Young Adult Meet Up event was held in person on June 9 to 11, 2023, in San Diego, California. The Meet Up was jointly organized and facilitated by TREND Community and the Fabry Support & Information Group (FSIG). A total of 9 YAs with FD ages 17 to 30 years and 1 partner who is not living with FD attended the live event. A pre-event survey was distributed electronically to potential participants 8 weeks before the planned Meet Up to identify high-value topics for discussion. A list of 11 potential topics was provided, along with 2 open-ended questions to source any additional topics not included in the list (Table 1). The pre-event survey was completed by all 9 YAs living with FD.

Audio proceedings from the Meet Up event were collected by facilitators during the event, then transcribed and analyzed qualitatively, while preserving the anonymity of each participant. The data analysis method aligns with the standards outlined by O'Brien et al for qualitative research.[32]

Results

Sourcing Topics for Discussion From Young Adults With FD

Seven out of 9 survey completers identified "managing the insurance system" and "staying on top of health" as key topics for discussion out of the 11 proposed topics. A full list of the rankings of preidentified discussion topics can be found in Table 1. Additional topics flagged by some respondents through open-ended questions were mental health and cognitive functioning as they relate to living with FD (2/9 respondents) and information about new treatments on the horizon (2/9 respondents).

Table 2. Respondents' ranking of proposed topics in the premeeting survey

Topic	No. of Respondents (N = 9)
Managing the insurance system	7
Staying on top of health	7
Family planning	6
Building connections with others living with Fabry	5
Dating/relationships	5
Coping with the unknown	5
Advocacy for those living with Fabry	5
Advocating for myself	4
Managing medical appointments	3
Managing treatments	3
Living on my own	2

Opportunities to Engage YAs With FD

A key objective of the YA Meet Up was to ascertain engagement preferences from the Fabry YA patient community. Historically, it has been challenging to engage and retain YAs living with a chronic medical condition in psychosocial support programming. Participants in the YA Meet Up shared that in-person small group meetings were more conducive than large gatherings for a discussion of the topics listed in Table 2. Importantly, they also noted that the presence of peers living with FD encouraged them to speak in their own voice and share their experiences. They further noted that the absence of parents and guardians allowed them freedom to openly share their perspectives, as parents/guardians sometimes speak for them.

Regarding the preferred means of building community and receiving educational information, the group identified Facebook and Instagram as the 2 platforms they engage with the most frequently (Table 3). The preferred format for content is platform specific, with Facebook seen as the best platform for groups, whereas TikTok was viewed as most suitable to share short educational content with the broader general public while also catering to the shorter attention span of YAs. Respondents recommended Instagram stories and TikTok as the best short-video tools, and that sharing the same

videos across platforms would help make regular posting easier. Of note, they reported concerns about incorrect FD information encountered online and stressed the importance of debunking false claims.

Table 3. Social media platforms and content format preferentially used by YAs living with FD

Platform	Content Format
facebook	Groups
Instagram	Stories
TikTok	Videos/reels

Empowering Conversations Around Diagnostic Disclosure

Disclosure of a chronic diagnosis to partners, family members, friends, and coworkers can present many challenges, including concerns of being seen differently, being asked if the disease is contagious, and being discriminated against in a professional setting. Participants shared that they often delay telling a loved one about their FD diagnosis, waiting on average 1 to 1.5 years to disclose the diagnosis to a romantic partner. Importantly, YAs living with FD in long-term romantic partnerships indicated that they begin family planning discussions earlier in adulthood than do peers who do not live with a rare disease. They are interested in learning about options, which has consequences for timely access to genetic counseling, family planning services, prenatal screening, and other support services.

Personal Reflections: Advice to Younger Self and Others

Participants reflected on their experiences as a YA living with FD and shared advice they would give to their younger self and healthcare professionals (Fig. 1). Their responses shed important light on their lived experience and can inform how fellow patients, caregivers, family, friends, and the medical community can strengthen the FD community and enhance the patient experience.

Figure 1. Participants' reflections on advice for their younger self and others about living with FD

Supporting the Mental Health of Young Adults Living With FD

Participants identified coping with the uncertainty associated with living with FD, including physical and psychosocial impacts, as an important topic for discussion (see Table 1). They also identified the importance of helping others in their social circles understand the mental health symptoms and associated issues that accompany a rare chronic condition such as FD. They noted that their loved ones could better support their mental health if they understood the wide range of psychological stressors associated with living with a rare chronic condition. They also reported that although disclosing their diagnosis and symptoms/limitations to family and friends can be difficult initially (see section, "Empowering Conversations Around Diagnostic Disclosure," above), it can ultimately create a close support network where loved ones can actively encourage a YA with FD to engage in self-care and employ coping skills such as resting or hydrating. The consensus among the group was that they would not allow an FD diagnosis to take over their lives.

Decreasing Barriers to Care and Interactions With the Medical Community

Manifestations of FD can vary widely, and medical management often includes FD-specific interventions and non–FD-specific treatments to manage organ-specific symptoms.[10] Participants noted that the frequency of symptoms and limited efficacy of current treatment options are barriers to seeking care.

They identified specific disease-related symptom areas where improved interventions would be welcome (Fig. 2).

Figure 2. FD-associated symptoms for which participants identified opportunities for more-efficacious treatments

As a group, YAs with FD reported that they are interested in staying informed about treatment options in development and about ongoing clinical trials. They expressed a desire for a reliable resource to learn about clinical trials and whether they may qualify to participate.

Building Support by Engaging and Educating Community Members About FD

As is the case with many rare diseases, awareness of FD beyond the patients themselves and certain medical communities is limited. Yet, increasing awareness and understanding of the clinical manifestations, chronicity, and potential complications of FD were noted as key by the YAs who participated in the Meet Up event. Specifically, they reported that although they see a need for education and awareness for their loved ones and social networks, they do not wish to take on the burden of explaining and raising awareness of their disease. Rather, when friends and loved ones take the initiative to learn about FD, they experience this as a deep expression of caring. This points to the need for accessible tools that facilitate learning by family, friends, and the broader community.

Educating Relatives, Partners, and Friends to Be the Best Support They Can Be

As part of the discussion during the Meet Up event, input was solicited from YAs living with FD on the best ways to educate their support networks, and the broader community, about the disease and its

many impacts on QoL and daily functioning. As shown in Figure 3 below, participants drew from their own experiences and shared various ideas on how to empower their support networks to become better advocates and allies.

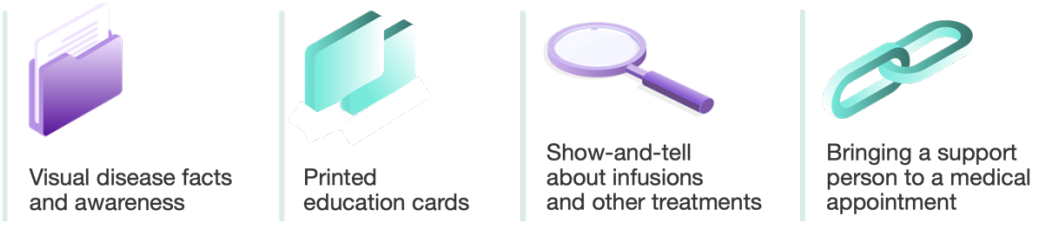

Figure 3. Educational tools identified by YAs living with FD to share disease information with their support networks

Discussion

The Fabry Young Adult Meet Up was held to gain insights into how to best support YAs living with FD and add real-world evidence to the growing body of literature focused on this rare genetic disease. FD is a complex chronic disease, with notable variability in the severity of symptoms and onset of disease.[1-3] Whether diagnosed in childhood (classic phenotype) or in adulthood (nonclassic phenotype),[33] YAs living with FD represent a unique subgroup of this patient community facing age-specific challenges, including transitioning to independent living, family planning, and financial considerations. This natural yearning for adult responsibilities while potentially still navigating complex healthcare needs and relying on caregivers for support can constrain their independence and limit their ability to engage in social activities.[34]

A shared priority among Meet Up participants was a desire to increase disease awareness and educate their community at large about the everyday impacts of FD. This is consistent with other surveys of YAs living with chronic illnesses, which indicate that information sharing with teens, YAs, and their caregivers is a large unmet aspect of care.[34] Additional key findings included a marked interest in access to updated information to take ownership of their medical care, including support in navigating health insurance options and keeping up with medical management (Table 2). Family planning and the impact of living with this diagnosis on romantic relationships were also of high importance to the participants. It is noteworthy that, without any prompting, some participants flagged a need for more information on coping with mental health challenges and interest in keeping up to date with emerging treatment options and ongoing clinical trials (see Results section). Coupled with the high prevalence of depression and

other neuropsychiatric disorders among those living with FD,[23,24] these data underscore the importance of addressing the mental and emotional health of YAs living with an FD diagnosis.

Furthermore, these data highlight an opportunity to meet these patients where they are. The consensus among the participants was that social media platforms such as Facebook and Instagram are well suited for building community and sharing educational content (Table 3). For general education and disease awareness, the preference was for short content, such as TikTok reels, noting attention span as a key consideration when choosing an educational medium. As with any patient education and communication efforts, it is essential to communicate via preferred tools to ensure the broadest reach and retention, as well as to offer age-specific programming to create engaging and safe spaces for sharing, reflecting, and building community.

Meet Up discussions, such as this event, can yield valuable information for all stakeholders involved in the lives of YAs living with a rare, chronic genetic condition, including FD: family and friends, medical and research communities, those from school and professional settings, disease advocates, as well as the biopharma community. In this study, patient-led discussions spotlighted unmet needs and generated original ideas to meet those needs. These learnings may be applicable to YAs living with other rare conditions and offer concrete solutions to remedy these gaps in a patient-centered way.

Conclusion

The Fabry Young Adult Meet Up event was a catalyst for awareness and a forum for support. Insights gathered during the event provide qualitative data on the patient experience in 3 key focus areas: 1) challenges faced by YAs living with FD; 2) unmet medical, mental, and emotional needs; and 3) a path toward solutions for tailored educational and psychosocial interventions to improve overall care and QoL. Participants noted the small size of a live Meet Up as a conducive setting to gather this often very personal and relevant information.

This white paper adds to the existing body of evidence on the impacts of FD and sheds light on the particular opportunities to support YAs living with this rare genetic condition. Although medical and psychological treatments have progressed and new therapeutic candidates are on the horizon, patient-provided experiences can continue to fill knowledge gaps and promote continuous improvements in care and QoL. Learnings from the Meet Up event will be used to guide the planning and implementation of additional programming by TREND and FSIG to empower YAs living with FD to manage their condition and build sustainable community within family, peer, and broader social circles. Tactics being

explored to reach these objectives include maintaining contact with YAs living with FD through text messages and preferred social media platforms, hosting additional live events, closing knowledge gaps about this condition among the medical community, and developing YA-focused programming to retain participation and to ensure that their contributions translate to real impact in the lives of current and future patients living with FD.

Declarations

Ethical Approval, Consent to Participate and Publish

All Meet Up participants provided their written and verbal consent for the contents of the discussions to be collected and transcribed with the purpose of publishing anonymized key insights gathered during the event.

Acknowledgments

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