



Barth Syndrome  
Foundation

# The Voice of the Patient: Barth Syndrome

A report on the Externally-Led Patient-Focused  
Drug Development Meeting

**Externally-Led Public Meeting: July 18, 2018**

**Report Date: March 8, 2019**

**Hosted by**  
Barth Syndrome Foundation



## The Voice of the Patient: Barth Syndrome

This report represents the summary report composed by Barth Syndrome Foundation as a result of an Externally-Led Patient-Focused Drug Development meeting, a parallel effort to FDA's Patient-Focused Drug Development Initiative. This report reflects the host organization's account of the perspectives of patients and caregivers who participated in the public meeting.

### Submitted to

Center for Drug Evaluation and Research (CDER) &  
Center for Biologic Evaluation and Research (CBER)  
U.S. Food and Drug Administration (FDA)

**Authors and collaborators:** Valerie M. Bowen, Emily Milligan MPH, Susan McCormack, MBA, Kate McCurdy, MBA, Theo Smart, technical writer, Lance Sherriff, transcript reviewer, Matthew Toth, PhD, and James Valentine, JD, MHS. Bowen, Milligan, McCormack, McCurdy, and Toth are all affiliated with BSF and have no additional disclosures. Smart and Sherriff have no disclosures. Valentine is employed by Hyman, Phelps & McNamara, P.C., a law firm that represents sponsors who are developing drugs for rare diseases as well as rare disease patient advocacy organizations, including BSF.

**Funding received:** The Barth Syndrome Foundation receives funding from Stealth BioTherapeutics in the form of sponsorship of programs and events. The Barth Syndrome Foundation Externally-Led Patient-Focused Drug Development Meeting was designed and implemented entirely by BSF. The resulting The Voice of the Patient: Barth Syndrome report also was prepared by BSF. Sponsorship of the meeting was provided by Stealth BioTherapeutics, the Wilkins Family, Amicus Therapeutics, Healx, Cayman Chemical, Chondrial Therapeutics, ThermoFisher, Cambridge Isotope, and Randall Hall. These funds were used to secure meeting space and to support other logistical and consulting services for the initiative. BSF explicitly states that the sponsoring companies had no control over the meeting content or related activities.

**Statement of use:** Barth Syndrome Foundation has the necessary permissions to submit The Voice of the Patient: Barth Syndrome report to U.S. FDA. Linking to the report from the FDA website will not violate the proprietary rights of others.

**Version Date:** Aug. 20, 2019

**Revision statement:** This document has not been revised and/or modified after the version date listed above. The submitters have received all necessary permissions to submit this external resource to FDA. Linking to this resource from the FDA website does not violate the proprietary rights of others. Permission to link from the FDA website is granted by BSF ([barthsyndrome.org](http://barthsyndrome.org)).

**Point of Contact:** Emily Milligan, BSF Executive Director, [emily.milligan@barthsyndrome.org](mailto:emily.milligan@barthsyndrome.org)



# Table of Contents

(Please call up the Bookmarks for a clickable link to each section)

<b>Introduction</b> .....	<b>1</b>
<i>Overview of Barth syndrome</i> .....	1
Barth syndrome etiology .....	2
Clinical manifestations .....	2
<i>Meeting overview</i> .....	6
<i>Report overview and key themes</i> .....	7
Key messages on the burden of disease in Barth syndrome .....	8
Key messages regarding patient perspectives on the treatment options in Barth syndrome .....	9
Appendices .....	10
Benefit-Risk Framework .....	10
<b>Topic 1: Most significant symptoms of Barth syndrome and their impact on daily life</b> .....	<b>11</b>
<i>Perspectives on symptoms that matter most to patients and their caregivers</i> .....	13
A. Skeletal muscle weakness and exercise intolerance .....	13
B. Extreme fatigue .....	14
C. Eating or digestive problems/nutritional issues/nausea .....	15
D. Neutropenia and infections .....	16
E. Cardiomyopathy, heart failure, and arrhythmia .....	17
F. Pain .....	18
G. Short stature/delayed growth .....	18
H. Learning/attention/cognitive issues .....	19
I. Sleeping difficulty .....	19
J. Mood disorders (including depression, anxiety, anger) .....	20
K. Other symptoms .....	20
<i>Impact on daily life of patients and their caregivers</i> .....	21
A. Repeated hospitalization and other healthcare utilization .....	21
B. Time missed from school or work .....	22
C. Setbacks, sacrifices, lost employment, fewer prospects as a consequence of Barth syndrome .....	23
D. Other sacrifices and missed opportunities due to Barth syndrome .....	24
E. The psychosocial and emotional impact of Barth syndrome on caregivers and family .....	25
<b>Topic 2: Patient and caregiver perspectives on treatment/management of the condition</b> .....	<b>25</b>
<i>Experiences with existing Barth syndrome management overall</i> .....	27
<i>Approaches to manage cardiac issues and neutropenia associated with Barth Syndrome</i> .....	28
A. Heart medications .....	28
B. Medications for neutropenia and neutropenia-related infections (G-CSF and antibiotics) .....	29
C. Heart transplants .....	30
D. Defibrillators .....	30
<i>Approaches to address skeletal muscle weakness, exercise intolerance, and related symptoms associated with Barth syndrome</i> .....	31
A. Physical therapy, occupational therapy, gym, and activities to increase exercise tolerance .....	31



B. Mobility equipment (cane, walking stick, adaptive stroller, motorized scooter, wheelchair) .....	31
C. Ankle/leg or other braces .....	32
D. Surgical procedures .....	32
<i>Approaches to manage eating/ feeding challenges and nutritional deficiencies associated</i>	
<i>with Barth syndrome</i> .....	32
<i>Approaches to manage pain, fatigue, sleep problems, and mental health issues associated with Barth</i>	
<i>syndrome</i> .....	33
<i>Perspectives on future treatments and considerations in decisions regarding treatment and clinical trial</i>	
<i>participation</i> .....	34
A new treatment for Barth syndrome should address which symptoms? .....	34
Preferences regarding modes of treatment administration .....	35
Perspectives on the side effects/risks of treatment .....	36
Perspectives on clinical trials .....	36
The ultimate goal of treatment .....	38
<b>Post-meeting questionnaire</b> .....	<b>38</b>
<i>Symptoms that matter the most—over the last year and over a lifetime</i> .....	39
<i>Activities that cannot be done as well or fully as one would like, or at all, due to Barth syndrome</i> .....	39
<i>A day in the life with Barth syndrome</i> .....	40
<i>Changes in Barth syndrome over time</i> .....	42
<i>What worries one the most about Barth syndrome</i> .....	43
<i>Other non-medical impacts of Barth syndrome: practical, financial, psychological, and</i>	
<i>socioeconomic</i> .....	44
<i>Barth syndrome management and its downsides</i> .....	45
<i>Making decisions about using a therapy or treatment</i> .....	46
<i>An ideal treatment would address</i> .....	46
<i>Preferences regarding modes of treatment administration and convenience of a new treatment</i> .....	46
<b>Incorporating patient input into a benefit-risk assessment framework for Barth syndrome</b> .....	<b>47</b>
<b>Conclusion</b> .....	<b>49</b>
<b>Appendix 1: Meeting program, includes agenda and discussion questions</b> .....	<b>51</b>
<b>Appendix 2: Meeting participants</b> .....	<b>63</b>
<b>Appendix 3: Polling questions and results</b> .....	<b>64</b>
<b>Appendix 4: Barth syndrome EL-PFDD follow-up questionnaire</b> .....	<b>72</b>



## Introduction

On July 18, 2018, Barth Syndrome Foundation (BSF) hosted an Externally-Led Patient-Focused Drug Development (EL-PFDD) meeting to share with officials at U.S. Food and Drug Administration (FDA) and other stakeholders (e.g., industry and research institutions) the perspectives of people living with



Barth Syndrome (BTHS), its impact on their daily lives, and their expectations and priorities for current and future treatments for BTHS. BSF held an externally-led PFDD meeting intended to more systematically gather patients' perspectives on their condition and available therapies to treat their condition. This report contains information about patients' experiences with Barth syndrome and their perspectives about treatment options, current and future. It is submitted to FDA for the Agency's consideration in review of applications for new drugs to treat or prevent BTHS. In an effort to maximize attendance, BSF opted to host the EL-PFDD meeting in Clearwater Beach, Florida, as part of the 2018 biennial international conference, which was expected to convene more than 25% of the world's known BTHS population.

More information on the FDA Patient-Focused Drug Development meetings can be found at <https://www.fda.gov/drugs/development-approval-process-drugs/cder-patient-focused-drug-development>.

## Overview of Barth syndrome

BTHS is a complex, multisystem, X-linked metabolic and neuromuscular disease.<sup>1</sup> Its cardinal features include life-threatening dilated cardiomyopathy and neutropenia, which put individuals at risk of infectious morbidity, as well as skeletal myopathy and growth retardation—but there are many other symptoms. Although the mixture of complications is similar, each patient has his or her own unique manifestation of the disease—even within the same family. For example, one brother may have mild cardiomyopathy but persistent neutropenia, while his brother may have severe cardiomyopathy and cyclic neutropenia.

Current estimates are that BTHS occurs in 1/300,000-400,000 live births. BSF is aware of 111 individuals currently living with BTHS in the United States and 230-250 worldwide. In addition, the community includes the families of 74 individuals with confirmed BTHS who have died. Although in most cases the condition is inherited, data suggest that in approximately 12% of children born with BTHS, it is the result of a *de novo* mutation.<sup>2</sup>

<sup>1</sup> Clarke SL, Bowron A, Gonzalez IL et al. Barth syndrome. *Orphanet J Rare Dis*. 2013 Feb 12;8:23. doi: 10.1186/1750-1172-8-23.

<sup>2</sup> Kirwin SM, Manolagos A, Barnett SS, Gonzalez IL. Tafazzin splice variants and mutations in Barth syndrome. *Mol Genet Metab*. 2014 Jan;111(1):26-32. doi: 10.1016/j.ymgme.2013.11.006. Epub 2013 Nov 19.



BTHS is believed to be a rarely recognized cause of fetal death. A record review in the United Kingdom (UK) has reported that stillbirths, miscarriages, neonatal, and infant deaths that were likely due to the syndrome occurred in one in three BTHS-affected families.<sup>3</sup> Approximately 50% of deaths due to BTHS occur within the first year of life, 85% before the fifth year of life.

## Barth syndrome etiology

In 1996, the gene responsible for BTHS was discovered.<sup>4</sup> Pathological variants in the *TAZ* gene, located on the q arm of the X chromosome at position 28, interrupt the production of tafazzin proteins. Because



this is an X-linked disorder, it mostly affects males, but it should be noted that several female BTHS patients also have been confirmed. This report will use male pronouns and discuss “boys and young men,” but know that females also can be affected.

Among other functions of tafazzin, the primary protein that is affected in BTHS, is the catalysis of an essential reaction that contributes linoleic acid

to cardiolipin, a phospholipid that plays critical roles in the structure and processes of mitochondria. Absence of tafazzin results in a deficiency of mature cardiolipin (L4-CL) and an accumulation of monolysocardiolipin (MLCL)—ultimately leading to abnormalities in mitochondrial structure and function. Many unique *TAZ* gene mutations have been detected in the population affected by BTHS—but, as of yet, there is little clear correlation between the genotype and the phenotype of the disease.

## Clinical manifestations

**Cardiomyopathy:** The single most common symptom in BTHS is cardiomyopathy, occurring in about 90% of boys with the syndrome. Cardiomyopathy may start to develop early in the womb—it has been documented as early as 18 weeks *in utero*. Consequently, neonatal presentations are common. At least two-thirds of boys with BTHS develop heart failure and die during the first year of life. Although life threatening at presentation, the condition often improves if the child lives through this crisis period. Echocardiogram parameters may then normalize completely, at least for a time, in about half of those affected. This has led to some individuals being misdiagnosed with viral cardiomyopathy.

BTHS-related cardiomyopathy is typically a dilated cardiomyopathy in which the heart muscle becomes stretched and thin. The ventricles can also thicken and become hypertrophic or may alternate between the two presentations. Despite the apparent clinical improvement in boys who survive the presentation

<sup>3</sup> Steward CG, Newbury-Ecob RA et al. Barth syndrome: an x-linked cause of fetal cardiomyopathy and stillbirth. *Prenat Diagn.* 2010 Oct;30(10):970-6.

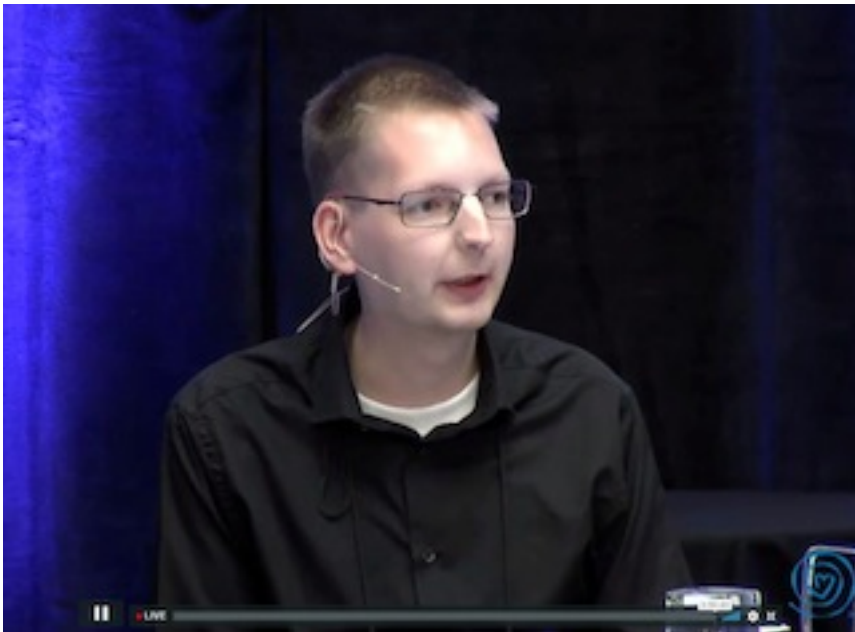
<sup>4</sup> Bione S, D'Adamo P, Maestrini E, Gedeon AK, Bolhuis PA, Toniolo D. A novel X-linked gene, G4.5, is responsible for Barth syndrome. *Nat Genet.* 1996 Apr;12(4):385-9.



of cardiomyopathy in their first year of life, ventricular strain patterns remain persistently abnormal on longitudinal studies in all patients who have been followed. Consequently, individuals with BTHS are prone to arrhythmias later in life.<sup>5,6</sup>

Histopathological features of BTHS-related cardiomyopathy may include an opaque white glistening endocardium (endocardial fibroelastosis) with diffuse thickening, creating pockets in the base of the left ventricle where clots can form. This left ventricular non-compaction (LVNC) is a common feature of BTHS and may lead to strokes when there is severe cardiac failure. Electrophysiological issues also are common.

**Neutropenia:** Approximately 85% of patients with BTHS have neutropenia, but it is highly unpredictable. While neutropenia has not been detected in some affected individuals, others have severe, chronic neutropenia with dangerously low neutrophil counts at all times. However, for reasons that remain unclear, many patients have cyclic neutropenia (normally high neutrophil counts that can plummet to exceedingly low levels and then be followed by the sudden return of high neutrophil counts), thereby making it very difficult to diagnose and treat.



Low neutrophil counts put individuals at risk of morbidity and mortality from opportunistic infections—sometimes even due to the body’s own normally harmless microbiota. Common infections become severe and can lead to septicemia. This can occur at any time but is particularly problematic for patients who have foreign materials in their bodies (e.g., gastrostomy tubes used to address nutritional feeding issues, implanted defibrillators—ICDs—used to revert cardiac arrhythmias, or central lines used to deliver medications or nutrition). Over their lives, many boys

and men with BTHS experience numerous life-threatening infections that may lead to frequent hospital visits, severely affecting quality of life.

**Skeletal myopathy:** BTHS is also characterized by a proximal muscle weakness (mainly in a limb girdle distribution) that may delay achievement of early motor milestones. The muscles are moderately hypoplastic (underformed) and weak but permit unsupported walking. However, many young men

<sup>5</sup> Spencer CT, Byrne BJ, Gewitz MH et al. Ventricular arrhythmia in the X-linked cardiomyopathy Barth syndrome. *Pediatr Cardiol.* 2005 Sep-Oct;26(5):632-7.

<sup>6</sup> Spencer CT, Bryant RM, Day J et al. Cardiac and clinical phenotype in Barth syndrome. *Pediatrics.* 2006 Aug; 118(2):e337-46. Epub 2006 Jul 17.



experience problems when they have to walk longer distances. This weakness may cause fatigue that interferes with other daily activities—and some individuals opt to use mobility aids such as wheelchairs simply to conserve energy. Skeletal myopathy is progressive over time and becomes severe by the fourth decade of life. Some young men also develop respiratory weakness and become reliant upon mechanical support—continuous positive airway pressure (CPAP) machines—to help them breathe at night.

**Growth retardation:** Another hallmark of the disorder is a constitutional delay of growth and puberty. Boys may have a delayed bone age ranging from 8 months to 3½ years, with late sustained growth until early in their 20s. When growth does occur, it can be quite rapid and young men may become taller than the average of their parents. This often occurs without a commensurate increase in food intake—feeding problems, including lack of appetite and food intolerance, are common and may be aggravated by mouth ulcers in the neutropenic. Many young men become emaciated and need GI tubes at this stage to receive adequate nutrition. This physically challenging stage of life is when it is most common to experience arrhythmia, and some individuals fall back into heart failure.

**Metabolic consequences:** As a mitochondrial disease, BTHS has various metabolic effects including lactic acidosis, hypoglycemia (including late nocturnal hypoglycemia, which may require late-night dietary supplements to manage), hyperammonemia, and hypocholesterolemia. These metabolic abnormalities can present as acute neonatal problems, when under stress by infections, or may be occult, as in the case of nocturnal hypoglycemia.

**Exercise intolerance and fatigue:** Impaired mitochondrial function is associated with diminished skeletal muscle O<sub>2</sub> extraction. When combined with myasthenia, poor cardiac performance, metabolic abnormalities, and nutritional deficiencies, this contributes to an incessant and profound fatigability in some young men that greatly impairs their quality of life. Studies have found a very low ventilatory threshold in individuals with BTHS during performance of even the light physical activity of routine daily activities.<sup>7</sup>

**Patient variation:** While Figure 1, drawn from the cohort of BTHS patients in the UK, illustrates the frequency of symptoms overall among patients, one of the key features of BTHS is the wide degree of variation between the symptoms and severity of the disease from one patient to another. For instance, some may have severe neutropenia but little cardiomyopathy, while in others the opposite pattern is seen.

There is also a small population of individuals who appear to have “intermediate BTHS” with no neutropenia and better muscle and heart function. Notably, they have relatively normal levels of mature cardiolipin (L4-CL), though they continue to have high levels of MLCL.

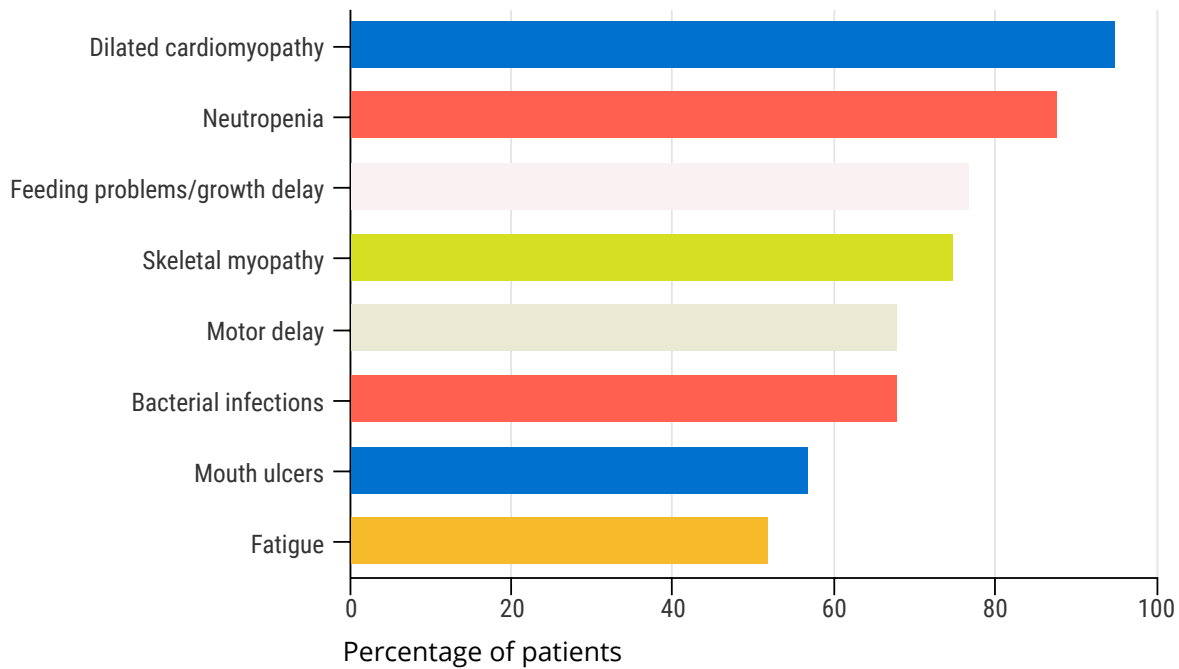
---

<sup>7</sup> Spencer CT, Byrne BJ, Bryant RM et al. Impaired cardiac reserve and severely diminished skeletal muscle O<sub>2</sub> utilization mediate exercise intolerance in Barth syndrome. *Am J Physiol Heart Circ Physiol*. 2011 Nov;301(5):H2122-9. doi: 10.1152/ajpheart.00479.2010. Epub 2011 Aug 26.





**Figure 1. Frequency of Symptoms in UK BTHS Patients**



**Treatment:** Multidisciplinary care is required to manage this multisystemic disease. In addition to their primary care providers, individuals with BTHS may require specialists in genetic counseling and clinical genetics, pediatric cardiology (as well as transitional and adult cardiology, later in life), echocardiography, pediatric hematology, pediatric metabolic specialists, physical and occupational therapy, speech and language therapy, dietitians, and specialized dentistry. With the exception of a limited number of BTHS-treating pediatric clinics, services are rarely located within the same center—which means that the pursuit of essential care can be very time-consuming, costly, and detrimental to work or schooling.

Care is individualized to address the clinical conditions that affect each patient—but for many, the treatment approach comes with its own set of complications. For instance, heart failure has been successfully managed with heart transplantation in some cases. There is a severe shortage of donor hearts, however; and children (and men) waiting for a transplant may become hospitalized, spending months on left ventricular assist devices (Berlin Heart devices). Some have died due to complications on bridging procedures.

The burden of pharmaceutical treatment is also great. A host of drugs are used simply to manage cardiac disease—and those who have had heart transplants must take a variety of immune suppressive treatments throughout their lives. In addition, many individuals with BTHS take granulocyte-colony stimulating factor (G-CSF) (often several times over the course of a week) to improve their neutrophil counts and prevent infections. Additional drugs and supplements are used to improve various other organ dysfunctions and for general supportive care.

Despite a number of new therapeutic approaches currently under evaluation that target different disease pathways, including elamipretide and bezafibrate, there is also considerable interest in gene therapy, which may better address acute cardiac involvement.



## Meeting overview

BSF hosted the meeting to provide the community affected by BTHS (patients, caregivers, and other patient representatives) and specialists in the field an unprecedented opportunity to share with FDA their stories about the burden of this life-limiting disease and the shortcomings of existing management strategies. BSF's hope was that the meeting would contribute to the development of "new pathways for meaningful therapies," according to Emily Milligan, Executive Director of the patient advocacy organization.

---

**BSF's hope was that the meeting would contribute to the development of new pathways for meaningful therapies.**

---

Overall, 310 individuals registered for the meeting (203 in person, and 107 via webcast). More than 25% of the community known to be affected by BTHS participated. This included 14 individuals living with BTHS, 123 caregivers and family members from more than 12 countries who attended in person—a particularly impressive figure given that many came from other continents. Some were too ill to travel (8 people living with BTHS and 59 caregivers/family members attended

via live webcast). There were seven government officials as well as a broad cross-section of researchers, healthcare providers, and representatives from the pharmaceutical industry, academia, and non-governmental organizations also attending the meeting.

After a brief review of the purpose of PFDD meetings, and scientific presentations on the condition, the meeting was divided into two sessions focusing on different aspects of the patient and caregiver experiences. The first topic explored the burden of the disease—including which symptoms or conditions associated with the disease had the greatest impact on their daily lives. The second topic gathered input on patient perspectives on current treatment, unmet needs in management of the disease, and what they want from future treatments. Feedback was also sought on which treatment benefits are considered clinically meaningful and how patients and caregivers would balance the benefits versus the risks of potential treatment options—including their interest in clinical trial participation.

As with other PFDD meetings, each session began with a panel of patients and/or caregivers representing the spectrum of types, ages, and stages of the disease. These individuals brought their voices and stories to depict the debilitating impact of BTHS upon almost every aspect of their lives. Some panelists also presented a slide show along with their narrative that helped to illustrate what it is like for the child and family to live with BTHS.

After each round of panelists, a series of polling questions were posed to the participants at the meeting and, via a live-streaming webcast, across the US and internationally; these were followed by facilitated discussions. Participation in the polling questions was voluntary. A total of 115 individuals registered in advance to take part in the live polling, though there were 139 responses to the first demographic question to which all family members were invited to respond. For most of the remaining questions, the meeting organizers asked participants to designate just one person to respond for each individual with BTHS—either the patient himself or one of his caregivers. On the basis of demographic question 3, the polling respondents represented 96 unique individuals with BTHS. The results were used as a launching



point for discussion and to gain a better understanding of the full impact of the disease—but should not be seen as a rigorous statistical sampling.

In something of a departure from the format of most PFDD meetings, three other key testimonials from caregivers and patients were offered over the course of the meeting. The first of these, which preceded the panel statements, provided a particularly rich and comprehensive description of the struggles and triumphs of a young man who was something of a pathfinder self-advocate and patient with BTHS, as he experienced virtually all of the disease complications (with the exception of a heart transplant) before he passed away at the age of 28. His story, shared by his mother, illustrated most of the complexities of this disorder and served as a framework and embarkation point for the other patients and caregivers sharing aspects of their lives over the course of the meeting. In this report, the experience of this patient and his mother will henceforth be referred to as the “cofounder caregiver testimony.”

Another patient voice was offered in the form of a video biopic at the conclusion of the first session on the burdens of BTHS. The video shared the story of a 57-year-old man with severe degenerative BTHS who could not attend the meeting in person due to late-stage advanced disease progression, along with feedback from his friends, family, and caregivers. This will be referred to as the “Video Testimony” in this report.

In addition, another one of the cofounders of BSF summarized some of the key messages from the day at the close of the meeting.



Finally, after the meeting, a questionnaire was sent out for patients and caregivers to provide further feedback about their experiences that could not be shared that day. Overall, 36 individuals responded, 18 of whom completed the entire survey, including some individuals who were physically unable to attend the meeting.

## Report overview and key themes

This report summarizes the input provided by the patients and caregivers during the meeting. It also includes a summary of comments submitted to the post-meeting survey. To the extent possible, the terms used in this report to describe specific symptoms and treatment experiences reflect the words used by in-person participants and language used in submitted survey responses. There may be symptoms, impacts, treatments, or other aspects of BTHS that are not included in the document.

This report follows the basic structure of the meeting: Each topic section begins with a summary of the testimony from the key testimonials and panelists relevant to that topic, followed by the findings from the polling and group discussions. A short report on the post-meeting questionnaire follows along with



appendices and other meeting materials (including the polling results). Finally, a draft Benefit-Risk Framework is included to help guide regulators during product reviews, as well as support industry sponsors when charting product development plans.

## Key messages on the burden of disease in Barth syndrome

The first meeting session, and part of the post-meeting questionnaire, focused on the burden of disease in BTHS. The feedback during the panelist testimonies, polling and facilitated discussions, and post-meeting questionnaire portrayed a devastating, debilitating, and life-limiting disease with many multisystemic manifestations and complications affecting the heart, skeletal muscle, immune system, growth, and metabolism. Underlying all the symptoms, there is a common thread of mitochondrial insufficiency with insidious effects, perhaps most keenly felt by individuals as weakness, exercise intolerance, and extreme fatigue that severely limit the ability to perform the routine day-to-day activities of normal life.

### *A few key themes emerged:*

Although the cardinal symptoms of BTHS (cardiomyopathy, neutropenia, skeletal myopathy, and growth retardation) are usually present, they manifest and vary in degree and intensity for each individual. Each meeting participant described his own unique manifestation of the disease, even of the same symptoms.

There does seem to be a pattern, for most, in how the disease manifests, with different symptoms taking precedence at different times of life:

BTHS is very often fatal in newborns and is often a cause of stillbirths. Infants may be in severe heart failure at delivery or soon afterward; babies may also have difficulty nursing or feeding adequately and have abnormal sleeping patterns. Symptoms at this time may include severe neutropenia with life-threatening infections. In young children who survive this period, heart function may improve (and then worsen again later in life) while development and growth delays become more visible signs of the illness complicated by ongoing feeding problems in many. *"Small and skinny,"* sometimes sickly, weak, and easily exhausted boys then enter schools where they are often bullied—yet, this is commonly considered a time of relatively good health, referred to as the *"honeymoon period."* Entering adolescence, however, challenges increase with spikes in neutropenia and frequent infections—often leading to many months of missed school or, later in life, work—and/or recurrent cardiac problems exacerbated by other health issues including a pervasive and relentless fatigue, increased eating/digestive problems, sleep issues, and pain. During their school years, even academic pursuits may drain their energy. In early adulthood, a delayed growth spurt may tax the heart, further deplete the body's reserves of energy, and trigger new rounds of neutropenia.

---

**Years of anger and frustration with their limitations often give way to depression.**

---

These symptoms, particularly weakness, intolerance of almost any physical activity, and profound fatigue, make it extremely difficult for many individuals with BTHS to pursue an avocation that they would enjoy, or even support themselves. Years of anger and frustration with their limitations often give way to depression. A life-ending heart problem or infection could occur at any time. To date, most adults known to have BTHS have not lived beyond their fourth decade. Those who do live past their 40s appear



to experience progressive myopathy that, ultimately, may render it impossible to walk or perform the most routine tasks of daily living without assistance.

However, more than the specter of death, participants indicated that what they most feared, as one participant wrote, was *“living unfulfilled,”* due to the symptoms that kept them from becoming independent and maintaining relationships.

## Key messages regarding patient perspectives on the treatment options in Barth syndrome

The second section of the meeting focused on patient perspectives on current and future treatment options. Several key themes emerged from the patient and caregiver testimony and comments:



- Although patients may receive lifelong treatment and multidisciplinary care to manage the symptoms of BTHS, **there are no therapies available to treat the underlying cause of the disease.**
- **The burden of the variety of medical and non-medical care required to manage the various symptoms of BTHS can be quite onerous,** in terms of financial costs, time, and their already limited energy. Additionally, while treatments for some of the symptoms appear to work well for some individuals, they have significant downsides:
  - **Heart transplants come with problems of their own**—such as lifelong therapy with drugs to prevent graft-versus-host disease. In addition, there are not enough hearts for all the patients who need them, and many young children who have a transplant will need another, one day.
  - **G-CSF has been a major advance for managing neutropenia, but the route of administration is painful,** and many young men must self-inject it. A recurrent complaint was the difficulty titrating the drug in light of the cyclic neutropenia being experienced by many with BTHS. Therefore, the dose may often not be sufficient, and infections remain prevalent.
  - **Feeding tubes and TPN may provide necessary nutrients that individuals with diet and digestive problems would not otherwise receive, but they are inconvenient, invasive, and unpleasant.** Furthermore, these and any other device that must be inserted into the body are prone to becoming infected in neutropenic patients.
  - **Many children with BTHS presenting with cardiac emergencies appear to stabilize on heart medications, but to some degree this stabilization might be independent of treatment.** In fact, given the incomplete understanding of how the damage to mitochondria and the imbalance of cardiolipin are involved in the pathogenesis of the cardinal symptoms, it can be unclear how to dose symptomatic treatments or to what extent they are actually responsible for improving outcomes. There may also be a point at which the medications’ complications start outweighing their benefits.
  - Additionally, as some pointed out, complex multidisciplinary treatments and care may interact with one another—**the treatment for one symptom may make another worse.**



- Finally, there are no treatments for skeletal myopathy, the weakness and exercise intolerance that place such severe constraints on the lives that these individuals can lead and upon their ability to support themselves. There is nothing to treat the soul-crushing and ambition-defeating fatigue that makes it difficult to do anything, including essential activities like seeing friends and preserving relationships.
- For this reason, most participants stated that as long as it did not cause life-threatening side effects, they would try almost any treatment—no matter how inconvenient the route of administration—that would effectively target the underlying cause of the disease and provide them with gains in function and energy to live a fuller life.



Treatments to reduce weakness and fatigue were ranked higher than ones that would extend life (though those are needed as well) because individuals with BTHS are desperate to be able to live a life without being dependent upon their parents and others. Meeting participants expressed an eagerness to participate in clinical trials in order to identify such a treatment.

The patient input generated through the BTHS EL-PFDD meeting and post-meeting questionnaire is submitted to strengthen FDA's understanding of the burden of BTHS on patients and their perspective on the treatments currently used to manage its wide and complex spectrum of symptoms. It is our hope that FDA staff will carefully consider this input as it fulfills its role in the drug development process, including when advising sponsors on their drug development programs and when assessing products under review for marketing approval.

This input may also be of value to the drug development process more broadly. Specifically, it may be particularly useful to drug developers as they explore potential areas of unmet need for BTHS patients, for example with regard to managing the life-limiting affects (such as fatigue), reducing the risk of sudden death, or increasing overall symptom control. It could also point to the potential need for development and qualification of new outcome measures in clinical trials.

## Appendices

The appendices include the meeting agenda, polling questions and results, and responses to the follow-up questionnaire. Additional information on the meeting has been posted [online \(www.barthsyndrome.org/newsevents/pfddmeeting/whatyouneedtoknow.html\)](http://www.barthsyndrome.org/newsevents/pfddmeeting/whatyouneedtoknow.html).



## Topic 1: Most significant symptoms of Barth syndrome and their impact on daily life

The meeting's first topic for exploration was focused on the experiences of the patients with BTHS and their caregivers—including the impact and burden of the disease on their daily lives. The session began with a panel of individuals with BTHS and caregivers/parents of children with the condition. However, the first caregiver/patient story presented at the meeting was the heartrending testimonial offered by one of the BSF cofounders about the life of her son. She described how, like most people with BTHS, he suffered from different symptoms of the disease, experienced with varying intensity, at different stages of his life. He experienced virtually all the hallmark symptoms of BTHS:

- Dilated cardiomyopathy with LVNC; two bouts of heart failure
- Cyclic neutropenia
- Cardiac arrhythmia
- Multiple GI and nutritional issues
- Skeletal muscle weakness
- Healing problems
- Pain (especially headache, abdominal, and leg)
- Extreme fatigue
- POTS (postural orthostatic tachycardia syndrome)
- Sleep problems (severe apnea)
- Various metabolic and endocrine abnormalities
- “Barth syndrome” delayed growth pattern

**“The medical roller coaster that he experienced over his life is not unusual. BTHS commonly varies over one’s life like a series of overlapping waves and symptoms of assorted lengths and varying severities. Together these result in diminished quality of life and abbreviated lifespan.”**

**- BSF cofounder**

*“The medical roller coaster that he experienced over his life is not unusual. BTHS commonly varies over one’s life like a series of overlapping waves and symptoms of assorted lengths and varying severities. Together these result in diminished quality of life and abbreviated lifespan,”* the BSF cofounder said of her son.

He died shortly before his 29<sup>th</sup> birthday.

Though they did not all share the same cardinal symptoms, at least to the same degree, taken together, the panelists’ experiences highlighted many of the same issues:

- The first panelist was the 21st member of his family diagnosed with BTHS—but the only one to survive past his fifth birthday, as he did not share their fatal cardiac issues. Now a 31-year-old man, he said, *“My main symptoms have always been growth delay, muscle weakness, leg pain, eating problems, and fatigue.”*
- The second panelist was a caregiver to a 21-month-old whose early life-threatening heart complications resolved with good medical care. Feeding problems and growth delay have been key challenges as a toddler.



- *“Over the years, I have experienced the full spectrum of Barth syndrome symptoms, from bouts of severe headaches to general aches and pains to the more serious feeding issues, muscle weakness, chronic fatigue, and cardiac issues,”* said the third panelist, a 29-year-old man with BTSH who has had eight cardiac arrests.
- The fourth panelist had recurrent fevers and seizures during the first years of life but was only diagnosed with BTSH when he was 10 years old. He said his *“honeymoon period”* ended at the age of 14 when he was admitted to the hospital several times within a two-month period. Despite that, now 17, he said that he is most frustrated by his continued small stature.
- *“My first son died when he was 2 weeks old. I had no idea that he was sick,”* said the fifth panelist, the mother of two boys born with BTSH. Her second son had a successful heart transplant, which has introduced its own set of issues—and yet he still must cope with the other major symptoms of BTSH such as neutropenia, muscle weakness, and fatigue.
- **Video testimony:** As many boys and men with BTSH age, progressive muscle weakness and fatigue can make it difficult to travel, and thus, attend such a meeting as this document is describing. So, in an effort to share the experiences of one such individual, a video was shown of a 57-year-old man with BTSH. Only a small number of individuals diagnosed with BTSH are known to have survived into adulthood—and he was the second-oldest living individual in the world known to have BTSH at the time of this meeting. He used to be a farmer but with age, he suffered profound muscular degeneration because of BTSH that made it impossible to continue working. He has spent the last six years in a nursing home.

**“Everyone with Barth syndrome seems to have essentially the same constellation of issues, though the degree and severity of each varies by patient.”**

**- BSF cofounder and caregiver**

As explored in greater detail below in the group discussion section, each panelist illustrated his or her experiences as a person living with or caring for someone with a poorly understood and extremely difficult-to-predict disease, which had exacted a devastating toll on patients’ and families’ physical, emotional, and psychosocial well-being. Parent caregivers recounted how their lives were completely upended by their infants’ life-threatening health emergencies due to a mysterious cause, navigating crucial health decisions while still in shock and, for the lucky ones, trying to provide ongoing care to their sons who survived these early threats. As the cofounder caregiver emphasized, *“Everyone with Barth syndrome seems to have essentially the same constellation of issues, though the degree and severity of each varies by patient.”* Consequently, those on both panels described their own unique mix of the disease—focusing on which symptoms preoccupied them the most. Some with BTSH were worried more about the threat of heart failure or sudden cardiac death; while others were more afraid that contracting severe infections from interacting with family and friends or from what would, for other people, be inconsequential injuries would lead to another prolonged hospital stay. Others were more focused on how BTSH made them too weak to complete the activities of a normal life or earn a living and how their extreme fatigue limited what they could expect to achieve, and even their participation in relationships. By the end of their testimony it was clear: BTSH is a complex, cruel, and volatile disease that has a





profound impact on both the quality of life of those affected by the illness (patients and caregivers alike) and survival—with premature sudden death a risk at virtually any point from infancy to adulthood.

Pertinent insights about the burdens and symptoms of disease offered by members of the second panel are also integrated into the thematic analysis below.

## **Perspectives on symptoms that matter most to patients and their caregivers**

Following the first panel, a polling session systematically explored the issues raised by the panelists, and during the scientific and clinical overview presentations, by asking meeting participants (in person and online) how BTHS has affected them or the person they represented.

The polling responses were used as a basis for the facilitated discussion that reiterated that while the salient signs and symptoms of BTHS were usually, though not always, present, they were packaged in somewhat different ways for different patients, and sometimes augmented by other complications. The testimony of the individuals in the room also provided more detail into how these symptoms were being experienced by the patient and the impact on their loved ones.

For instance, the first topic one polling question (Appendix 3, topic 1, question 1) asked was which of a list of 13 symptoms (or other) had the most significant impact on their lives. Participants could choose more than one symptom; and 91 respondents submitted 430 responses.

Each of the 13 symptoms listed as an option was selected by at least 10% of the respondents—illustrating the range of experiences with BTHS in the community. However, they shared the key symptoms more often than not. More than 80% of the respondents indicated that “muscle weakness/exercise intolerance” and “fatigue” were among those symptoms that most affected their lives; and more than half listed “eating or digestive problems/nutritional issues/nausea” and “neutropenia and infections” as being among their most significant symptoms. In addition, more than a third listed “heart failure” as having or having been one of those with the most significant impact on their lives. Around a quarter of the participants also indicated that “pain (headaches, stomach aches, etc.),” “short stature,” and “learning disability/attention problems or some other cognitive issue” were among symptoms that most affected their lives. (Full polling results can be found in Appendix 3.)

### **A. Skeletal muscle weakness and exercise intolerance**

*“Most of the normal activities to some kids were more difficult for me, like running or climbing stairs, and walking two blocks or more took every bit of energy away from me. I could not keep up with the other kids. I would get tired very fast. I wanted to sit down and rest.”*

Although other symptoms and complications pose a greater risk to survival, the polling results suggest that muscular weakness and exercise intolerance are foremost in the minds of patients and caregivers. This may not be so surprising, given the many times a day people with BTHS are frustrated and put in danger by strength that abandons them, often at the moment they need it most. The experience can be humiliating: *“My lack of strength forces me to ask for help often, which I find difficult,”* said one of the panelists.

The muscle weakness can manifest in different ways. One father said his son with BTHS *“is not strong*



enough to open up a bag of chips. He cannot pop off the top of a ketchup bottle and the list goes on and on.” “He had one set of books in his classroom and another set at home because he couldn’t lift his backpack,” the cofounder caregiver said of her son. Such physical lack of strength puts limits on the type of career young men with BTHS can pursue: “He would have dearly loved to become a chef, but he can’t do it. He doesn’t have the strength in his hands,” said one caregiver of her son.

In addition, several meeting participants mentioned some physical complications of skeletal myopathy, such as delayed attainment of developmental milestones, and once a child could walk, recurrent falls and resultant injuries. One father said that his son was “very floppy” and “missed all of his developmental milestones.” “He rolled over late, sat up late; he could speak a full sentence before he could walk,” said one caregiver during the facilitated discussion. “If he fell down, he couldn’t get himself back up on his feet,” said one of the cofounders of BSF about her son. “He falls all the time ... His tiny legs and knees look constantly scratched up and bruised,” said one father who described how, during a recent Cub Scout hike in the woods, he had to accompany his son, “so that I could carry him up the hill. He wasn’t strong enough.”

**“My lack of strength forces me to ask for help often, which I find difficult.”**

**- Patient**

Although boys and most adult men retain the ability to ambulate, at least until middle age, ambulation may be impaired in more than one way. For instance, weakness can lead to strain and injuries. “The arch of my foot collapsed due to muscle weakness,” said one of the young panelists with BTHS. In most cases, though, it is exercise intolerance that makes it difficult to get from Point A to Point B. One caregiver said that during trips to the grocery store, her “13-year-old must sit in the shopping cart as he doesn’t have the stamina to make it throughout the store.” Another mother spoke about how she hated when, as her son played baseball, they had to have a substitute “runner come in for him at first base to give his team a chance to win.” “Exercise” intolerance may be something of a misnomer, however, because what most of the participants with BTHS described was an intolerance to even routine activities. Several described their muscles giving out while walking, including one panelist: “Walking more than two blocks leaves my legs unbearably tired. Walking up three flights of stairs leaves me out of breath.”

Among those young men with BTHS reaching adulthood, there appears to be ongoing subtle deterioration, which becomes even more pronounced with age. One example of this was provided by the farmer in the video, who no longer “has the strength to use a bathroom without help, let alone drive his tractor or truck.”

## **B. Extreme fatigue**

**“The only word in the English language that comes even close to describing how I feel is ‘depleted.’ I get so utterly exhausted that I have to really concentrate just to lift my arm.”**

At least four out of five polling participants identified the “chronic fatigue” associated with BTHS as being one of their most significant symptoms—and it was extensively discussed. Many participants described this “all-encompassing fatigue” as affecting virtually every aspect of their lives: “On a bad day, I have no energy to chew meat,” said one young man. More than one parent even observed this fatigue in their



infants. *“Nursing was exhausting for him. He tired very quickly and would often work up a sweat.”* One caregiver said that her toddler with BTHS *“is so exhausted that he needs a three- to four-hour nap each day.”* Another said that by the end of the school day, her 13-year-old son *“is completely exhausted—too tired for extracurricular activities, homework, or playing outside.”* *“The chronic fatigue is there every day whether you like it or not,”* said one father of his son.

*“The fatigue is by far the most difficult to deal with,”* said one young man, who mentioned how it limited his life goals and daily activities: *“I must make impossible choices every day ... to conserve energy.”* He added: *“At the moment, I’m sedentary literally 95% of the time, sitting down or lying down ... but it’s very socially unacceptable to do nothing and so everybody just labels you as lazy.”*

**“I must make impossible choices every day ... to conserve energy.”**

**- Patient**

A few young men at the meeting remarked that they were often so tired, they *“could not get out of bed.”*

*“The most profound and primary issue for me is the significant and all-encompassing fatigue,”* said one 36-year-old man. *“As I have gotten older, my fatigue continues to get worse. My lifestyle is not what I wish it to be due to fatigue. I have very little energy. Some days, I’m too tired to leave home. I need to plan ahead and pace myself for how many things I can do or I can schedule in one day or even in the same week. After activities, I feel worse and must rest, sometimes for the rest of the day. Sometimes, I feel so exhausted that I am sick.”* Finally, one concern noted by many participants was that the fatigue seemed to be increasing as they were getting older: *“He always had fatigue, to different degrees, but it’s definitely much worse now than it was when he was younger,”* said one caregiver of her son. *“As I get older and older, I feel like my fatigue is getting worse and worse; and I wonder, ‘Where does it [end]? Does it cap at where I just can’t move ever?’”* one young man asked.

### **C. Eating or digestive problems/nutritional issues/nausea**

***“Eating is a struggle. I rarely have any appetite whatsoever and often get heart palpitations during meals. I have little motivation to eat, let alone cook. My body rejects many food types based on smell and looks by gagging. If I get past this, lots of food types make me throw up shortly afterwards.”***

Difficulty eating and obtaining adequate nutrition plagues most individuals with BTHS at some point, if not throughout their entire lives. *“Abnormal eating patterns”* are often first noticed in infancy when the baby becomes too exhausted to feed. *“He was too weak to eat,”* one father said of his son, *“and where most babies were drinking full bottles of milk, [he] was lucky if he drank 3 to 5 ounces in one sitting.”*

The eating and digestion problems in BTHS are complex and multifactorial. Aside from becoming exhausted by the effort of feeding, several factors appear to be involved in the evolution of eating and nutritional complications over the course of a person’s life with the disease. For instance, one new father, who remarked on how it took his son an inordinately long time to nurse, added, *“then even when he is feeding, he vomits once to twice a day his entire meal and his medicine.”* Meanwhile, neutropenic patients with BTHS have frequent mouth sores, making eating *“nearly impossible.”*

*“Trouble swallowing,” “gagging,” “nausea,”* and *“throwing up”* were mentioned by several caregivers and



people with BTHS of various ages. One patient described “*heartburn, stomach problems, and irritable bowel syndrome.*” During the caregiver testimony from the BSF cofounder, she mentioned that her adult son “*vomited frequently,*” which was a major dilemma particularly because “*he couldn’t eat enough ... to support his accelerated growth and without any external nutritional support, malnutrition set in.*”

“*Chronic diarrhea*” also often compounds the nutritional challenges of people with BTHS.

Hypoglycemia, which can quickly become an emergency, was also identified as an issue by patients and caregivers. During the group discussion, one young mother, who said that her 2½-year-old son vomits “*at least three times a day,*” and that during a hurricane evacuation with “*a 16-hour journey in heavy traffic with a threat of no gas and no place to stay*” her family’s overriding concern was “*how are we going to manage this to make sure that his blood sugar doesn’t drop?*”

## D. Neutropenia and infections

***“I would get rather sick and catch any kind of cold and infection that anyone around me had. I would get cold sores in my mouth and any kind of cut, scrape, or bruise would get infected. I was put in the hospital on antibiotics and placed in isolation all by myself.”***

Another cardinal symptom affecting most individuals with BTHS is neutropenia, which makes them susceptible to frequent and often life-threatening infections, though the pattern and intensity vary from one patient to another. “*Infection is a constant worry,*” one mother said of her 13-year-old son, who had problems warding off dangerous infections since infancy.

***“The common cold or stomach bug that most kids ... can fight off can be just too much for him.”***

**- Caregiver**

For others, neutropenia becomes more problematic as they reach adolescence: “*At the age of 14, nothing could have been as bad ... I had several hospital stays within a two-month period because of recurrent staph and cellulitis in my belly button,*” said one of the young male panelists. He added that his white blood cell count “*could be as low as 200.*” One of BSF’s cofounders also said that at 13, her son “*began to get painful mouth sores every three weeks when his neutrophil count would regularly go down near zero.*” Another caregiver during the group discussion said that her son’s neutropenia became a “*massive issue for him*” causing “*chronic diarrhea, water diarrhea. He couldn’t leave the house.*”

Many participants described lives in constant peril from commonplace threats: “*The common cold or stomach bug that most kids, including his sister, can fight off can be just too much for him,*” said one caregiver. Another mentioned that her son spent several days in the hospital on IV antibiotics, “*just because of a scraped elbow.*” Many noted that recurrent infections related to neutropenia were a major contributor to frequent hospital stays and missed school and work (discussed more below).

The neutropenia and infections may, in the end, precipitate health emergencies that lead to loss of life. “*During the last few years of his life, [he] suffered numerous infections and other complications resulting in multiple operations and hospitalizations, including for most of his final year,*” the BSF cofounder said of her son, who ultimately died of sepsis.



## E. Cardiomyopathy, heart failure, and arrhythmia

***“The threat of a cardiac episode is always present. It’s a constant worry for all of us in our family.”***

Cardiomyopathy is the most common complication, frequently the presenting symptom of BTHS. When it occurs in a newborn, it is particularly traumatizing to caregivers. *“For the first few minutes of his life, he was an unsettling shade of blue—his heart was not pumping enough blood to his lungs,”* said one caregiver. Another said that 36 hours after a completely normal pregnancy and delivery: *“Our world would forever change. The ideas in our head of having our perfect little family were crushed—our little boy was in severe heart failure.”*

The heart problems in BTHS can also lead very rapidly to death. *“When he was 3 weeks old, he suddenly was dead, and we reanimated him on the carpet on our own. Two days later, we found out that he had had a stroke because of his LVNC heart,”* one mother said during the discussion. Many of the meeting participants said that heart failure and arrhythmias were the cause of death of some of their children, or of other family members who had or were suspected of having had BTHS. One of the panelists described how 20 other male family members with BTHS *“ran into problems with their heart function and immune systems shortly after birth. Many died within days and not a single one made it past their fifth birthday.”*

Since heart issues can sometimes appear to improve over time (in some cases, perhaps due to treatment or to heart transplants), this symptom may not always be at the forefront of patients’ and caregivers’ minds when they are thinking about which complication of BTHS affects their daily lives the most. However, for some, the threat of a cardiac emergency is always with them.

*“A Barth individual who may be sick enough to be awaiting a heart transplant may then improve so dramatically as to be taken off the list. Unfortunately, the reverse can also happen, and heart function can deteriorate significantly, suddenly, and unexpectedly, especially when other stresses such as a poor nutritional state or a respiratory infection intervene,”* said the caregiver who helped cofound BSF. In the case of her son, heart problems reemerged with his growth spurt: *“Shortly after entering his new school, he was back in the ICU with heart failure again, and his LVNC was more pronounced. Could this cardiac episode have been precipitated by the onset of his accelerated growth?”*

Later, after another boy from the community had an arrhythmia and died suddenly, she insisted that her son be checked to see whether this was also a possibility for him. *“No non-invasive evaluation gave any hint of [his] vulnerability, but an intracardiac electrophysiology study showed that he was at a severe risk of sudden death,”* she said.

These heart problems may be closely linked with exercise intolerance as some have had arrhythmias and died while playing. Regardless, concerns of triggering a cardiac event severely limit the type of activities in which some can participate. One panelist, who had already survived eight cardiac arrests, said that one

**“A Barth individual who may be sick enough to be awaiting a heart transplant may then improve so dramatically as to be taken off the list. Unfortunately, the reverse can also happen ...”**

**- Caregiver**



of them was triggered when he tried to move a cinder block, although he added: *“Despite taking every precaution possible, I still had another cardiac arrest just a couple of months ago.”*

## F. Pain

*“He curled up into a ball on our living room floor, crying: ‘Somebody please help me! Every part of my body aches deeply from my toes to the top of my head. Every cell in my body is affected by Barth syndrome and so although I know that no such thing exists in textbooks, I feel like I have cellular pain.’”*

Panelists and meeting participants described experiencing various types of pain, including *“headaches,” “chronic abdominal pain,”* and leg, back and shoulder pain that may be ever-present and at times profound: *“I have experienced ... bouts of severe headaches to general aches and pains,”* said one young man.

The pain in BTHS may have different causes. Some attributed their pain to high lactic acid levels that develop after physical exertion. *“The increased lactic acid production makes my muscles sore after a small exercise ... [My] acidification [level] was once measured as 200 times the normal levels and often as ‘too high’ to determine accurately. This mainly affects my leg muscles, but other ones can get rather painful, too,”* said one of the patient panelists.

**“Some days I am in so much pain that I'm stuck in bed all day.”**

**- Patient**

Another young man said he had *“real bad sciatic nerves in my back and in my neck ... I'd work probably five hours a night, but it gets to the point where it's so bad that I can't bend my neck or bend over. I just have to lie there.”*

One caregiver said that muscle weakness in her son's hips made *“sitting ...over long periods of time”* painful, and that it in fact led him to leave a job driving a mail truck for the post office. She said that he told her that *“the pain level ... just from sitting, and trying to do a*

*normal job, was at its worst for him.”*

Muscle weakness and fatigue may also increase the risk for injuries and subsequent pain, as one individual with BTHS said during the group discussion: *“I had an accident [a fall] that caused me a lot of back pain. On top of that I found out that I had scoliosis and so pain has been a huge problem for me, and I haven't really found a solution to it.”*

The pain can be debilitating—one of the panelists said that he was *“in pain 24 hours a day. Some days I am in so much pain that I'm stuck in bed all day.”*

## G. Short stature/delayed growth

*“From the time that I could remember, I knew that I was different—my height, my weight. I was the smallest kid in my school. I weighed about 50 pounds in the fifth grade. I would get bullied every day verbally and physically.”*

Though not life-threatening, many individuals with BTHS report that their short stature and delayed growth have had a profoundly negative effect on their lives—in some cases, leading to bullying and other forms of bias. *“I was about a foot shorter than my classmates and my desk being much lower than the others made it difficult to work together,”* one adult with BTHS said about his school years. *“I get so*



upset and aggravated about my size because people will look at me and say that I look like I'm 12," said one 18-year-old young man.

"Small size has been an issue his entire life," one of the panelists said of her 14-year-old son. Caregivers were also concerned about the impact on their child. One said that a cousin to her toddler, who was eight months younger, had "surpassed [him] in weight and height, weighing in at 23 pounds while he has been in the 20-pound range for several months. [His cousin] is now using him as a step stool to climb up on furniture."

Another said that strangers often questioned [her son's] age and size and that: "On his first day of middle school, the bus driver nearly left him at the bus stop, telling him that the elementary bus would come later. Now nearly 14, [he] is the size of many 8-year-olds. While most of his classmates look forward to driver's training, his size requires that he still sits in the back seat in a child booster seat."

## H. Learning/attention/cognitive issues

***"I find mental strain exhausting, almost as much as physical activity. Even though I never expended much energy or physical movement, my issues with fatigue were not better. Nobody really understands getting fatigued in that way ..."***

Nearly a quarter of the polling respondents indicated that learning, attention deficits, and other cognitive issues were among the major daily burdens of the disease. It is important to note that boys with BTHS face many challenges pursuing an education, particularly with frequent absences due to weakened immunity, hospitalization from illness, and physical fatigue. One young man described how, together, these barriers thwarted his academic pursuits: "It's not because I didn't try hard enough or because I'm too stupid, I hope, but I just couldn't keep up with the work required. You miss lessons, days, even weeks, because you're sick or in hospital with appointments. Then you never have enough energy to do the work, do the homework, catch up. It becomes a vicious cycle and you can just never pull yourself back up."

***"It's not because I didn't try hard enough or because I'm too stupid, I hope, but I just couldn't keep up with the work required."***

**- Patient**

However, it should also be remembered that the brain uses more energy than any of the body's other organs—and mental activities may in some cases be more draining than physical activities.

"Memorizing school work was difficult for me," another one of the panelists said. "I needed more time to complete my work. I was even put in classes for learning disabilities in the third grade because of my attention span."

## I. Sleeping difficulty

***"Very few people know how horrible it is to go to bed to sleep, tired and drained, and to wake up after a full night's sleep still feeling exhausted like you may as well never have slept at all."***

Approximately 15% of polling respondents said that sleeping difficulties are one of the major symptoms of their BTHS. One patient described his problem as "insomnia." He said that "despite being tired, I can stay up for days at a time without sleep."



This could have several causes (including pain): *“His headaches, abdominal pain, leg pain ... profoundly affecting his sleep,”* said one caregiver. Severe apnea was also listed as a reason for troubled sleep.

A couple of the meeting participants said that fatigue itself was a major contributor. *“If he gets overtired, he can’t sleep,”* one mother said of her son.

## J. Mood disorders (including depression, anxiety, anger)

*“When I was young, I used to have bad mood swings—anger management issues. I used to get so upset and throw major tantrums over nothing at all really. Now I can see that those were outbursts of frustration at not being able to keep up with my friends, not being able to play in the way that they did, never winning at any physical game.”*

Nearly 15% of the caregivers and patients in the poll identified mood disorders and other emotional/psychological issues as part of the burden of the disease. These were described by most as being a consequence of the many challenges that individuals with BTHS face, which could include *“quite a lot of bullying,” “isolation,”* and *“not being able to keep up”* or do what others do.

One caregiver spoke about how his son often doesn’t feel well and this leads to *“mood swings. He doesn’t even realize it. The changes happen frequently, and they have lasting negative effects on everyone around him.”* An adult audience member described how the chronic pain and fatigue that limit his ability to lead the type of life he wants *“leads to depression, frustration, anger. You get fed up.”*

**“I felt like giving up and not trying anymore. It’s very easy to get down and depressed.”**

**- 17-year-old patient**

One 17-year-old patient added, *“This really affected me mentally, I felt like giving up and not trying anymore. It’s very easy to get down and depressed.”* He also said the medications that he takes may also contribute to his *“psychological problems.”*

An adult panelist said that when he was growing up, *“I would get rather depressed and anxious because I felt left out, as if I didn’t fit in with society.”* *“[He] doesn’t really have any close friends. He too often can’t do what other kids are doing but feels ashamed to play with the younger kids,”* one caregiver said. Another panelist said

that he feels *“lonely”* and *“guilty”* for not contributing as much as he thinks he should to society and for neglecting his friends. He added that all of this *“drove me into chronic depression and a tendency towards various addictions.”*

At the conclusion of his testimony, the 17-year-old panelist also said that he has *“very sad moments ... that made me ball up and cry sometimes.”* He stressed that the very saddest part was seeing how his suffering from BTHS had affected his mother. *“I have to say, that’s one of the worst feelings that I have ever felt—the sight of seeing the one person that loves me more than life itself feeling hopeless,”* he said.

## K. Other symptoms

Finally, problems with healing (a grave issue in light of heart transplantation, surgeries, and the need to insert feeding tubes) and speech challenges were also listed as major concerns by at least 10% of the





polling respondents. Mouth sores can make it difficult for some to speak, but in the case described in the video presentation, with age, men with BTHS may lose the strength to speak *“loudly enough to be heard.”*

Other patients mentioned issues such as *“kidney stones”* and *“allergies,”* which may or may not be associated with their BTHS.

## Impact on daily life of patients and their caregivers



BTHS levies a terrible toll on the time, freedom, and quality of life of those affected by the disease (both patient and caregiver). Many participants spoke about how the combination of infections, pain, and fatigue was *“debilitating”* and *“severely restricting of daily activities.”* Another recurrent theme was how time was sacrificed to managing their illness, with visits to healthcare providers and emergency rooms, and during repeated hospital stays. Some participants also described routine adjustments and adaptations that they have had to make to manage symptoms such as fatigue. Many focused on the psychosocial impact of the disease, and how it had limited their options for schooling, careers, social activities, or even relationships.

### A. Repeated hospitalization and other healthcare utilization

***“Each year he makes multiple visits to the emergency room due to various viral and bacterial infections and nearly every fever guarantees an overnight stay in the hospital.”***

During polling, approximately 55% of respondents indicated that they or their loved one had to go to the hospital for emergency care or inpatient treatment due to BTHS at least once or twice in the previous year, and approximately 27% reported even more frequent trips or stays (Appendix 3, topic 1, question 2). *“Unscheduled hospitalizations [are] a normal part of our lives,”* said one father of a boy with BTHS.

It should be noted that these responses presumably represent the typical year in a life with BTHS but may be better than the norm, given that those present at the meeting were well enough to travel and a quarter of the polling participants were or represented boys between the ages of 6 and 11 who were likely in the *“honeymoon period”* of the disorder. About 14% had not been to the hospital at all in the year prior to the meeting. However, panelists and participants described visits to the ICU as being far more common in infancy and, again, with increasing health complications later in life. Consequently, approximately 7% of respondents reported that they had actually had to make 10 or more emergency room hospital visits or stays in the previous year.

*“Those first few years are somewhat of a blur, filled with endless appointments and regular hospital admissions due to illnesses that his body couldn't fight off due to his neutropenia,”* said one caregiver. *“For the first eight years of my life, I was hospitalized every 27 days,”* said a 36-year-old panelist.

Other healthcare appointments were reported to be far more common. In response to the third polling question of topic 1, 53% of respondents said that they had had one to three visits to healthcare



professionals within the past month alone; and for more than one-third, it was more often. Again, some required healthcare services much more intensively, with 11% indicating that they had had 13 or more visits to some type of healthcare provider in the past month.

## B. Time missed from school or work

*“He misses extended periods at school and, in a few cases, even months at a time.”*

Time ill, spent in the hospital or otherwise accessing healthcare for BTHS, is “corrosive” to the routine and daily activities in the lives of patients and caregivers, such as work or schooling. “[He] can’t physically get himself out of bed between hospitalizations, rest days, and doctors’ appointments,” one father said about his young son.

To better capture this impact of the disease, the fourth polling question of topic 1 asked participants how much time they had missed from school or work in the past year. Roughly 22% of the respondents said this question was not applicable—mostly because their child was too young for school. In the remainder, about 20% had missed some school or work, though less than a week, while 26% had missed one to two weeks. Once again, however, some are more severely impacted or in a more severe stage of their illness: 15% had missed three to four weeks, 10% had missed between one to three months, and 8% had missed more than three months of school or work in the previous year.

During the group discussion, a caregiver described a harrowing spell of neutropenia, illnesses, and fatigue when her son was 17. “He missed probably about two or three months of school at that time,” she said.

**“He can't sustain a full day at school due to his fatigue.”**

**- Caregiver**

The BSF cofounder caregiver said that her son spent even more time at the hospital: “[He] was hospitalized eight times for a total of 114 days the next year when he was 21. He endured 47 overnight hospitalizations for a total of 564 days ... and before he got sick the last time, he spent three-quarters of the year in the hospital.”

Approximately 11% of those who were old enough to go to school or work indicated that they were unable to attend school or hold a job *at all* due to BTHS. One example was provided in the video testimony about the farmer who can no longer work or drive, and is now confined to a nursing home.

In many cases, school or work also is avoided because severe neutropenia may put a child or young man at risk of contracting infections. “I missed a lot of school due to hospital stays from having a fever and a low white blood cell count,” one of the adult patients said about his school years. “I ended up missing eight straight weeks of school,” one young man said about a particularly bad period when he was severely neutropenic.

In other cases, participants described not having the stamina to keep a regular work or school schedule. “He can't sustain a full day at school due to his fatigue,” one caregiver panelist said of her 11-year-old son.



## C. Setbacks, sacrifices, lost employment, and fewer prospects as a consequence of Barth syndrome

*“He repeated ninth grade when he went to high school since he missed so many days at school the year before.”*

The final polling question of the session explored the net effect of coping with BTHS on school accomplishments and vocation and residence options for both patients and caregivers. Respondents could select more than one response.

The first part of the question focused on academic or work setbacks or accommodations for the patient with BTHS.

- 36% of those with BTHS had to repeat a year of school or took more time than usual to finish a school program.
- 50% had to reduce school or job responsibilities because of BTHS.
- Almost 16% could not attend regular schools and had to be homeschooled instead.

*“He is tutored twice a week to make up for what he misses at school,”* one caregiver said of her son. Several others mentioned being homeschooled.

- 45% had lost their jobs or needed to quit school or a job—with a quarter unable to go to school or work at all due to BTHS.

**“I was unable to [keep] a job because I didn’t know what days I won’t be able to make it due to illness or pain.”**

**- Adult patient**

*“I was unable to [keep] a job because I didn’t know what days I won’t be able to make it due to illness or pain,”* said one of the adult panelists.

In the video testimony, friends and family of one 57-year-old patient described how much he used to enjoy farming but said that deteriorating strength *“robbed him of the chance to make a living.”*

*“Chronic fatigue means that ... full-time jobs are out of the question ... One bad night of sleep or a day working overtime could send me spiraling towards a health crisis,”* said the adult panelist who has had multiple cardiac arrests, adding that this makes it difficult for him to even look for work. *“Telling a potential employer that I get tired easily is*

*hard to quantify because they have no idea just how easily it happens ... the threat of exhaustion or a cardiac event leaves a job with even a moderate amount of physical activity out of the question.”*

During the group discussion, another man with BTHS agreed that this was a key dilemma for him as well. *“I don’t work—I’ve tried—I’ve done one day of work as a gas station clerk and I had to quit. It took me a while to find that job because it’s like, how do I explain? I don’t want to say that I can’t do it because then they won’t hire me,”* he said.

*“Now I’m in the position where I’ve stopped doing anything. I’m not working or in education and I’m trying to figure out what am I going to do? If I am honest with you, I have no idea,”* one young man said in frustration.



Families also had to make sacrifices to care for their loved one with BTHS, with more than half of the caregiver respondents indicating that they had had to reduce their school or job responsibilities due to caring for someone with BTHS. Almost a quarter of the caregivers responded that they had either lost their job because of their caregiving responsibilities or had taken a different job or quit their school or job in order to care for their loved one with BTHS.

*"I have been unable to return to work because his needs are too much for a daycare setting,"* one caregiver said, describing how caring for her young son with BTHS has become her full-time job.



In some cases, the demands of access to care and treatment for BTHS have limited where caregiver families could live. Nearly 12% of respondents indicated that their family had to move to another location due to BTHS or that it kept them from moving to a different home when they otherwise would have.

#### **D. Other sacrifices and missed opportunities due to Barth syndrome**

*"I still have to be careful with little things, like being meticulous about wounds, staying clear of food sitting outside in buffets, not sitting in the hot tub for too long because it's bad on your heart to raise your core-body temperature too much—things that most people generally don't even think about."*

Life is not all school or work however, and panelists and meeting participants spoke about other ways in which BTHS limited their day-to-day lives.

One father described how his son in the Boy Scouts could not climb hills on his own during group hikes. For others, sports and recreational activities such as swimming were too strenuous or would lead to pain. One mother described her child's struggles: *"The neighborhood kids are going for a bike ride and [he] and I overhear someone saying that [he] needs to stay behind because he slows them down. We go to the pool and all of the kids are swimming in the deep end and he doesn't have the stamina to do so and so then he is stuck with the shower."* A father said the following of his son: *"[He] can't ride a bike, he's not even close. When we vacation with cousins in the summer, he stands by the side of the road and watches all of them—some younger—dash off to here and there on bikes."*

Some couldn't play or socialize with peers or family members for fear of contracting an infection. *"I couldn't leave my house, see friends or even some family because I might get an infection,"* said one patient.

Finally, in later life, activities that once gave great pleasure may be sacrificed. *"It's driving a car that perhaps he misses most,"* according to the video about the 57-year-old man with BTHS whose *"truck still sits in the nursing home parking lot on the chance that he will be able to go for one more ride."*



## E. The psychosocial and emotional impact of Barth syndrome on caregivers and family

*“My mom is crying because she feels like the battle is never-ending. I feel like I want to help her and for her to know that it’s not her fault.”*

Although not addressed in the polling questions, many patients and caregivers at the meeting spoke about the impact that BTHS has had on their family’s emotional health. One panelist spoke about how caregiving for a child “with a rare disease that has so many unknowns” has taken a great toll on her psychologically.

Another caregiver spoke about the “anxiety” she feels “every six months when we go to his cardiologist appointments. I think: ‘Will this be his appointment that we are told [his] heart is failing again? If that happens will he be able to get a heart in time?’”

“I have immense guilt from the pain and trauma that I regularly have to put my son through for the numerous but necessary medical procedures he requires,” one mother said.

Others spoke about the effect on other siblings. “We have another child, a daughter who’s 5, and I really worry about the impact of that,” said one mother. Another said, “His little brother is 4½ years old and does not have Barth syndrome. Yet the disease absolutely affects him, too. There are times when [we] have to focus much of our energy and time on [our son with BTHS, while the other] is shortchanged or has to sacrifice.”

Finally, some patients worry about the consequences on their caregivers and friends. “A while ago I heard my mom talking to a friend about my current situation ... I could feel that person judging her as a poor parent even though they had no idea what the situation was,” one young man with BTHS said.

**“I have immense guilt from the pain and trauma that I regularly have to put my son through for the numerous but necessary medical procedures he requires.”**

**- Mother of Barth patient**

## Topic 2: Patient and caregiver perspectives on treatment/management of the condition

The second part of the meeting focused on current and future approaches to treatment, as well as supportive care and medical devices used to help manage BTHS.

The session began with a presentation from Dr. Scott Winiecki, of FDA’s Center for Drug Evaluation and Research (CDER), who explained that the agency sought to understand what the community would consider “safe and effective” to mean in real terms. “Real effects on people’s lives are much more important than measuring a lab value,” he said. “Part of today is documenting how much this affects peoples’ lives.”

The panelists’ testimonies following Dr. Winiecki’s talk provided considerable insight into the complexity and many shortcomings of the currently available treatment and management for BTHS symptoms—including which medical needs currently remain addressed and what affected individuals would sacrifice for better treatment options.





- The session's first panelist, a 19-year-old man, said that his cardiac issues and neutropenia presently seem to be managed adequately by heart medications and G-CSF—however, his fatigue is not. Consequently, he is trying to increase his stamina on his own: *"I'm trying to make myself move a little bit ... [in] an attempt to increase exercise tolerance but it's difficult and I don't know if it's working yet."*
- The next panelist is the mother of a child who was born with *"LVNC dilated cardiomyopathy, high lactic acid, and neutropenia."* Although he was initially a candidate for a heart transplant, his heart function improved; he is now 10 years old. He *"is currently taking Losartan, carvedilol, and Digoxin for his heart. He also takes lansoprazole for his stomach ... and gives himself three injections a week to help raise his neutrophil counts."* But despite all of this, he still gets frequent infections and is *"admitted to the hospital several times a year due to illnesses."*
- *"Not only do I know what it is to live with Barth syndrome, I know what it means to take care of someone living with Barth and to watch them die,"* said the next panelist, a 36-year-old man with BTSH who became caregiver to his younger brother and his nephew, who eventually both passed away from heart failure. He said his two daughters are both carriers—and that he would gladly participate in research so that he would not *"have to live through another generation of this horrible disorder without any treatment."*
- The next panelist was another 36-year-old man who described how most of his symptoms—with the exception of fatigue, once again—are managed by rather complex medical care. In his case, this has included a variety of feeding interventions, including an individualized formula for tube feedings. Still, fatigue remains such an issue that he sometimes needs a motorized scooter to cover short distances.
- The final panelist is the father of a young boy who *"was not breathing"* at birth and *"diagnosed with dilated cardiomyopathy."* Now 8 years old, he still has severe heart disease and requires a portable AED and ongoing medical treatment.

Earlier in the meeting, the BSF cofounder had described her son's medical care in great detail.

*"He experienced a complex medical history and endured many medical procedures over the course of his life. Except for heart transplantation, [he] seemed to have experienced it all,"* she said.

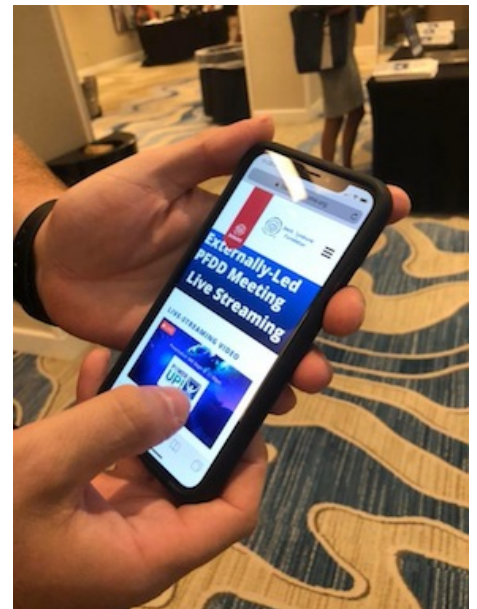


Summary of her son's medical history:

- 47 overnight hospitalizations; total of 564 days
- 57 procedures under anesthesia
- 16 central lines
- 9 operations to revise scars and aid healing
- 1 muscle biopsy
- 6 bone marrow aspirations
- 3 implanted defibrillators
- 2 gastrostomies
- 1 spinal tap
- 1 removal of umbilicus
- *Every day*: 29 pills, 2 IV medications, 2 injections, TPN through port-a-cath over 13½ hours, overnight tube feedings, and slept with BiPAP machine (before last year in the hospital)

The panelists' testimonies during both sessions shared stories about some of the same management strategies, describing episodic interventions, including many surgical operations, as well as chronic care with heart medications, the dosing of G-CSF for neutropenia, tube feedings, and, in some cases, heart transplants and defibrillators, as well as management of various downstream issues associated with metabolic abnormalities and stroke. In addition, participants described using a variety of other therapies, assistive devices/equipment for breathing and ambulation, and lifestyle changes in order to cope with their illness. Panelists also shared their opinions of what would be most important for future treatments to address or deliver, and their positions on enrolling into clinical trials (which is explored in detail in the thematic analysis below).

Following the panel testimonies, participants at the meeting and online were asked to respond to several polling multiple-choice questions about treatments and multidisciplinary care for the different symptoms of BTHS—with a separate question focused on heart transplantation.



## Experiences with existing Barth syndrome management overall

A few key themes emerged during the session. First, the use of some therapies is lifelong, with a high polypharmacy burden that can make side effects an ever-present and significant part of their lives. *"He takes 17 medicines and supplements up to three times a day to minimize the devastating symptoms of Barth syndrome,"* one mother said about her 14-year-old. *"I have to take close to six to eight medicines per day,"* said one 17-year-old boy, who pointed out that these medications often have undesirable side effects, affecting his health and moods in sometimes unpredictable ways.

Second, dosing strategies for treatments of some symptoms may be different from the labeling for the drugs used to treat the same symptom in other contexts—which may not be surprising given that research is still ascertaining the mechanisms whereby *TAZ* gene mutations lead to the complications of BTHS: *"Sometimes, not always, but sometimes a small dose of the medication can have a significant effect on*



*Barth syndrome. A number of Barth individuals have experienced this phenomenon with a variety of medications,”* the BSF cofounder caregiver said.

At present, there appears to be no effective way to manage some symptoms, such as fatigue, pain, and the ever-present myopathy that may be progressive in patients as they age.

The adequacy of all the treatments was addressed by one question (Appendix 3, topic 2, question 5), which had 87 responses, and asked whether any of the medicines, interventions, equipment, or lifestyle changes improve patients’ quality of life (or the quality of life of the person for whom they were responding). Only 22% indicated that these therapies “really help.” For 59%, existing medical management only “helps somewhat,” while 14% were unsure of how helpful treatments were and 6% said they were not very helpful at all. Comments from meeting participants indicated that taking all of these treatments is often difficult.

*“It gets hard at times and I want to just stop taking the medicines, but if I fight and take them then I can enjoy things like going to the lake, swim with friends, or go around the mall,”* said one young man.

It is also important to remember that individuals with BTHS each have somewhat different expressions of the disease—some with milder symptoms that may be more responsive to treatment and others with severe refractory conditions. Therapies that ameliorate the symptoms in some patients may not work for others—and this may change as their BTHS evolves over the course of their lifetime.

Finally, as one caregiver said, *“There are many treatments available that help to alleviate the symptoms of the condition, but really, they are Band-Aids to the underlying condition.”* And as another, the caregiver to the 14-year-old boy who takes so many medications, said: *“None of them are a treatment or a cure.”*

In light of these responses, the poll asked further questions about what individuals would want from future treatments and what they would do to receive those treatments. They were also asked about their perspectives on participation in clinical trials, and what outcomes would be of most importance to them. The participants then expanded on their responses in a facilitated group discussion.

## **Approaches to manage cardiac issues and neutropenia associated with Barth syndrome**

In the first polling question (Appendix 3, topic 2, question 1), participants were asked about medicines, equipment, or lifestyle changes that they (or the person for whom they were responding) were currently using to manage BTHS-related heart disease and neutropenia. There were 75 respondents to this question and 135 responses selected. Approximately 80% of these said that they were using heart medications, while more than 69% were on medical treatment either for neutropenia or for infections related to neutropenia. A little over 13% of the participants have to use defibrillators (ICD) to stay alive while over 17% have had heart transplants.

### **A. Heart medications**

*“He also takes four different cardiac medications two times daily and likely will for the rest of his life.”*

Several meeting participants listed various drugs they take to keep their heart functioning, such as losartan, lisinopril, carvedilol, captopril, digoxin, and Lasix. Many were first administered some of these





drugs in the pediatric ICU—and it may be a testament to the [improved] standard of cardiac care over the last few decades that some infants and young boys with BTHS survive this period and stabilize to the point where some could characterize their heart function as “near normal” or something close to it.

*“His heart function began to stabilize and although it does not pump normally, it has been stable with the assistance of multiple cardiac medications for almost a full year,”* one caregiver said about her 21-month-old son. Several adult meeting participants noted these medications continue to manage their cardiomyopathy. *“Meds seem to be keeping my heart function okay,”* said one young man, *“at the moment.”*

It is important to recognize that the quotes are from or regard individuals who are “responders” to treatment. Some infants and older patients with cardiac events do not stabilize and die from heart disease. Others require defibrillators or heart transplants. Some still fear that a life-threatening incident could be looming in their future.

## **B. Medications for neutropenia and neutropenia-related infections (G-CSF and antibiotics)**

*“Neupogen was a big turning point in my life. Today I take three injections into my abdomen per week, and it really helps my immune system ... At least I’m no longer sick all of the time.”*

Several panelists and meeting participants discussed positive experiences with G-CSF to “keep the neutropenia under control” and “cut down on all of the ER visits and fevers and infections.”

A common theme, however, was that dosing was highly individualized. *“When he was started on a standard dose per kilo, however, his neutrophil count skyrocketed over 850% and rose way up to 34,000, which was way too high,”* the caregiver who helped found BSF said about her son, who developed neutropenia as a teenager. *“So, we experimented with various doses and frequencies and determined that for him various small daily doses were most effective. He tried stopping G-CSF at one point, actually, but found out that those tiny doses actually made a huge difference to him, both through his neutrophil counts as well as to how he felt.”*

*“It took us a while to get his dosage right,”* said the caregiver of another young man.

Another downside is the route of administration—many boys and young men must learn to give themselves shots. *“I keep telling him that he may not be the biggest boy in his class, but he is certainly the bravest because how many of his other classmates are going home after school to take shots,”* said the father of one young boy with BTHS.

*“I do wish though that Neupogen was an oral medicine instead of injections,”* said the 17-year-old panelist.

Another issue, one that may be related to the difficulty with titrating the best dose, is that many boys and young men still get infections, despite G-CSF, and land in the hospital on IV antibiotics—sometimes in isolation because of their intractable neutropenia.

---

**Another downside is the route of administration—many boys and young men must learn to give themselves shots.**

---



Finally, antibiotic treatments are not always sufficient, however, and some of the meeting participants had lost loved ones due to sepsis.

### C. Heart transplants

*“[His] weakened and enlarged heart was treated with a heart transplant, but to be clear, ‘heart transplant’ is a treatment not a cure! His transplanted heart requires immune-suppression, semi-annual cardiology visits, and an annual heart [catheterization] and biopsy. And eventually, [he] will need another heart transplant.”*

Quite a few of the infants who are discovered to have heart failure soon after birth are placed on a waiting list for a heart transplant, though only a fraction of those actually receive a new heart. A separate polling question (Appendix 3, topic 2, question 6) asked participants to expand upon their experience with receiving or trying to receive a heart transplant, with 91 people responding. Of these, 15% indicated that they had been listed for a heart transplant and received one, while 13% had been listed, but they were removed from the list because their cardiac condition improved. One individual indicated that the person they were responding for had been listed but died while waiting for the heart. Finally, 6% had never been listed (and one person was unsure).

---

**While heart transplants can successfully treat cardiomyopathy, they come with their own set of complications.**

---

While heart transplants can successfully treat cardiomyopathy, they come with their own set of complications, including chronic treatment to prevent organ rejection. During the discussion, one meeting participant described how, during a difficult period, he had not adhered to his treatment regimen and had to take a year off of college due to “*major antibody mediated rejection.*” He also noted that the medications to prevent that have their own negative consequences—such as liver toxicity that makes it difficult to

consume alcohol and could potentially make it difficult for him to qualify for future clinical trials.

Others mentioned other rare complications, such as one father whose 10-year-old son “*ended up with an exploratory laparotomy after his heart transplant because he had two holes in his small intestine.*”

Finally, heart transplants do nothing to address the other cardinal symptoms of BTHS. As one caregiver said, “*Our son was transplanted and although it lengthens your life, the fatigue issues remain—and so your heart may be stable for some period of time, but the underlying condition doesn’t go away.*”

### D. Defibrillators

*“On April 23rd in 2000, I suffered my first cardiac arrest at age 11, and I had my first defibrillator implanted. On April 17<sup>th</sup>, 2018, I suffered my eighth cardiac arrest and was saved by the shock of my fourth defibrillator.”*

In a significant proportion of boys, heart problems persist despite taking a number of medications, and a defibrillator is required due to the constant threat of cardiac arrest. “*We own a portable AED and bring it with us many places,*” said the father of an 8-year-old boy. Some have to have their defibrillators implanted at a fairly early age.



Others have them implanted at some point later in life to avoid sudden death due to arrhythmias. The caregiver who helped cofound BSF spoke about how, after a boy in the community died unexpectedly while playing, her son wanted to avoid the same fate: *“No non-invasive evaluation gave any hint of [his] vulnerability, but an intracardiac electrophysiology study showed that he was at a severe risk of sudden death. And so, an internal defibrillator—also called an ICD—was implanted immediately,”* she said.

## **Approaches to address skeletal muscle weakness, exercise intolerance, and related symptoms associated with Barth syndrome**

The next polling question asked caregivers and patients to indicate whether they were currently using interventions and therapies commonly used to manage symptoms related to skeletal muscle weakness and exercise intolerance. A smaller number of participants (60) provided 101 responses to this question.

### **A. Physical therapy, occupational therapy, gym, and activities to increase exercise tolerance**

*“I called the physical therapist the next day and said, ‘What can you do to help him run fast?’”*

The greatest proportion of respondents (76%) reported using physical and/or occupational therapy. A few meeting participants mentioned physical or occupational therapy as a routine part of care. In some cases, this began quite early. *“At age 1 he began weekly physical and occupational therapy sessions,”* said one caregiver. But it is not clear how many consistently sustain formal therapy sessions. One man said that he *“would have physical therapy work with me, once a week ... and used to have occupational therapy, but around third or fourth grade, that stopped.”*

Others made reference of a commitment to a regular gym, walking, or swimming as a way to try to increase their exercise tolerance. One man said that he has to *“spend 30 minutes a week at the gym ... Not going to the gym would limit my energy even further in the long run.”*

**“When you’re doing nothing then it’s really hard to start doing something from doing nothing.”**

**- Patient**

Another young man said that he was trying *“to increase exercise tolerance but it’s difficult and I don’t know if it’s working yet ... It’s not really pleasant to exercise. When you’re doing nothing then it’s really hard to start doing something from doing nothing.”*

### **B. Mobility equipment (cane, walking stick, adaptive stroller, motorized scooter, wheelchair)**

*“I need a motorized scooter for sustained longer distances—like with a vacation.”*

More than half (53%) of the poll respondents indicated that they or their loved one with BTHS were currently using mobility equipment of some sort. Based on the participant testimonies, many individuals with BTHS make use of mobility equipment at some point in their lives to help them *“conserve energy,”* particularly when they have to go any significant distance.

*“He can just not walk long distances, so we have an assistance chair that we bring with us to many places,”* said the father of an 8-year-old with BTHS.



Some find the devices stigmatizing. *“I hate that the kids ask why [he] is riding in a stroller when he is actually in his assistance chair because walking long distances is just too much,”* said one caregiver. *“The school would provide special chairs, which obviously stood out. I would refuse the chair,”* another patient reflected.

One young man was frustrated that he remained fatigued despite being offered an electric wheelchair: *“I thought this [would] fix my problems with fatigue, but sadly I wasn't that lucky.”*

### **C. Ankle/leg or other braces**

*“Eventually he was fitted with plastic braces—hinged ankle-foot orthosis devices (AFOs)—to help support his legs.”*

Almost 27% of polling participants indicated currently using ankle/leg or other braces.

### **D. Surgical procedures**

*“[He] had to have his umbilicus surgically removed since it was persistently inflamed and infected.”*

About 12% of the polling respondents have had to undergo surgical procedures to address some of the consequences of BTHS. Unfortunately, given the frequency of neutropenia and infections, these procedures represent a much greater risk than faced by most individuals in the general population.

## **Approaches to manage eating/feeding challenges and nutritional deficiencies associated with Barth syndrome**

There were 114 responses from 71 participants to the next polling question (Appendix 3, topic 2, question 3) regarding what diet and feeding interventions they were currently using. Among these, 82% were currently using nutritional and/or amino acid supplements, while 38% were taking medications to manage stomach/gastrointestinal symptoms. Roughly 21% of the respondents are currently using a tube of some type for feeding, while nearly 20% are processing their food in some way either by pureeing, softening, or thickening it. Most of the discussion involved feeding tubes and total parenteral nutrition (TPN) delivered by tubes.

Many infants, boys, and young men with BTHS simply cannot eat enough to support their nutritional requirements—particularly when they are going through an accelerated growth period:

*“He had a feeding tube placed on Day 2 of his life and 21 months later he still receives all of his nutrition and all of his medications through a feeding tube.”*

*“I had a feeding tube for 15 years from age 13 to 28 because I wasn't getting proper nutrition through my normal diet.”*

*“We've been in some form of feeding therapy since he was 6 months old.”*

*“He was too weak to eat and required a feeding tube.”*

*“I was started on a nasal feeding tube when I was 7 months old ... At 2½ years old, a gastrostomy tube was surgically placed into my stomach. When I was 5 years old, I [started on a*



*specially devised] formula that my parents made at home, and with a few tweaks along the way, I was on this formula for 24 years. I continue the daily feed tube feedings."*

The experiences with these interventions varied. Many gained weight with tube feeding, particularly when TPN formulas *"included supplements of several amino acids commonly deficient in Barth syndrome."* But some reported that they have yet to have much success: *"He had a feeding tube during the first four years of his life with no significant gains to show for it,"* said one caregiver. The feeling of being full as a result of tube feeding has also been reported to make nausea worse.

Another issue is that gastrostomy sites often become infected. The cofounder of BSF reported that her son had trouble with his g-tube site healing and had to have it removed. Years later, *"a 'JG-tube' was placed in order to allow him to feed directly either into his stomach or his jejunum, hopefully then transitioning from TPN [administered through a central line] to these JG-tube feeds. He, unfortunately, had more trouble, though, with wound healing, exhaustion, and nausea. He was never able to fully make the transition to tube feeding."*

## **Approaches to manage pain, fatigue, sleep problems, and mental health issues associated with Barth syndrome**

A question about the use of therapies for pain, fatigue, sleep, and mental health issues (Appendix 3, topic 2, question 4), garnered fewer responses (60) from 39 polling participants. Of these, 59% reported using pain medication, and 59% also indicated use of talk therapy (psychotherapy). Medicine for anxiety or depression was used by 23% of respondents. Roughly 13% indicated using medication to enhance attention or prevent daytime sleepiness.

Most of the discussion focused on the inadequacy of pain management for some patients with BTHS.

***"I'm not good with pain medicine—it makes me super sick—and so I have to sit there and deal with it and fight through it."***

***- 17-year-old patient***

*"I'm not good with pain medicine—it makes me super sick—and so I have to sit there and deal with it and fight through it,"* said the 17-year-old panelist. He had also tried gabapentin (*"It caused extreme mood swings"*) and amitriptyline, which *"only suppresses [the pain] for so long and it just makes me sleep. I don't like sleeping all of the time."*

Others indicated that it has become very difficult to access adequate pain medication. According to the 36-year-old man who said that he was in pain 24 hours a day: *"I'm on no pain medications due to the opioid epidemic. State legislation and the opioid epidemic has made it very hard for me to get any kind of pain medication. I gave up fighting with doctors and started using Advil and Motrin. I'm still amazed at how much I can tolerate."*

There is a danger that patients may take over-the-counter medications at unsafe doses: *"I finally got medication for pain. Before I got that medication, I could take four of the 500 mg 'Advil liquid gels' and it wouldn't touch it. I couldn't get out of bed in the morning, and some days I couldn't get up and it would ruin days. And being in that much pain itself is exhausting,"* said one man with BTHS during the discussion.



## Perspectives on future treatments and considerations in decisions regarding treatment and clinical trial participation

Patients and caregivers were asked several questions to characterize what they were looking for in a treatment for BTHS.

### A new treatment for Barth syndrome should address which symptoms?

In light of the shortcomings in existing treatments, one question (Appendix 3, topic 2, question 7) asked polling participants to prioritize what they most want out of a treatment for BTHS. This largely reflected each individual's unmet medical needs in BTHS as was pointed out by one of the 36-year-old panelists: *"You could ask everyone, and they'll have a different answer because it depends upon what affects them the most."*

Patients clearly have more than one unmet need, however. Out of the 320 answers to this polling question from 87 respondents, the following responses were chosen most frequently:

#### Reduce fatigue

*"To get rid of fatigue is essentially to fix my personal problems. That's my ideal treatment."*

Seventy percent of respondents emphasized fatigue reduction as being what they most want to see from a new treatment. This was reflected by one panelist's comments during the meeting:

*"I've been plagued with this fatigue all my life and for any new treatment to have any positive effect that's the aspect it needs to tackle—something to improve my ability to do things I love to do in life, so I can spend the day or even an afternoon working and out with friends and not have to suffer,"* said the 19-year-old panelist.

---

**Seventy percent of respondents emphasized fatigue reduction as being what they most want to see from a new treatment.**

---

*"What I wish I could do: Work full or part time in a career. Take classes if needed for said career. Do more than one activity a day without having to rest after. Have the stamina to play actively with my niece, Anna; and have the energy to do normal everyday things without being exhausted,"* said one of the 36-year-old panelists.

#### Improve muscle strength

*"If he could fix one thing of his Barth syndrome then, what would it be? His answer was to have more strength. At this time of his life that's what means a lot to him."*

More than 64% of polling participants called for a treatment that would address their skeletal muscular myopathy, which is closely linked with stamina and energy. *"If somebody asked me what type of treatment I really wish we had, the answer would be something to improve his strength and his endurance,"* said the father of one boy.

One caregiver, whose son had just begun his first job, said that he told her he wanted a treatment that would give him *"better muscle tone to be stronger, which then would give me more energy."*



## Improving cardiac function/reduce arrhythmias

*“If I could remove one aspect, it would be the cardiac factor.”*

Among the respondents, 56% indicated that they want a treatment to address the leading cause of morbidity and mortality among people with BTHS by improving cardiac function/reducing arrhythmias.

*“Surviving a cardiac arrest is incredibly unlikely. I am no more likely to survive, it feels like, an inevitable ninth cardiac arrest, since I have lost other Barth brothers to these events. If I could live without that specter hanging over me, my life would be much improved,”* said the 29-year-old panelist who had thus far had eight heart attacks.

A future treatment that would delay, or better yet prevent, the need for a heart transplant *“would be ideal for the younger ones and those who might have the potential to go down the transplant route,”* said an adult heart transplant recipient who said that he had not foreseen negative consequences such as the side effects associated with the treatments to prevent organ rejection.

## Reducing neutropenia and risk of infection

A similar proportion indicated that they wanted a treatment that better reduces neutropenia, the risk of which can be life-threatening infection in BTHS (53%).

## Lengthen life expectancy

*“As a mother who has lost two children, I want more moments.”*

The next most desired positive treatment impact (selected by 48% of respondents) is closely related: a treatment that would lengthen life expectancy.

## Addressing other unmet needs

A smaller but significant proportion indicated that they would like a treatment that could improve eating, GI, and stomach issues (25%), lessen pain (headache, stomach ache, etc.) (22%), address anxiety and/or depression (10%), improve thinking/concentration (10%), and improve sleep (6%).

However, some meeting participants stressed that they wanted a treatment that went beyond addressing any one specific symptom.

*“The problem with this disease is it affects so many different systems and it affects everybody differently that we really almost need to fix the thing to cure all of it,”* said one 36-year-old panelist.

One caregiver in the audience put it succinctly: *“The ideal treatment for me ... would be something that fixes the underlying cause of the condition—a medication that effectively makes the defective mitochondria good again.”*

## Preferences regarding modes of treatment administration

The next question asked respondents to provide input on what approaches to administration and monitoring they would consent to in order to take a theoretical treatment (Appendix 3, topic 2, question 8). Again, there were 87 respondents, but this question garnered more responses (704) than any other question—which reflects a desire for an effective treatment regardless of how it is delivered. Virtually



everyone (95%) would be willing to take a daily oral medication, while 77% indicated that they would be willing to take a medication by infusion in a doctor's office once/month, and only somewhat fewer (61%) would be willing to go to the doctor's office every week for the infusion. Most (69%) would also be willing to take a medication delivered by subcutaneous injection. Having a device surgically implanted was the least selected option, but a significant percentage still indicated that they were willing to accept this for a treatment (36%).

---

**Overall, it could be inferred that if a treatment addresses their critical unmet needs, most people with BTHS would be willing to do almost anything to access it.**

---

Most respondents indicated they were willing to accept other inconveniences to access a BTHS treatment, such as having regular doctors' appointments (80%) to have treatment monitored or delivered or undergoing blood draws beforehand (78%) or at regular intervals (75%) for monitoring. Only a slightly lower number of participants would be willing to travel out of town for several days for treatment, whether it was once a year (65%) or up to four times a year (62%). The majority were even willing to undergo tests requiring

hospitalization before beginning a treatment (59%) or to undergo tests requiring anesthesia before start of treatment (52%).

Overall, it could be inferred that if a treatment addresses their critical unmet needs, most people with BTHS would be willing to do almost anything to access it. *"If he could have a needle a day that would give him the energy to get up, go to work, become a chef, without any real side effects—that would be his ideal,"* one father said about his adult son.

*"I don't really mind what I have to do to make that happen [alleviate his chronic fatigue]—whether it's testing, pills, or injections, it doesn't matter to me,"* said the 19-year-old panelist.

### **Perspectives on the side effects/risks of treatment**

Another question (Appendix 3, topic 2, question 9) asked about factors that would influence decisions regarding whether to use or stop a given treatment. The most common answer, chosen by all but one of the 84 respondents (99%), was that if a given treatment had significant risks of serious side effects such as cardiac arrhythmias or infection of implants, etc. Most (61%) said they might also discontinue treatment if there was a particularly onerous medical burden or administration considerations (such as the need for hospitalization, radiation exposure, etc.).

Some respondents suggested that cost (35%), the time a treatment might take away from daily activities such as job, school, etc. (26%), and common, less serious side effects such as nausea, headache, rashes, etc. (25%) might also be a disincentive to continue treatment. It should, however, be remembered that these perspectives regarded a hypothetical treatment—rather than one with known benefits.

### **Perspectives on clinical trials**

Participation in clinical trials will be required to develop future treatments. Consequently, another polling





question asked patients and caregivers to select up to four factors most important to their decision about whether to participate in a clinical trial to study an experimental treatment (Appendix 3, topic 2, question 10). There were 110 respondents who submitted 400 responses.

The most common response (selected by 84% of the respondents) was whether there was *“a risk of rare but more serious side effects (cardiac arrhythmias, infection of device implant, etc.)”*—which would clearly be a negative incentive to participate in a trial. Conversely, the majority also indicated that *“how the treatment might help”* (64%) and *“the reputation of the study doctor”* (58%) would also influence their decision.

Over 40% of the respondents indicated that their decision might also be influenced by whether participation in the trial might somehow affect medications that they were currently taking, and whether there were data on the safety of the treatment available ahead of time. Other common side effects (such as nausea or headache) might be a factor for a little over a quarter (27%) of the respondents.

During the meeting, there was some discussion about decisions to participate in one of the first clinical trials of a treatment for BTHS. The 17-year-old panelist noted that he was *“hesitant at first when they told me it was supposed to be daily injections.”* Over time, however, he believed he *“could notice a difference,”* and he strongly encouraged other boys to join the trial. Two adult men, both in their 30s, who also entered the study, noted that they did not observe a benefit. Both noted that one of the reasons that they had entered the study was that they respected the doctor running the study. One said the doctor had been *“quite adamant that if you don't feel comfortable with this, you can stop,”* which he did, as he was experiencing side effects that had been mentioned in the informed consent.

Another audience member, the father of two teenage boys, offered his endorsement of the trial based on their positive experiences on the treatment: *“If you're on the fence, please give it a try,”* he said.

Another real-world aspect of clinical trial participation mentioned by one of the adult participants who did not benefit was the difficulty accessing the trial site for individuals who already have mobility challenges. *“Travel is difficult. We had to go to Baltimore a bunch of times and that was tiring and stressful,”* he said. Nevertheless, he stated, *“I'm also hopeful for the possibility of more clinical trials in the near future.”*

Another 36-year-old panelist concurred. *“If there was any treatment or studies that were available, I would want to participate to help change the lives of those still here living with Barth, and the ones to come because there are carriers who will have children one day,”* he said.

**“If there was any treatment or studies that were available, I would want to participate to help change the lives of those still here living with Barth, and the ones to come because there are carriers who will have children one day.”**

**- 36-year-old patient**



Additionally, earlier in the meeting, the BSF cofounder said that her son would also have been eager to participate in the research: *“He would have wanted me to say today that he is fully behind all of the efforts to get treatments for the fight of his Barth brothers. Like many of his Barth brothers, he donated his blood, cells, DNA, and tissue for scientific endeavors and he even got some of his friends, and yes, some of his doctors, to contribute control samples. He absolutely would’ve participated in clinical trials.”*

## The ultimate goal of treatment

Values about the ultimate aim of treatment differ between diseases, often depending upon whether patients and caregivers are more concerned by the threat of progression, the intensity of symptoms, or the burdens of the day-to-day limitations forced upon them by the disease. More polling participants (121) provided their views to the final polling question (Appendix 3, topic 2, question 11) that addressed

**“Any treatments that would help in any aspect of what they have to endure would be a game-changer.”**

**- Mother of Barth patient**

this topic. More than two-thirds of the respondents indicated the single most important accomplishment of a treatment in BTHS would be to provide gains in function (which could mean increased strength and energy to do something the patient was unable to do before). A much smaller proportion (19%) said they most wanted a treatment that would lessen symptoms. Finally, 7% prioritized life extension, and 6% most wanted a treatment to stop or slow progression.

Ultimately, everyone wants a cure. Shy of that, most would be happy with *“something that will help them overcome [their] barriers”* and ways *“to alleviate some of the symptoms that come*

*with living with Barth syndrome.”*

*“Any treatments that would help in any aspect of what they have to endure would be a game-changer,”* one mother said.

## Post-meeting questionnaire

After the meeting, a questionnaire was sent out for patients and caregivers to provide further feedback about their experiences that could not be shared that day. Overall, 36 individuals responded, 18 of whom responded to most of the survey’s questions, including some individuals who were physically unable to attend the meeting. According to the survey’s first question (see Appendix 4, question 1), slightly over 21% of the respondents did not attend the meeting in person. In addition, according to the survey’s last question (Appendix 4, question 4), about 28% of the answers provided were characterized as new (in other words, the respondent had not answered any of the survey’s questions before), while about 61% of the information provided was in addition to that which was offered during or shortly after the meeting.

Given the relatively small number of responses in comparison to the meeting, too much emphasis should not be placed upon the percentages selecting particular choices on the multiple-choice portion of the questionnaire. In general, the responses were similar to the polling responses during the EL-PFDD meeting, though there were some questions on the survey that were not included in the live polling or during the discussions at the meeting. The open-ended answers in particular add nuance and allow this



report to more faithfully represent the voice of the patient with BTHS. Note, this narrative reorganizes some of the answers offered based upon a thematic analysis.

## **Symptoms that matter the most—over the last year and over a lifetime**

The ranking of some of the symptoms of BTHS was slightly different (question 5) than in the live polling results. While muscle weakness and exercise intolerance still ranked highest, a large percentage also chose neutropenia, which tied with fatigue as the second symptom that mattered most to the questionnaire participants. This may have been the consequence of slight differences in demographics between the poll and the questionnaire participants, such as the age of the person with BTHS for whom the respondent was representing.

In addition, the post-meeting survey included a question (#6) about the symptoms that mattered most over the course of the lifetime. Most of the

selections were ranked similarly, with muscle weakness followed by fatigue, then heart failure and neutropenia. Again, it should be noted that there would have been an inherent survival bias in both the polling and questionnaire responses, as not every individual with BTHS who has died due to heart-related complications or neutropenia-related infections (both common causes of death) will have had someone to represent them in this process.

---

**The post-meeting survey included a question about the symptoms that mattered most over the course of the lifetime. Most of the selections were ranked similarly, with muscle weakness followed by fatigue, then heart failure and neutropenia.**

---

Some of the responses to open-ended questions later in the questionnaire added more depth to the characterization of some of the symptoms. For instance, one consequence of muscle weakness and exercise intolerance appears to be *“heat intolerance. He gets hot really easily.”* This hearkened back and provided additional context to a comment made during the EL-PFDD meeting by one of the panelists about how *“the summer heat was my kryptonite,”* and others about how infants would break out into a sweat when nursing. *“I ... was drenched in sweat when I tried to feed,”* another adult panelist with BTHS said about his childhood.

Another point about the persistence of fatigue mentioned during the EL-PFDD meeting was restated in a particularly concise way by one caregiver who wrote that when her son became fatigued, *“that exhaustion can continue over several days.”*

## **Activities that cannot be done as well or fully as one would like, or at all, due to Barth syndrome**

At the EL-PFDD meeting, a few multiple-choice polling questions asked about the impact of BTHS on the ability to work and attend school. But life is not just work or school, and two open-ended questions included in the post-meeting survey elicited feedback about other activities—the sort that individuals would otherwise be able to do or do more fully or enjoy were it not for the limits imposed upon them by



BTHS. Many of these were activities that most people take for granted, such as *“eating,” “speak fully,” “studying/writing,” “learning,” “going to school,” “full days at school,” “work full time,”* and *“keeping a job.”* A couple caregivers wrote about issues related to delayed developmental issues, such as how their child was *“slow to walk,”* or able to *“sit, walk.”* Others had trouble with *“steadiness on his feet ... causing him to fall when going up or down stairs.”* *“Going up and down the stairs”* was cited by more than one respondent. BTHS also limits mobility for some later in life, with some writing about not being able to *“simply walk around town”* or to *“walk very far without becoming exhausted.”*

Others indicated that BTHS limited the ability to partake in many of the joys of life:

- *Play sports (repeated by several), exercise, skip, jump, run*
- *Go for hikes or bike rides; participate in sports like his brother (soccer, martial arts)*
- *Play drums (he loves it but doesn't have the stamina to complete a song)*
- *Keeping up/staying in touch with friends, socialize with friends at university, join in social events/days and nights out to concerts, etc., with friends/peers*
- *He has to nap often so we cannot go out a lot*
- *Planned events (due to fatigue), some independence from adult help/supervision*
- *Drive long distances*
- *Dating, intimacy*

There were similar responses to the same question when respondents were asked what activities could not be done at all due to BTHS. Many of these were about *participating in sports*, including particular sports the boy is attracted to, such as *“rugby,” “riding a bike”* (which was mentioned by a couple of participants), or *“sports of any nature.”* A couple mentioned the psychological impact of these losses. One said her son could not *“play with other kids at recess (he cries because he is not included or when included, he gets singled out).”* Another said their son *“can't play sports at a level that would allow him to play on the team and feel more like ‘one of the guys.’”*

A couple responses were even more stark, stressing the life-limiting nature of the disease, including activities such as eating *“by mouth,”* being *“near sick individuals,”* or being able to *“survive with a Barth syndrome-ravaged heart.”*

## **A day in the life with Barth syndrome**

One of the survey questions tried to draw out more feedback about how BTHS affected the daily lives of people with the syndrome. However, this is quite difficult to synopsise because as one of the clinical experts said during the EL-PFDD meeting, there *“is no one with average Barth syndrome—each person seems to have their own unique flavor of it.”* Consequently, there were as many different daily experiences with BTHS as there were responses (see question 9).

*“His day revolves around Barth,”* said one caregiver, who along with others wrote about how muscle weakness and fatigue limit what can be accomplished in a day. [He gets] *“tired and needs to rest throughout the day.”*



One individual with BTHS stressed the bad days, when he could be *“fatigued to the point where I barely move in a day.”* For another, days are spent trying to *“manage a terrible fatigue and pain.”*

Another caregiver wrote that their son *“gets tired easily”* and that they *“have to plan ahead to get from point A to B.”* In addition, he is *“always monitored to ensure proper medicine/supplements intake.”*

Another mentioned that each day, it *“requires more time to prepare and administer medicines.”*

*“Meals are always hard times,”* wrote another caregiver. Others mentioned days *“interrupted by feeding times,”* and another said their son was *“having a hard time eating without having a g-tube.”*

Others have days that are more affected by neutropenia, their weakened immune systems, and described *“constant fear with constant infections, fevers, [and] anal sores, too.”*

*“Always getting sick. Belly issues: that’s a daily battle,”* wrote another who added that the day contains *“little sleep because he doesn’t sleep.”*

Others described days impacted by BTHS in a variety of ways: *“The fatigue has a huge impact and affects him to varying degrees daily. Hot weather makes this even worse. It makes it difficult to study and retain knowledge and participate in normal activities a teenager generally would. He has pain daily to varying degrees and also has a lot of trouble sleeping, which also further impacts fatigue and ability to perform or cope with daily activities. He also struggles with anxiety, which greatly affects his quality of life and ability to enjoy things.”*

One caregiver wrote about how fatigue and low muscle tone affects their son’s *“independence, social life, not many friends. I know he would love a girlfriend, but he feels like this doesn’t seem possible. My son worries that his heart may stop while he is asleep and has told us this on many occasions. He worries that if this happens then ‘how would we know where to find him.’ This breaks my heart. I can do all that I can helping with all the practicalities of his medical care, appointments, school, doctors etc., but this, I cannot take away for him.”*

Another caregiver wrote about her son’s *“heroic”* effort *“not to let it get to him,” “but it wasn’t easy for him. He didn’t like to complain because complaints didn’t make it better. He avoided thinking of himself as ill but as he once said, ‘Being in the hospital waiting for someone to die so that I might live [with a heart transplant] makes it impossible for me to escape the fact of just how sick I really am.’”*

The last person to respond to this question was a man with BTHS who wrote: *“The fatigue requires me to give up on half the activities that are important to me, which lead to depression and loneliness. I also have to force myself to eat despite a complete absence of appetite and aversion to almost any kind of food, making every meal a struggle.”* The same respondent added a related comment in response to the last question on the survey:

**“His day revolves around Barth. [He gets] tired and needs to rest throughout the day.”**

**- Caregiver**



**“Barth syndrome influences every part of life. It affects what food you enjoy, what topics you grew interested in, what hobbies, education, and jobs you chose, who you became friends with, how confident you are in general and in specific areas, how important quantity of life is, what quality of life means, what you enjoy, and so much more. No consideration of treatment should stop at physical changes or even mental state. The impact on every aspect of life should be considered.”**

## **Changes in Barth syndrome over time**

Another question (#10) asked about whether BTHS had changed over time. The responses should perhaps be looked at in light of the questionnaire’s demographics, half of whom were under 15 years of age, or still in the honeymoon period (see question #4). Consequently, some respondents had not yet seen profound changes in the disease, and some had even seen improvement in heart function on heart medications or due to heart transplants.

**“The symptoms themselves haven't changed much, but responsibilities increased as I grew older, making the fatigue much more prominent than early in life. And as a result, loneliness and depression became a much bigger issue as an adult than they were in childhood.”**

**- Adult patient**

Others have not been so fortunate. One wrote that their child did not survive. Another caregiver wrote that their loved one’s heart function improved and appeared normal on medications, and then the doctor took the child off treatment and his heart failed. Others mentioned that *“over time the symptoms got worse”* or that they had *“less energy”* or had *“gotten more fatigued.”* Another wrote: *“My son has had ups and downs over the years with cardiac issues/infection/weight gain/low stature/back and leg pain and, of course, the every-single-day presence of fatigue.”*

Several individuals with BTHS had grown into adulthood. One noted that it occurred suddenly: *“Small stature was an issue throughout his life until*

*senior year in high school when he grew at a rapid rate. Each cardiac arrest, without an explanation of why, affects not only his heart but his fear of living. Having a protruding stomach while you are still only in the 15th percentile for weight is also demoralizing.”* This caregiver also cited some of the pressures that come with adulthood. *“Dating, or should I say NOT dating, is an issue. Still living with your parents because you cannot live on your own ... so many real-life obstacles.”*

One adult respondent with BTHS similarly noted challenges, including mental health issues, that come with growing up, even if his health status had not changed much: *“The symptoms themselves haven't changed much, but responsibilities increased as I grew older, making the fatigue much more prominent than early in life. And as a result, loneliness and depression became a much bigger issue as an adult than they were in childhood.”*

In an answer to another question about treatment-related issues, one caregiver described similar challenges: *“My son is almost 18 and trying to keep him in his daily physio routine is becoming harder. He is doing his own G-CSF injections, his own medications, and I am currently trying to get him to deal with*



reordering his repeat prescriptions/dealing with receptionists at hospitals, etc. My son is currently transitioning from pediatric care to adult services at hospitals, and because he sees so many doctors/specialists (seven different ones), he is finding this very overwhelming. He is finishing school at the same time ([asking] 'What is next for me? How will I cope out of the school system, etc.?) and all the change is too much for him to deal with at the same time (his own words)."

## What worries one the most about Barth syndrome

Question #11 asked participants to describe what worries them the most about BTBS. For some, this appeared to be another way to describe the symptom that mattered most to them, and so they focused on "neutropenia," or "heart function/arrhythmia/infection/fatigue," or "the need for another heart transplant."

Many wrote stirringly about their young child's fear of death: "He worries too much about things a 9-year-old should not worry about. He asks me every night to listen to his heart. Sometimes he says he doesn't want to die. We went for a trip to Italy this year and had to toss a coin in a fountain and make a wish. His brother wished for getting all the Transformer toys. He wished for a cure to Barth."

For some, such fears have led to desperate decisions: "He didn't want a heart transplant because he knew there would be no treatment to cure rejection. He didn't want to die, either. So he agreed to the transplant, but he said, 'The transplant is like being in death's waiting room. You're gonna die, it just takes longer till the reaper calls your name.' Science can't move fast enough."

Others who worried about death seemed to be almost, if not more, worried about what would become of them in adulthood. According to three caregivers:

- "That he will never get to eat right, die before he's 40 years old, or be able to do things that other kids can do."
- "My husband and I are scared he could die, as his little brother, or become an adult that can't work or have a normal life."
- "He worries about his future and ability to support himself and participate in things like a job and a social life."

And finally, two men with BTBS voiced similar concerns. One worries most about a day in which he can no longer look after himself. He wrote about "the inability to keep up with society's increasing demands. I've gotten to a point where I hardly have any energy for what is important to me, and at this rate it will be a matter of time before I can't manage my healthcare and paperwork for disability benefits anymore, either."

Another was very direct: "Death. Not accomplishing what I want out of life. Not finding an ideal life partner, never moving out of the parents' house, living unfulfilled."

**"He worries too much about things a 9-year-old should not worry about. He asks me every night to listen to his heart. Sometimes he says he doesn't want to die."**

**- Parent of Barth patient**



## Other non-medical impacts of Barth syndrome: practical, financial, psychological, and socioeconomic

Question #15 of the survey, which asked participants to elaborate on some of the other burdens of BTBS, generated some of the most feedback. Despite the different manifestations of the syndrome, many of these were the same:

**Practical:** In practical terms, BTBS constrains many aspects of life: *“Due to feeding problems, sometimes difficult to be on the move,”* and *“he cannot participate in life like most of his peers.”*

Dealing with it *“takes planning”* and effort *“juggling and educating doctors about his condition”* on the part of families and their loved ones with BTBS. *“He has to carefully choose what he participates in on weekends as it will impact him for the rest of the week.”* Ultimately, it limits one’s independence: *“He cannot live on his own for so many reasons ... muscle weakness for daily chores, transportation issues, independence for finances since he only works part time.”*

**Financial:** Several respondents mentioned the financial burden the illness places on the family and individuals with BTBS:

- *“Financially it is an endless list of medical bills.”*
- *“It’s been expensive paying for all his treatments and medicines.”*
- *“Our family’s financial life has been affected by the tremendous [amount of money] spent on medical care to protect him, for ‘vacations’ to conferences and outreaches and clinics that are not reimbursed.”*

**“Financially it is an endless list of medical bills.”**

**- Questionnaire respondent**

Both individuals with BTBS and their caregivers may find it difficult to work full or even part time:

- *“He depends on government support whilst studying as he is unable to work and study. He would not be able to work in a physically demanding job and his career options are limited.”*
- *“It’s hard for me to work when he has bad days, hard to find a sitter because he’s medically fragile.”*
- *“Only being able to work a few hours a week means money is always really tight.”*
- *“Even though he is getting a disability check, which is helping a little, I’m having to stay at home instead of getting a job. I’ve had to stop working to be able to take care of my son.”*
- *“Loss of economic earning power for me. Had to quit job to take care of him.”*

**Psychological/Social:** Questionnaire respondents repeated the word stress (stressed or stressful) six times with regard to the impact of BTBS on the patient and all affected family members: *“We are often stressed because of the unpredictable disease.”*

Many comments addressed the impact of caregiving and grief upon the family, where *“siblings sometimes had to take a back seat to the needs of their brother.”* This could be particularly difficult when BTBS had already led to the death of one family member. *“We had already lost one son and this was very hard on all of the family [including] the two girls. [We were] new to the area and had no family nearby and no support system,”* one caregiver wrote. A couple described the psychological effects as *“heavy,” “really heavy.”* *“Only when we get a break do we notice the near constant source of anxiety,”* wrote one. Another said that these





effects not only affected family but their teen son's friends as well, who "go away," leaving him "always alone at home ... depressed."

Many young boys and young men with BTHS are isolated. Some are stigmatized by others for their "small stature." One caregiver wrote, "He does not have the energy to socialize." Another wrote that her son "hates not being as independent as his friends/peers. He loves sports and hates he cannot take part as much as he would like. He worries about getting/holding down a job/college. He watches his older brother go to university/ have a busy social life/leaving to stay in another city and wants this for himself. He is currently 17 years old and seems to resent his wheelchair at the minute, he seems frustrated with his fatigue."

## **Barth syndrome management and its downsides**

Questions #12, #13, and #14 all focused on how individuals have managed their BTHS—as well as the benefits and downsides of those therapies. Most of the medications and therapeutic modalities were the same as described during the EL-PFDD meeting, though due to the way the question was framed much of the feedback to question #12 was focused on lifestyle accommodations and "everyday life adaptations (computer at school, less walking, less sports)," "limiting my activities and taking antidepressants," said one participant with BTHS.

"He has a place at university where he can rest. He is allowed to miss lectures and access from home if needed but he loves the social aspect of university and hates to miss out. He has a disability sticker for his car, so he can park close to where needed," wrote one caregiver.

One caregiver who had lost their son wrote strictly about the medical therapy—and its failure: "His biggest issue was always cardiac-related. His heart got better and worse, better and worse throughout his life. Over the last year of his life it was like a vortex. He had to have a transplant to survive but he couldn't tolerate the standard dose of medications required to reach 1A status and I am convinced his metabolism fluctuated, which caused it to be very difficult to manage anticoagulation therapy."

The next question focused specifically on how well available treatments manage the most significant symptoms of BTHS, and, given the variable presentations of the disease over the course of a lifetime, answers ranged from "my current treatments manage my symptoms completely" to "not well." Most reported that heart medications, defibrillators, heart transplants, and G-CSF appeared to be working fairly well. But again, a point that came up during the EL-PFDD meeting was reiterated: "There is no real treatment or therapy for the fatigue, which is the biggest issue."

"He doesn't get sick too often but fatigue and muscle weakness, which is his primary barriers to a fulfilled life, have not improved," wrote one caregiver.

However, many did report that there are significant downsides to the therapeutic approaches to BTHS. Several mentioned the hassle of G-CSF injections ("annoying"), which were self-administered. A couple of those focused on the fact that their therapies were "time-consuming, exhausting." "It takes up most of my limited energy, leaving little for things that make my life enjoyable," wrote one man with BTHS.



Though some were willing to trade downsides for benefit, *“as he remains with us,”* others wrote that the medications *“did not work.”* *“We see no improvement. We see no worsening, too, but sometimes he has medicine intake fatigue. Why take all this if the quality of life seems to remain the same?”*

As BTHS is a multisystemic syndrome, sometimes *“the current therapy to treat a symptom exacerbates worsening of another,”* wrote one respondent. The immunosuppressant medications for those who have had heart transplants are a case in point for an individual who already may have neutropenia. *“Not being anywhere near a sick or coughing individual. Immunosuppressive meds might require me to have a liver transplant as well. I might require multiple heart transplants.”*

## **Making decisions about using a therapy or treatment**

In response to question #16, respondents made comments about factors they take or would take into consideration regarding whether or not to try or use a new treatment. Many wrote about the *“risk/benefit,”* or *“risking benefits against severity of negative side effects.”* *“Dangerous down side effects”* could include the impact on other treatments currently being taken. *“Cost”* and *“the commitment of time”* are also considerations. Most want the treatment *“to improve quality of life.”*

One wrote that their son *“is open for trying new therapy/ treatments.”* However, one man wrote describing a delicate balance of *“the body ... mind, personality, social environment”* and having to be *“reasonably sure a physical change would not break my body's compatibility with who I am, what I find important and mental limitations.”*

***“I'd be willing to accept almost any inconvenience if that leads to improvement afterwards.”***

**- Patient**

## **An ideal treatment would address**

Like a similar question asked during the EL-PFDD meeting, most respondents to question #17 wrote that an ideal treatment would address the particular BTHS symptoms most affecting them, whether it be heart trouble, infections, feeding problems, muscle weakness, or fatigue (which was mentioned by at least 11 of 17 respondents). A couple wrote about a more general treatment or cure:

- *“Something that can make him live a long, happy, healthy life.”*
- *“I would look for a treatment that would help my son to have a more normal life.”*
- *“A cure that will cure everything that would take away everything associated with the syndrome.”*

## **Preferences regarding modes of treatment administration and convenience of a new treatment**

In response to question #18, most respondents wrote that they would make similar sacrifices and be willing to try most modes of treatment administration in exchange for something that could improve the symptoms of BTHS. *“I'd travel and pretty much do any kind of procedure if I thought it would work,”* wrote one. Another wrote that they would even *“travel overseas”* for an effective treatment.

*“I'd be willing to accept almost any inconvenience if that leads to improvement afterwards,”* one individual with BTHS wrote.



One caregiver wrote about the perspective voiced by her son who has passed away: *“In his life he was often the first to try an idea out before it was even put into a protocol. He tried anything that might improve outcomes. He once said, ‘I participate in research because what I do today will make a difference after I am gone.’ I believe nothing would stop him from participating in research. He was painfully aware that Barth syndrome is extraordinarily rare. He knew he didn't have the luxury of denial that someone else could do it.”*

## **Incorporating patient input into a benefit–risk assessment framework for Barth syndrome**

Over the past several years, FDA has developed an enhanced structured approach to benefit-risk assessment in regulatory decision-making for human drugs and biologics. The Benefit-Risk Assessment Framework involves assessing five key decision factors: Analysis of Condition, Current Treatment Options, Benefit, Risk, and Risk Management. When completed for a particular product, the framework provides a succinct summary of each decision factor and explains FDA's rationale for its regulatory decision.

In the framework, the Analysis of Condition and Current Treatment Options rows summarize and assess the severity of the condition and therapies available to treat the condition. The assessment provides an important context for drug regulatory decision-making, including valuable information for weighing the specific benefits and risks of a particular medical product under review.

The input provided by patients and patient representatives throughout the Barth syndrome EL-PFDD meeting may inform the understanding of the Analysis of Condition and Current Treatment Options for this disease.

The information in the top two rows of the sample framework for BTHS, below, draws from what was discussed at the Barth syndrome EL-PFDD meeting held on July 18, 2018. This sample framework contains the kind of information that, it is anticipated, could be included in a framework completed for a drug under review for BTHS. This information is likely to be added to or changed over time based on a further understanding of the condition or changes in the treatment armamentarium.



# Decision factor: Analysis of Barth syndrome

## Evidence and uncertainty

Barth Syndrome (BTHS) is an extremely rare, X-linked disease caused by mutations in the TAZ gene that interrupts the production of the tafazzin protein, which is essential to the synthesis of cardiolipin. Absence of tafazzin results in a deficiency of mature cardiolipin (L4-CL) and an accumulation of monolysocardiolipin (MLCL)—ultimately leading to abnormalities in mitochondrial structure and function.

The clinical consequences of this mitochondrial damage are profound and multisystemic:

1. Cardiomyopathy is the most common complication that may begin in the womb, leading to death in two-thirds of those born with BTHS, often in infancy. This may resolve for years, however, the risk of cardiac events, including arrhythmia, remains high later in life.
2. Neutropenia (chronic, intermittent, or cyclic) leaving people with BTHS susceptible to frequent life-threatening infections and recurrent hospitalization.
3. Skeletal myopathy and exercise intolerance, that together with chronic fatigue have the most profound effects upon individuals' ability to function in society, study, find employment and, as the syndrome becomes progressive in later life, perform the routine activities of daily living.
4. Delayed growth and small stature for much of life.
5. Feeding and digestive problems necessitating tube feeding for many.
6. Metabolic abnormalities, problems with sleep, pain, learning challenges, mood disorders, and speech in some.

Although the cardinal symptoms are usually, though not always, present, there is significant variation in the symptoms that matter most from person to person—and this may vary for each person over the course of their disease.

## Conclusions/Reasons

BTHS is a very rare inherited life-threatening disease with wide-ranging complications that vary in intensity from person to person and in the individual over time.

BTHS-related cardiomyopathy has been fatal in most cases during the first year of life and remains a threat throughout life.

Individuals with BTHS who survive the first year of life endure a debilitating multisystemic disease that includes neutropenia, life-threatening infections (resulting in long hospitalizations), skeletal myopathy, and fatigue that exact a devastating toll on the ability to live independently and enjoy the routine activities of daily life.

Other complications: growth retardation, feeding and digestive problems, metabolic abnormalities, pain, and others profoundly compromise quality of life.

The disease appears to be progressive during adulthood, with worsening myopathy. Few survive beyond the fourth decade of life.



# Decision factor: Current treatment options

## Evidence and uncertainty

Management of the conditions, symptoms, and complications of BTHS requires complex multidisciplinary care that includes medical and non-drug supportive care, surgical interventions, such as heart transplants for some patients and implanted defibrillators, and may require other equipment.

These treatments only manage some of the symptoms and clinical consequences of BTHS and have many downsides, including long-term side effects from lifelong therapy, inconvenient and painful administration (G-CSF), invasive procedures, and related complications. There is no satisfactory treatment for BTHS-related skeletal myopathy, exercise intolerance, or the extreme fatigue experienced by most people with BTHS. Moreover, these treatments only stabilize disease progression rather than addressing the underlying pathology.

Participants expressed a desire for safe and effective treatments that would improve their strength and endurance and address their fatigue—and provide gains in function—even if those treatments involved an inconvenient route of administration (injections requiring hospital stays). Patients also called for treatments that lessen other symptoms.

See the *The Voice of the Patient: Barth Syndrome* report for a more detailed narrative.

## Conclusions/Reasons

There IS a significant unmet need for effective and tolerable FDA-approved therapies to treat BTHS, particularly ones that address skeletal myopathy, exercise intolerance, and chronic severe fatigue—providing gains in function and the ability to lead a more normal, full life.

There is also a need for improved treatments for the other cardinal symptoms such as heart disease and neutropenia—particularly with a more convenient route of administration—that take into account the unique etiology and cyclic nature of these conditions in individuals with BTHS.

## Conclusion

This meeting emphasized the urgent need for increased awareness, early diagnosis, and treatment for BTHS. A presentation by a leading clinical expert provided insight into the complex issues faced by clinicians and scientists in developing better treatments for this disease. Furthermore, FDA was provided with a unique opportunity to hear in great detail directly from patients, living on different continents, at this EL-PFDD meeting and to better appreciate the physical and emotional burdens related to living with BTHS.



At the conclusion of the meeting, another one of BSF's cofounders spoke as a mother who was the caregiver to two sons who died from BTHS. *"I want more moments. I want my children. I want to know who they would be—not dream about it—I want to see these kids I've seen grow up, work and have a life of their own."*

She summarized some of the critical themes that she heard repeated during the meeting:

People with BTHS want to have the energy and strength to do things. The young children with BTHS want to be able to keep up with their peers and run without falling. Those entering adulthood need the energy and strength to be a part of society and to contribute—to have the opportunity to work and not be dependent upon others. For others who are more progressed, it may be the energy and strength to be able to go to the bathroom on their own and not be a fall risk.

Skeletal myopathy—to the point of not being able to perform routine activities without one's strength giving out—was the symptom that most affected the daily lives of people living with BTHS, but participants stressed that the related exhaustion that could go on for days after minor activities was a very close second. More time was spent discussing the life-constraining fatigue than any other symptom.

However, the other symptoms also have a ruinous effect on the quality of life. Cardiomyopathy is the most common complication—but heart failure and arrhythmia have eliminated the voices of many patients with BTHS, leaving only caregivers behind to speak of their grief. Neutropenia and frequent infections also kill, and short of that, lead to repeated trips to the hospital, and for some, time in isolation unable to meet with friends or family. Many children and adults are unable to eat without nausea or feeding tubes. Some are bullied for being small and weak. The psychological consequences of this are substantial, and for many, BTHS leads to profound depression.

Though treatments are available for some of the symptoms, they have significant downsides. Individuals with BTHS called for treatments that addressed the cause of the disease, and that they hope will address their core complaints of feeling depleted and fatigued. They stated that they would want a therapy that would provide gains in function even if it caused significant inconvenience to them—as long as it would allow them to enjoy the activities of a normal life. The only risks that would not be acceptable in exchange for such benefit would be severe, life-threatening side effects.

The community is eager to participate in trials that would identify even one such treatment.

The Barth Syndrome Foundation is grateful to the patients and their representatives and to the physicians and scientific experts who participated, and to the FDA for its support and participation and for bringing this initiative to life. It is hoped that this information will be used to guide approvals of much needed therapies for Barth syndrome.



Appendix 1: Meeting program, includes agenda and discussion questions  
(on the following pages)



Barth Syndrome  
Foundation



**POWER  
UP!**

**Clearwater Beach, FL ~ July 2018**

**Externally-Led Patient-Focused Drug Development  
Meeting for Barth Syndrome (BTHS)**

---

PUBLIC MEETING / JULY 18, 2018



# MEETING AGENDA

11:00am—12:00pm **Lunch** will be provided in Grand Ballroom Foyer

12:00pm—12:30pm **Registration**

## Opening Remarks and Overviews

12:30pm—12:35pm **Welcome**  
*Emily Milligan, MPH; Executive Director, Barth Syndrome Foundation*

12:35pm—12:45pm **Opening Remarks**  
*Celia M. Witten, PhD, MD; Deputy Director, FDA Center for Biologics Evaluation and Research (CBER)*

12:45pm—1:00pm **Clinical Overview of Barth Syndrome (BTHS)**  
*Colin Steward, PhD, FRCP, FRCPC; Professor of Pediatric Stem Cell Transplantation and Consultant in Bone Marrow Transplantation, Bristol Royal Hospital for Children; Medical Advisor to NHS Barth Syndrome Clinic*

1:00pm—1:15pm **Introduction to Barth Syndrome Foundation and One Family's Experience with BTHS**  
*Kate McCurdy; Founding BSF Board Member and Ex-officio Member, Emerita, BSF Scientific and Medical Advisory Board (SMAB)*

1:15pm—1:25pm **Introduction and Overview of Meeting**  
*James Valentine, JD, MHS; Meeting Moderator*

1:25pm—1:35pm **Audience and Remote Demographic Polling**

## Session 1: BTHS Patient Voice: Symptoms and Daily Impacts

1:35pm—2:50pm **Panel 1: Symptoms and Daily Impacts**

- Presentations by five affected individuals and caregivers (30 minutes)
- Audience & remote polling (10 minutes)
- Moderated audience discussion (35 minutes)

2:50pm—3:05pm **Break**

3:05pm—3:15pm **FDA Comments**  
*Scott K. Winiecki, MD; Director, Safe Use Initiative, FDA Center for Drug Evaluation and Research (CDER)*

3:15pm—3:25pm **Video of BTHS Individual Unable to Travel**

## Session 2: BTHS Patient Voice: Current and Future Approaches to Treatments

3:25pm—4:40pm **Panel 2: Current and Future Approaches to Treatments**

- Presentations by five affected individuals and caregivers (30 minutes)
- Audience & remote polling (10 minutes)
- Moderated audience discussion (35 minutes)

## Summary and Closing Remarks

4:40pm—4:50pm **Closing Comments – What I Heard Today**  
*Shelley Bowen; Director of Family Services & Awareness, BSF*

4:50pm-5:00pm **Closing Remarks**  
*Elizabeth Hart, MD; Medical Officer, Division of Gastroenterology and Inborn Error Products, Office of New Drugs (CDER) (10 minutes)*





# WELCOME LETTER

---

## Dear PFDD Participants,

Welcome to the externally-led Patient-Focused Drug Development Meeting for Barth syndrome!

Barth Syndrome Foundation (BSF) is thrilled to have you participate in today's meeting. BSF leads the global research and advocacy effort to create a world without Barth syndrome while we provide ongoing education and community for affected individuals and their families. If you are an affected individual or family member, whether you are joining us in person or participating through our live webcast, we are grateful for your participation and for taking the time to come together as a community to voice your experiences and perspectives.

We are also excited to have influential leaders from the U.S. Food and Drug Administration (FDA), industry professionals, and researchers from academia also with us, both in person and on-line. Our organization's goal is to deliver effective therapies into the hands of affected individuals and their caregivers, to eliminate the suffering and loss of life from Barth syndrome. Your participation is important for us to foster strong ties and collaborate across the research and development continuum to achieve our mission. The fact you are involved in this PFDD meeting highlights the attention Barth syndrome requires.

And to our panelists, we especially want to thank you for exercising your voices. Today's meeting simply would not be possible without your contributions. We recognize it takes courage to share your personal stories about the impact of Barth syndrome on your lives. Your sacrifice is a statement of hope and inspiration.

We also wish to thank the speakers from the FDA: Dr. Celia M. Witten, PhD, MD, Deputy Director, FDA Center for Biologics Evaluation and Research (CBER); Dr. Scott Winiecki, MD, Director, Safe Use Initiative, FDA Center for Drug Evaluation and Research (CDER); and Dr. Elizabeth Hart, MD, Medical Officer, Division of Gastroenterology and Inborn Error Products, Office of New Drugs (CDER). In addition, we are grateful to Dr. Colin Steward, PhD, FRCP, FRCPC, Professor of Pediatric Stem Cell Transplantation and Consultant in Bone Marrow Transplantation, Bristol Royal Hospital for Children and Medical Advisor to NHS Barth Syndrome Clinic for delivering important remarks about the clinical impact of Barth syndrome. Your continued partnership is vital to paving pathways for scientific breakthroughs and novel therapies. On behalf of the community we represent, BSF thanks you for your support today and in the future as we advance therapies.

Today's meeting is about many things, but most of all it is about our shared optimism. Together we forge new collaborations. Together we chart new pathways for novel therapies. Together we not only dream about but mobilize around a world without Barth syndrome.

Sincerely,



Emily Milligan  
Executive Director



Susan McCormack  
Chair, BSF Board of Directors



Michael Schlame, MD  
Chair, BSF Scientific and Medical  
Advisory Board



# ABOUT THIS EXTERNALLY-LED PATIENT-FOCUSED DRUG DEVELOPMENT MEETING

Barth Syndrome Foundation (BSF), a patient advocacy organization representing those who suffer from and care for individuals with Barth syndrome (BTHS), is holding the EL-PFDD meeting on BTHS between our community and the U.S. Food and Drug Administration. The EL-PFDD meeting for BTHS will advance BSF's mission: *Saving lives through education, advances in treatment, and finding a cure for Barth syndrome.*

Namely, the EL-PFDD meeting will enable us to share with key FDA officials and other stakeholders the burdens of BTHS across the lifespan, current unmet needs, prognosis and current standards of care. Discussion themes will include ways in which BTHS-affected individuals attempt to mitigate symptoms of the condition through cardiac medications (e.g., beta blockers, ACE inhibitors, anti-arrhythmics, anticoagulants), implantable defibrillators and heart transplantation for cardiac related issues, bone marrow stimulants (figrastim) for neutropenia, strollers and wheelchairs for reduction of fatigue and lifestyle modifications. Given the lack of a current therapy for BTHS, it is important for stakeholders to understand how patients are impacted by the condition, their

current treatment options (or lack thereof), and hear their input for future trial design and therapeutic review.

The EL-PFDD meeting is a key component of realizing these objectives, by capturing patient and caregiver insights that can set the context for FDA benefit-risk considerations. It will enable a comprehensive understanding of this rare condition for key reviewers in the FDA CDER Division of Neurology Products and Division of Gastroenterology and Inborn Errors Products, CBER Office of Tissues and Advanced Therapies, CDER Rare Diseases Program, Office of Pediatric Therapeutics, and Office of Orphan Products Development.

The EL-PFDD meeting will include panelists that represent a spectrum of perspectives in terms of age, geographic region, and severity of symptoms. We understand some BTHS individuals may be too ill to travel to this meeting and we feel it is essential to hear their perspectives as well. Therefore, BSF is producing and will present video testimonials in order to overcome this challenge.

## The goals of this meeting are to:

- Collect data and discern key insights for clinical trial design from affected BTHS individuals and their caregivers so that the outcomes of potential therapeutics can be measured in ways that are both clinically sound and therapeutically impactful.
- Develop and provide the FDA with a robust understanding of patients' and caregivers' experiences with Barth syndrome. This would include BTHS individuals' views on their quality of life, aspects of the disease that are most problematic for them, and actions they currently perform to cope with this disease.



## Instructions for Polling Questions

Each session in today's meeting will include a series of polling questions on Barth syndrome (BTHS) and its impact on your family's life. In-person attendees are encouraged to use their mobile phones or computer to participate in these polling questions. **Note: Please do not cast a response through the poll platform if you are not an adult who has been diagnosed with BTHS or the parent designee representing a minor or deceased individual. No more than one vote should be cast for each individual who has BTHS.**

If texting, download the Poll Everywhere App (on Google Play or Apple App Store) to your smart phone prior to the meeting and create your account. When the event is taking place you will need to enter powerup1.

If using your ipad, tablet or computer, visit [PollEv.com/powerup1](http://PollEv.com/powerup1) prior to the meeting and create your account.

**Standard message and data rates apply.**





## **Kevin B.**

Kevin is a 29-year-old affected individual who lives in Pennsylvania. He received his Barth syndrome diagnosis at the age of seven. He has worked part-time as the Grants & Scholarships Administrator at the Chester County Community Foundation since 2016. His hobbies include reading, gaming, and rooting for Philadelphia sports teams.



## **Darryl B.**

Darryl is 36 and lives in Philadelphia, PA. He was diagnosed with Barth syndrome at the age of 20. He graduated from South Philadelphia High and currently assists in the ministry at his church, St. Paul Chapel Baptist Church. Darryl served as the primary caregiver for his brother, Jamal, who passed away from Barth syndrome in 2009 at the age of 25.



## **Jasmine C.**

Jasmine lives in British Columbia, Canada, with her husband, Mark, and sons, Jordan (4, unaffected) and Caleb (21 months, BTHS). Caleb was diagnosed with Barth syndrome at three weeks of age. Jasmine works as a first grade teacher. She enjoys attending music festivals, all sports and spending time with her friends and family.



## **Nicholas D.**

Nicholas is 19 years old and lives in Hampshire, U.K., with his parents, Mic and Marco, and his younger brother, Matthew (16, unaffected). Nicholas was diagnosed with Barth syndrome in April 2001. He enjoys playing video games, building models, and spending time with friends. He is also a film buff.



## **Nicole D.**

Nicole has been active with the Barth Syndrome Foundation since attending the BSF conference in 2008. Nicole is the mother of two boys born with Barth syndrome: Nathaniel, who passed away at just two weeks of age in 2002, and Devin, age 13, who underwent heart transplantation as an infant. Nicole has dedicated much of her time with BSF offering her unique perspective of raising a Barth boy after heart transplant surgery. Professionally, Nicole has worked on numerous political campaigns, ranging from local millage renewal to US Congressional campaign. She currently works as a legislative aide in the Michigan House of Representatives. She, her wife, Sarah, and Devin live just outside of Flint, Michigan.

Nicole has served on the BSF Board of Directors since 2016.

# PANELIST BIOS



## Peter VL.

Peter is 31 years old and lives in the Netherlands. He was diagnosed with Barth syndrome at the age of two. Peter enjoys programming a website and additional features for a Minecraft community he manages as well as watching various TV series on Netflix.



## Amanda M.

Amanda is 33 years old and lives in the Pittsburgh, Pennsylvania area. Her and her husband, Tim, have two children — Sydney (age 11) and Wyatt (age 10, BTHS). She has been a part of the foundation since 2007, and they attended their first conference in 2008.



## John W.

Being affected by Barth syndrome gives John a unique insight into the issues facing the Barth Syndrome Foundation. John recently earned an A.S. in Computer Information Technology from Southeast Community College in Lincoln, Nebraska, and works part time as a computer consultant. John lives in Lincoln, Nebraska.

John has served on the BSF Board of Directors since 2012 and was elected Corporate Secretary in 2018.



## Jacob W.

Jacob is 17 years old and recently graduated from Richland High School in Richland, MS. He and his parents searched for years for a diagnosis before Jacob was found to be affected by Barth syndrome at age 10. Jacob lives with his mother, Amy, his father, Marvin, and his brother, Damon (unaffected). His interests include hunting, fishing and spending time with friends.



## Kevin W.

Kevin is the father of an affected boy named Connor. Connor was diagnosed with Barth syndrome (BTHS) when he was 18 months old. Kevin lives in Phoenix, Maryland, with his wife, Stacey, and his two sons, Connor (age 8, BTHS) and Ryan (age 5, unaffected). Kevin works as a Technology Director for T. Rowe Price. He enjoys spending time with his family, jogging, and playing and listening to music in his spare time.

Kevin has served on the BSF Board of Directors since 2014 and was elected Treasurer in 2017.





**Shelley Bowen** ~ Director, Family Services & Awareness, BSF

Mrs. Bowen is a founder of the Barth Syndrome Foundation (BSF) and currently serves as Director of Family Services and Awareness. Both of her sons lost their lives to Barth syndrome. She believes it possible for everyone who has Barth syndrome to have an accurate diagnosis and every parent has the capacity to be transformed from a powerless bystander into an empowered advocate when given the proper tools. Mrs. Bowen has worked tirelessly to ensure that not one more child will suffer or perish from the disorder.



**Elizabeth Hart, MD** ~ Medical Officer, Division of Gastroenterology and Inborn Error Products, FDA Center for Drug Evaluation and Research, Office of New Drugs (CDER)

Dr. Hart evaluates the efficacy and safety of new drugs and biologics intended for inborn errors of metabolism and advises companies and researchers on clinical drug development for these rare diseases. Prior to joining the FDA, Dr. Hart treated children and adolescents with a variety of serious conditions and held academic appointments at George Washington University and Harvard University. She also conducted translational and clinical research at the National Institutes of Health.

Dr. Hart received her Medical Degree from the University of Pennsylvania, and completed a pediatric residency at Rainbow Babies and Children's Hospital and a fellowship in pediatric endocrinology at Boston Children's Hospital.



**Kate McCurdy** ~ Member *Emerita*, Scientific & Medical Advisory Board, BSF

Mrs. McCurdy was a founding member of The Barth Syndrome Foundation's (BSF) Board of Directors and was responsible for establishing the Science and Medicine Program of BSF. She currently serves as an *Emerita* member of the Scientific & Medical Advisory Board. Mrs. McCurdy has a BA from Duke University and an MBA from the Harvard Business School. She has worked in both economics and the corporate world and has held positions on the boards of various other non-profit organizations.

Her son, Will, was affected by Barth syndrome and passed away in 2014 at the age of 28, but she, her husband, Steve, and their daughter, Eliza, continue to be strongly committed to the mission of BSF.



**Emily Milligan, MPH** ~ Executive Director, BSF

Ms. Milligan has spent her career dedicated to improving the lives of children and their families through scientific advancements and social equality. In May 2018, Ms. Milligan joined Barth Syndrome Foundation (BSF) as the Executive Director. Trained in public health and international relations, Ms. Milligan brings years of experience managing research portfolios and transforming business processes. Previously, she worked for the United Nations in Brazil and Nicaragua, and was a vital contributor at Columbia University and New York University. She went on to join JDRF (formerly known as the Juvenile Diabetes Research Foundation) where she headed the research operations and scientific teams and oversaw an average annual \$100 million research portfolio. Most recently prior to joining BSF, Ms. Milligan launched an \$80 million, mission-driven venture fund that invests in companies developing life-saving products for individuals living with type one diabetes. She is an active member of her community in Needham, Massachusetts, and volunteers her time for other organizations focused on social change and alleviating human suffering.

# SPEAKER BIOS



**Colin Steward, PhD, FRCP, FRCPCH** ~ Professor of Pediatric Stem Cell Transplantation and Consultant in Bone Marrow Transplantation, Bristol Royal Hospital for Children; Medical Advisor to NHS Barth Syndrome Clinic, Bristol, United Kingdom; Scientific and Medical Advisory Board, BSF

Prof. Steward recently retired from his post as Clinical Lead for the multidisciplinary NHS National Barth Syndrome Service which was established in 2010 and is run in partnership with Michaela Damin and her colleagues at the Barth Syndrome Trust. This will allow him to concentrate on research at the University of Bristol whilst having more time for hobbies such as travel, walking, watching wildlife and gardening. His current Barth syndrome research focuses on the CARDIOMAN Trial looking at use of the drug bezafibrate in Barth syndrome together with his colleagues at Bristol Royal Hospital for Children and mechanisms of neutropenia in conjunction with Dr Borko Amulic.



**James Valentine, JD, MHS** ~ Associate, Hyman, Phelps & McNamara (Moderator)

Mr. Valentine assists medical product industry and patient advocacy organization clients in a wide range of regulatory matters, including new drug and biologic development and approval issues. Before joining his current firm in 2014, Mr. Valentine worked in FDA's Office of Health and Constituent Affairs where he facilitated patient input in benefit-risk decision-making and served as a liaison to stakeholders on a wide range of regulatory policy issues. There, Mr. Valentine administered the FDA Patient Representative Program, launched the Patient-Focused Drug Development program, and developed the FDA Patient Network. Mr. Valentine also worked at the Center for Drug Evaluation and Research's (CDER) Office of Regulatory Policy where he coordinated implementation of new statutory authorities.

Mr. Valentine earned his law degree from the University of Maryland and his master of health science from the Johns Hopkins School of Public Health.



**Scott K. Winiecki, MD** ~ Director, Safe Use Initiative, FDA Center for Drug Evaluation and Research (CDER)

After 12 years in private pediatric practice, Dr. Winiecki joined the U.S. Food and Drug Administration in 2011. In 2012, he received the FDA's "Outstanding New Reviewer" Award. After five and a half years working on biologics, he joined the Center for Drugs in September, 2016. He is currently Director of the Safe Use Initiative, a group whose goal is to reduce preventable harm from medications by collaborating with both public and private groups within the healthcare community.

Dr. Winiecki received his MD degree from the University of Maryland and completed his pediatric training at the Children's Hospital of Philadelphia.



**Celia M. Witten, PhD, MD** ~ Deputy Director, FDA Center for Biologics Evaluation and Research, FDA Drug Administration (CBER)

Between 2005 and 2016, Dr. Witten served as the Director of the Office of Cellular, Tissue and Gene Therapy at the FDA/CBER. Between 1996 and 2005, she served as Director of the Division of General, Restorative, and Neurological Devices in the Office of Device Evaluation in the Center for Devices and Radiological Health (CDRH). Previous to FDA, Dr. Witten worked for over 10 years as a practicing physician at the National Rehabilitation Hospital (NRH) in Washington, D.C.

Her educational background includes a BA earned at Princeton University (Magna Cum Laude), a PhD from Stanford University, and an MD from the University of Miami School of Medicine. In addition to her academic achievements she is Board Certified in Physical Medicine and Rehabilitation.



# BTHS PATIENT FOCUSED DRUG DEVELOPMENT — TOPIC QUESTIONS

---

## Topic 1 Questions: Symptoms and Daily Impacts

1. Of all the symptoms that you experience because of your condition, which 1-3 symptoms have the most significant impact on your life? (Examples may include: heart problems, feeding issues, fatigue, pain, infection)
2. Are there specific activities that are important to you but that you cannot do at all or as fully as you would like because of your condition? (Examples of activities may include: go to school, participate in sports, hold a job, keep up with friends)
  - a. How do your symptoms and their negative impacts affect your daily life on the best days? On the worst days?
3. How have your condition and its symptoms changed over time?
  - a. Do your symptoms come and go? If so, do you know of anything that makes your symptoms better? Worse?
4. What worries you most about your condition?

## Topic 2 Questions: Current and Future Approaches to Treatments

1. What are you currently doing to help treat Barth syndrome or its symptoms? (Examples may include prescription medicines, over-the-counter products, other therapies including nondrug therapies such as exercise, etc.)
  - a. What specific symptoms do your treatments address?
  - b. How has your treatment regimen changed over time, and why?
2. How well does your current treatment regimen treat the most significant symptoms of your disease?
  - a. How well do these treatments improve your ability to do specific activities that are important to you in your daily life?
  - b. How well have these treatments worked for you as your condition has changed over time?
3. What are the most significant downsides to your current treatments, and how do they affect your daily life? (Examples may include bothersome side effects, going to the hospital for treatment, restrictions on driving, etc.)
4. What specific things would you look for in an ideal treatment for Barth syndrome?



# THANKS TO OUR SPONSORS

---



Friends & Family of John Wilkins









Barth Syndrome  
Foundation



**POWER  
UP!**

**Clearwater Beach, FL ~ July 2018**

**Barth Syndrome Foundation**

2005 Palmer Avenue #1033

Larchmont, NY 10538

Phone: 914-303-6323

Email: [bsfinfo@barthsyndrome.org](mailto:bsfinfo@barthsyndrome.org)

Website: [www.barthsyndrome.org](http://www.barthsyndrome.org)



## Appendix 2: Meeting participants

<b>Patients - Total</b>		<b>22</b>
	<b>On Site</b>	<b>14</b>
	<b>Remote</b>	<b>8</b>
<b>Caregivers - Total</b>		<b>182</b>
	<b>On Site</b>	<b>123</b>
	<b>Remote</b>	<b>59</b>
<b>Industry Professionals</b>		<b>28</b>
<b>Researchers</b>		<b>40</b>
<b>Non-Profit Org</b>		<b>23</b>
<b>Other</b>		<b>41</b>
<b>Government</b>		<b>7</b>
<b>Health Care Professionals</b>		<b>19</b>
<b>On Site Total</b>		<b>203</b>
<b>Remote Total</b>		<b>107</b>
<b>1st PFDD Meeting Attended?</b>		<b>287</b>



## Appendix 3: Polling questions and results

### DEMOGRAPHIC INFORMATION

<b>1) Where do you currently live?</b>	<b># of Responses</b>	<b>% of Responses</b>
Australia	4	3%
North America	105	76%
European Union	28	20%
South America	1	1%
Total	138	

<b>2) You are responding for...</b>	<b># of Responses</b>	<b>% of Responses</b>
Yourself (affected with BTHS)	19	20%
Someone living with BTHS	61	65%
Someone deceased who had BTHS	14	15%
Total	94	

<b>3) Age of you/person for whom you are responding (age at death if person is deceased)</b>	<b># of Responses</b>	<b>% of Responses</b>
0-1 year	12	13%
2-5 years	16	17%
6-11 years	24	25%
12-15 years	10	10%
16-19 years	10	10%
20-29 years	17	18%
30-39 years	5	5%
40-49 years	0	0%
50-59 years	2	2%
Total	96	

<b>4) Age of you/person for whom you are responding was diagnosed with BTHS</b>	<b># of Responses</b>	<b>% of Responses</b>
In utero	2	3%
0-1 year	40	51%
2-5 years	19	24%
6-11 years	9	12%
12-15 years	2	3%
16-19 years	0	0%
20-29 years	1	1%
30-39 years	0	0%
40-49 years	1	1%
50-59 years	0	0%
Unsure	4	5%
Total	78	



<b>5) You are a...</b>	<b># of Responses</b>	<b>% of Responses</b>
Person living with BTHS	17	8%
Carrier	42	19%
Parent of an individual living with BTHS	86	40%
Parent of a deceased individual who had BTHS	21	10%
Sibling of an individual living with BTHS	8	4%
Sibling of a deceased individual who had BTHS	12	6%
Grandparent of an individual living with BTHS	10	5%
Grandparent of a deceased individual who had BTHS	3	1%
Spouse/SO of an individual living with BTHS	1	0%
Spouse/SO of a deceased individual who had BTHS	0	0%
Offspring of an individual living with BTHS	1	0%
Offspring of a deceased individual who had BTHS	0	0%
Other relative of an individual living with BTHS	10	5%
Other relative of a deceased individual who had BTHS	5	2%
Total	216	

<b>6) Are you aware of any family history of BTHS for yourself or the person with BTHS for whom you are responding?</b>	<b># of Responses</b>	<b>% of Responses</b>
Yes	34	35%
No	52	54%
Unsure	11	11%
Total	97	

<b>7) Who provides daily caregiving for yourself or the person with BTHS for whom you are responding?</b>	<b># of Responses</b>	<b>% of Responses</b>
Myself	24	25%
Parent	68	72%
Grandparent	2	2%
Other	1	1%
Total	95	



## Topic 1 – EFFECTS OF BARTH SYNDROME

<b>1) Which of the following symptoms has the most significant impact on you (the person for whom you are responding)?</b>	<b># of responses (from 91 respondents to this question)</b>	<b>% of respondents who chose this as one of their responses</b>
Heart failure	34	37%
Arrhythmia	12	13%
Neutropenia, infections	49	54%
Fatigue	76	84%
Muscle weakness/exercise intolerance	78	86
Eating problems/digestive problems/nutritional issues/nausea	53	58%
Pain (headaches, stomach aches, etc.)	28	31%
Sleeping difficulties	14	15%
Speech problems	10	11%
Mood disorder/depression/anxiety	14	15%
Learning disability/attention problems/other cognitive issues	22	24%
Short stature	26	29%
Healing	10	11%
Other	4	4%
TOTAL	430	

<b>2) In the past year, how often have you (the person for whom you are responding) had to go to the hospital for emergency care or inpatient treatment due to BTBS?</b>	<b># of responses</b>	<b>% of responses</b>
No times	8	14%
1 – 2 times	31	55%
3 – 5 times	10	18%
6 – 9 times	1	2%
10+ times	4	7%
I'm not sure	2	1%
TOTAL	56	

<b>3) How many times per month do you (person for whom you are responding) usually visit a health care professional of any kind?</b>	<b># of Responses</b>	<b>% of Responses</b>
No times	17	22%
1 – 3 times	40	53%
4 – 6 times	7	9%
7 – 8 times	4	5%
9 – 10 times	0	0%
11 – 12 times	0	0%



13+ times	8	11%
I'm not sure	0	0%
TOTAL	76	

<b>4) In the past year, how much time have you (person for whom you are responding) had to miss school/work due to BTHS?</b>	<b># of responses</b>	<b>% of responses (% of age where applicable)</b>
No days	5	6% (8%)
Less than 1 week	12	15% (20%)
1 – 2 weeks	16	21% (26%)
3 – 4 weeks	9	12% (15%)
1 – 2 months	3	4% (5%)
2 – 3 months	3	4% (5%)
3+ months	5	6% (8%)
Not able to attend school/have a job due to BTHS	7	9% (11%)
Not applicable (too young, too old, etc.)	17	22%
I'm not sure	1	1% (2%)
TOTAL	78	

<b>5) Which of the following have you (person for whom you are responding) experienced as a result of coping with BTHS?</b>	<b># of responses (from 94 respondents to this question)</b>	<b>% of respondents who chose this as one of their responses</b>
Need for BTHS individual to repeat year of school or take more time than usual to finish a school program	34	36%
Need for BTHS individual to reduce school or job responsibilities	47	50%
BTHS individual losing job or needing to quit school or job	42	45%
BTHS individual not able to go to school or work due to BTHS	24	25%
Homeschooling due to BTHS	15	16%
Family moves location due to BTHS or does not move location when otherwise would have	11	12%
Need for caregiver to reduce school or job responsibilities due to BTHS	50	53%
Caregiver losing job, taking different job or quitting school or job due to BTHS	22	23%
None of these	15	16%
I'm not sure	3	3%
TOTAL	263	



## TOPIC 2 – POTENTIAL TREATMENTS FOR BARTH SYNDROME

<b>1) Indicate medicines, equipment, or lifestyle changes that you (person for whom you are responding) currently use to manage BTHS symptoms (cardiac/neutropenia)</b>	<b># of responses (from 75 respondents to this question)</b>	<b>% of respondents who chose this as one of their responses</b>
Medication for heart problems	60	80%
Defibrillator (IDC)	10	13%
Heart transplant	13	17 %
Medication (neutropenia, infections, etc.)	52	69%
TOTAL	135	

<b>2) Indicate medicines, equipment, or lifestyle changes that you (person for whom you are responding) currently use to manage BTHS symptoms (myopathy)</b>	<b># of responses (from 60 respondents to this question)</b>	<b>% of respondents who chose this as one of their responses</b>
PT and/or OT	46	76%
Ankle, leg or other braces	16	27%
Cane, walking stick, stroller, motorized scooter, wheelchair	32	53 %
Other surgical procedure	7	12%
TOTAL	101	

<b>3) Indicate medicines, equipment, or lifestyle changes that you (person for whom you are responding) currently use to manage BTHS symptoms (feeding and nutrition)</b>	<b># of responses (from 71 respondents to this question)</b>	<b>% of respondents who chose this as one of their responses</b>
Medicine for stomach/intestinal symptoms	27	38%
Feeding tube of any kind	15	21 %
Nutritional and/or amino acid supplements	58	82%
Pureeing, softening, or thickening food	14	20%
TOTAL	114	

<b>4) Indicate medicines, equipment or lifestyle changes that you (person for whom you are responding) currently use to manage BTHS symptoms (pain, fatigue, mental health)</b>	<b># of responses (from 39 respondents to this question)</b>	<b>% of respondents who chose this as one of their responses</b>
Medicine for pain management	23	59%
Medicine to enhance attention or prevent daytime sleepiness	5	13%
Medicine for anxiety or depression	9	23%
Talk therapy	23	59%





TOTAL	60	
-------	----	--

<b>5) In general, how much do these medicines, equipment, or lifestyle changes improve the quality of life for you/person with BTHS?</b>	<b># of responses</b>	<b>% of responses</b>
Really help	19	22%
Help somewhat	51	59%
Not much help	5	6%
Unsure	12	14%
TOTAL	87	

<b>6) Have you/the person for whom you are responding ever been officially listed for a heart transplant?</b>	<b># of responses</b>	<b>% of responses</b>
Yes, and received a transplant	14	15%
Yes, but was removed from the list because cardiac condition improved	12	13%
Yes, but person for whom you are responding died while waiting for a heart	1	1%
No	63	69%
I'm not sure	1	1%
TOTAL	91	

<b>7) What would be the most positive impact(s) from a new Barth syndrome treatment?</b>	<b># of responses (from 87 respondents to this question)</b>	<b>% of respondents who chose this as one of their responses</b>
Improve cardiac function/reduce arrhythmias	49	56%
Reduce neutropenia and risk of infection	46	53%
Reduce fatigue	61	70%
Improve muscle strength	56	64%
Improve eating/GI and stomach issues	22	25%
Lessen pain (headache, stomach ache, etc.)	19	22%
Improve anxiety and/or depression	9	10%
Improve thinking/concentration	9	10%
Improve sleep	5	6%
Lengthen life expectancy	42	48%
Other	2	2%
TOTAL	320	



<b>8) Which of the following would you (person for whom you are responding) consider doing to get treatment?</b>	<b># of responses (from 87 respondents to this question)</b>	<b>% of responses</b>
Take a daily oral medication	83	95%
Take a daily medication by subcutaneous injection	60	69%
Take a medication by infusion in a doctor's office once/week	53	61%
Take a medication by infusion in a doctor's office once/month	67	77%
Have a device surgically implanted	31	36%
Take a treatment requiring blood draws at regular intervals	65	75%
Take a treatment requiring doctor's appointments at regular intervals	70	80%
Undergo tests requiring a blood draw before beginning a treatment	68	78%
Undergo tests requiring anesthesia before beginning a treatment	45	52%
Undergo tests requiring hospitalization before beginning a treatment	51	59%
Take a medication requiring a several-day trip out of town 4 times/year	54	62%
Take a medication requiring a several-day trip out of town once/year	57	65%
TOTAL	704	

<b>9) Which of the following factors would influence the decision for you (the person for whom you are responding) to NOT use or to stop a given treatment?</b>	<b># of responses (from 84 respondents to this question)</b>	<b>% of responses</b>
Risks of serious side effects (cardiac arrhythmias, infection of implant, etc.)	83	99%
Common, less serious side effects (nausea, headache, rashes, etc.)	21	25%
Method of delivery of treatment	10	12%
How much time the treatment will take away from daily activities (job, school, etc.)	22	26%
Medical burden or administration (need for hospitalization, radiation exposure, etc.)	51	61%
Cost	29	35%
Other	5	6%
TOTAL	221	



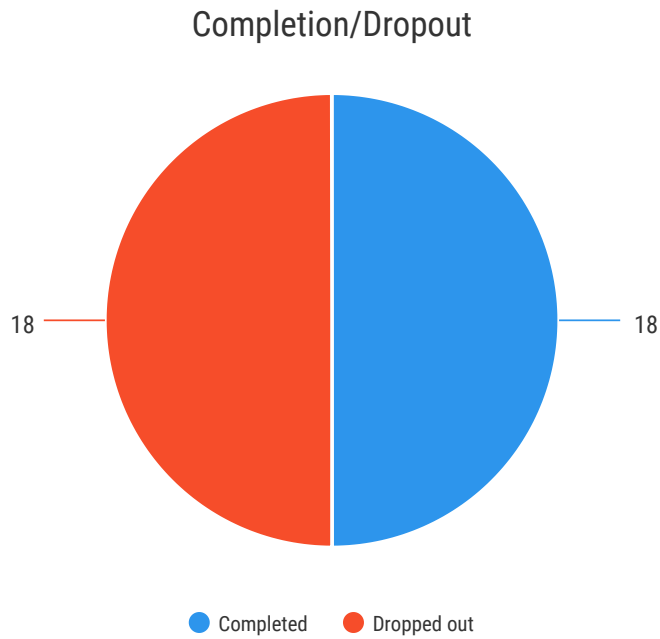
<b>10) Which of the following factors would you rank as most important to the decision about whether you (person for whom you are responding) participate in a clinical trial to study an experimental treatment?</b>	<b># of responses (from 110 respondents to this question)</b>	<b>% of responses</b>
Reputation of study site and doctor	64	58%
Common side effects (nausea, headache, etc.)	30	27%
Risk of rare but more serious side effects (cardiac arrhythmias, infection of device implant, etc.)	92	84%
How the treatment might help	70	64%
How the trial might affect current medications taken	45	41%
Distance of travel to study site	19	17 %
Frequency of visits required	14	13%
Length of visits required	11	10%
Availability of safety data ahead of time	44	40%
Availability of animal model data ahead of time	8	7%
Other	3	3%
TOTAL	400	

<b>11) Which of the following would be MOST IMPORTANT for a Barth syndrome treatment to accomplish?</b>	<b># of responses (from 121 respondents to this question)</b>	<b>% of responses</b>
Gains in function	82	68%
Lessen serious BTHS symptoms	23	19%
Stop or slow progression	7	6%
Extend life expectancy	9	7 %
TOTAL	121	



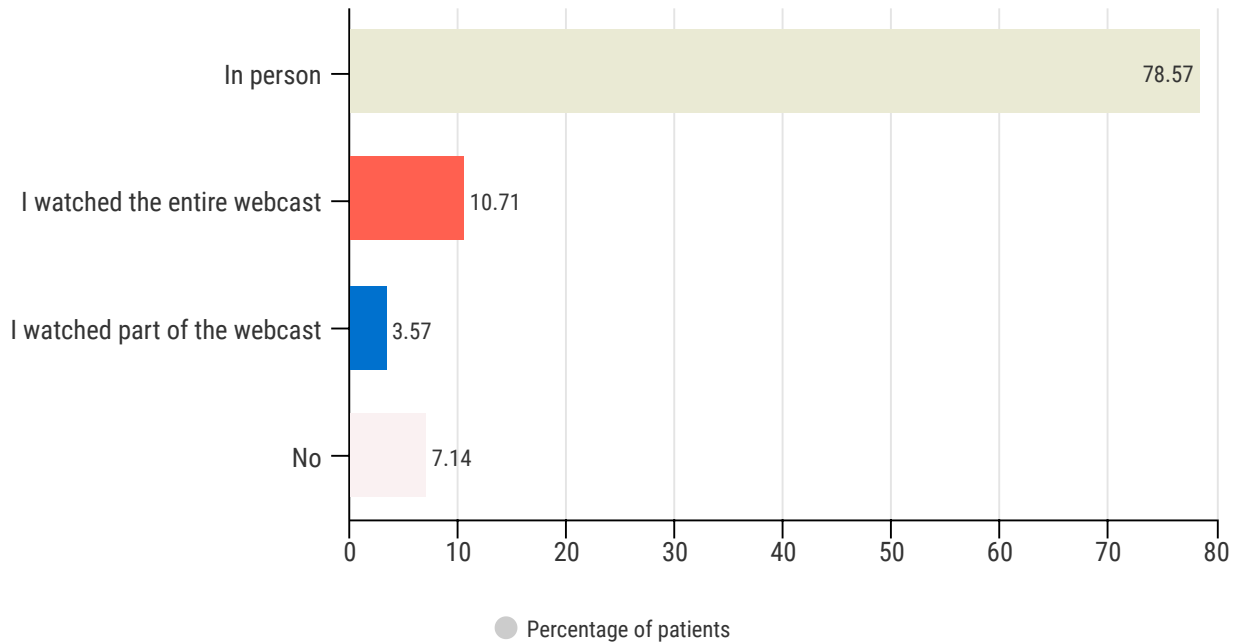
# Appendix 4: Barth syndrome EL-PFDD follow-up questionnaire

## Survey Overview



Questionnaire stats
Viewed: 77
Started: 36
Completed: 18
Completion rate: 50%
Dropouts (after starting): 18
Average time to complete survey: 30 minutes

### Did you participate in the PFDD Meeting? (SELECT ONE)

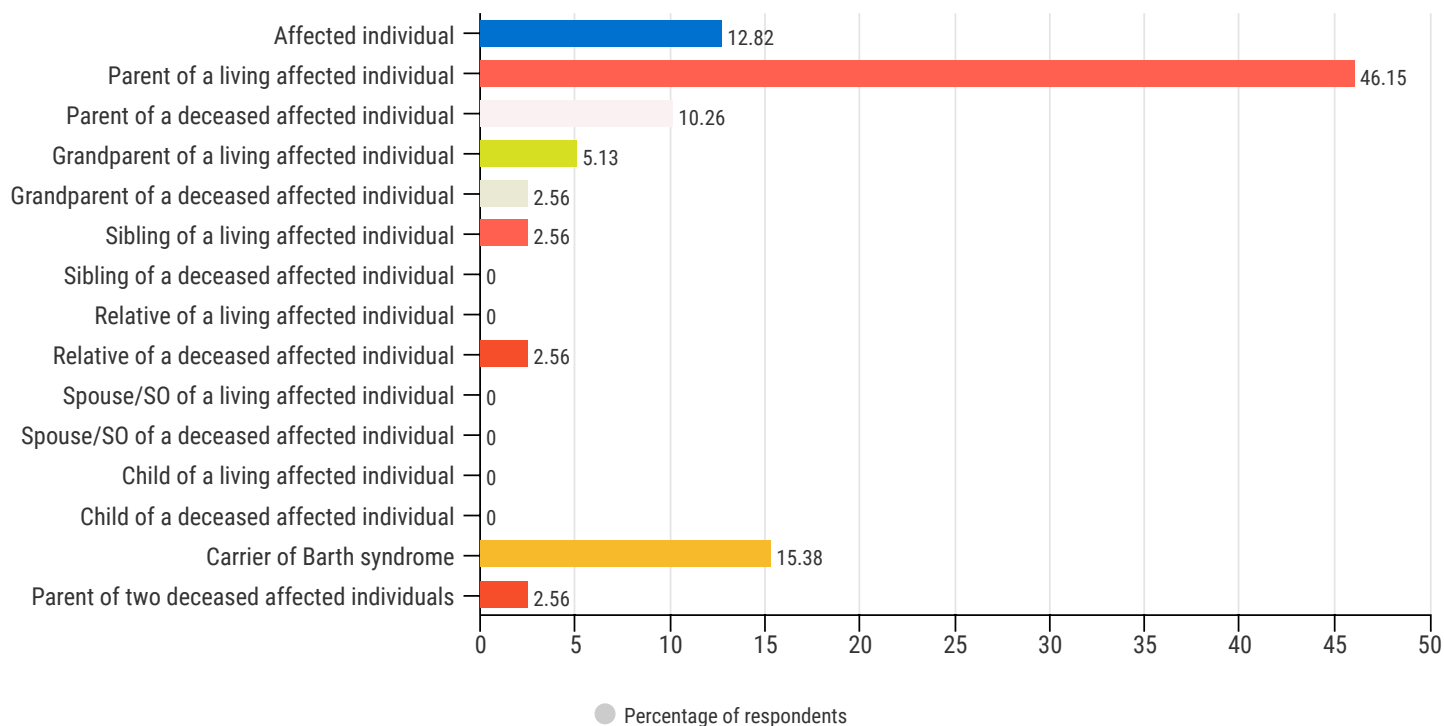


In person: 22 people. Watched the entire webcast: 3 people. Watched part of webcast: 1 person. No: 2 people.  
TOTAL: 28 people.

Mean	Confidence Interval @ 95%	Standard Deviation	Standard Error
1.393	[1.069 - 1.717]	0.875	0.165



## What is your relationship to Barth syndrome? (SELECT ALL THAT APPLY)

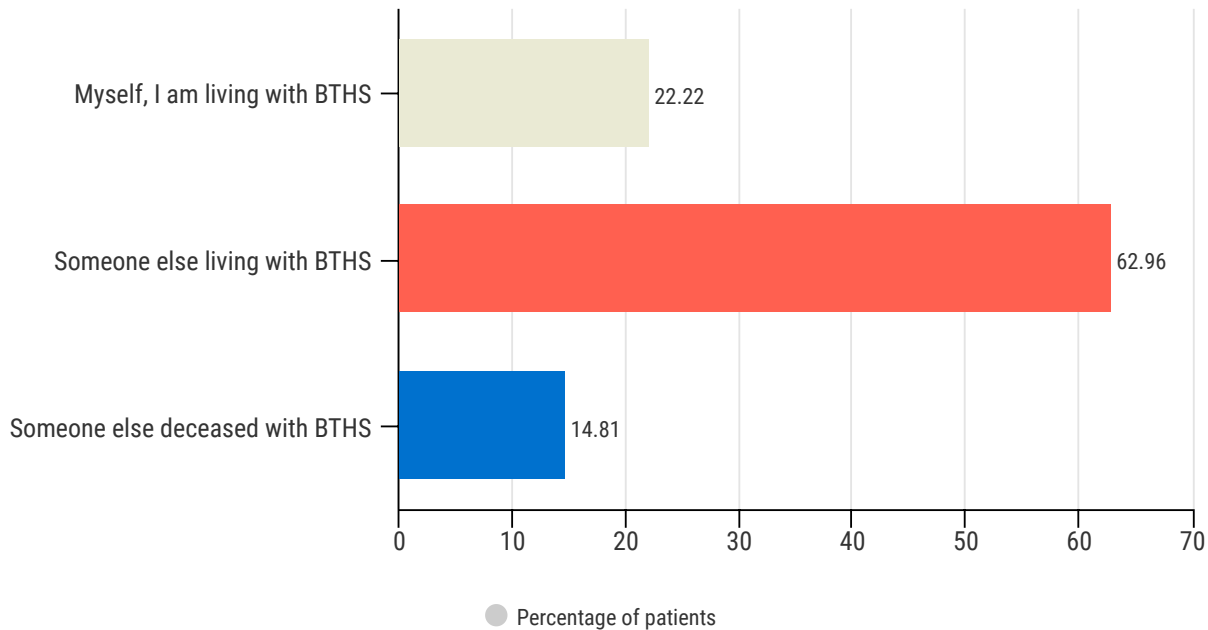


Answer	Count	Percent
I am an affected individual	5	12.82%
I am the parent of a living affected individual	18	46.15%
I am the parent of a deceased affected individual	4	10.26%
I am the grandparent of a living affected individual	2	5.13%
I am the grandparent of a deceased affected individual	1	2.56%
I am the sibling of a living affected individual	1	2.56%
I am the sibling of a deceased affected individual	0	0.00%
I am another relative of a living affected individual	0	0.00%
I am another relative of a deceased affected individual	1	2.56%
I am the spouse/significant other of a living affected individual	0	0.00%
I am the spouse/significant other of a deceased affected individual	0	0.00%
I am the child of a living affected individual	0	0.00%
I am the child of a deceased affected individual	0	0.00%
I am a carrier of Barth syndrome	6	15.38%
Other: I am the parent of two deceased affected individuals	1	2.56%
<b>Total</b>	<b>39</b>	<b>100%</b>

Mean	Confidence Interval @ 95%	Standard Deviation	Standard Error
4.615	[3.125 - 6.106]	4.750	0.761



**For whom are you filling out this questionnaire? (Please fill out a separate questionnaire for each affected individual, if there are/have been more than one in your life. Also, please make sure, though, that only one questionnaire is filled out for each affected individual. For example, if the affected individual has filled one out him/herself, then no one else should do so for him/her.) (SELECT ONE)**

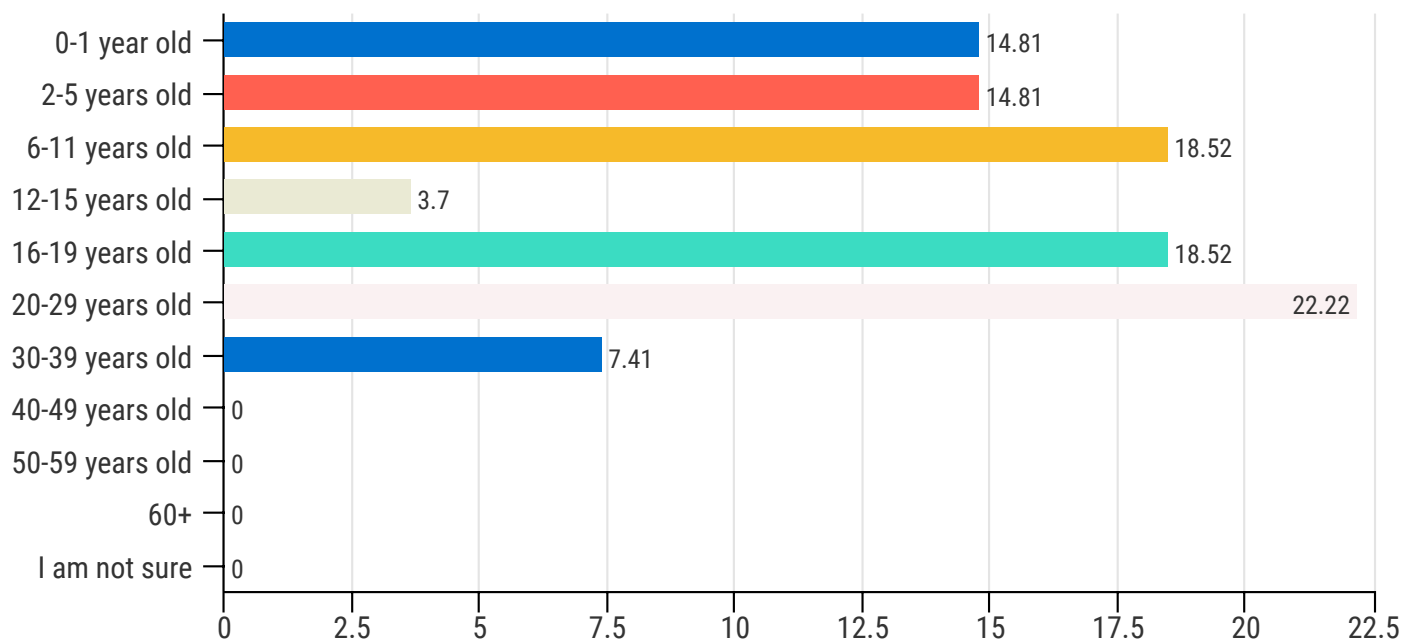


Myself: 6 people. Someone else living with BTHS: 17 people. Someone else deceased with BTHS: 4 people.

Mean	Confidence Interval @ 95%	Standard Deviation	Standard Error
1.926	[1.694 - 2.158]	0.616	0.118



## Age of the person for whom you are responding (or age at death, if the individual is deceased). (SELECT ONE)



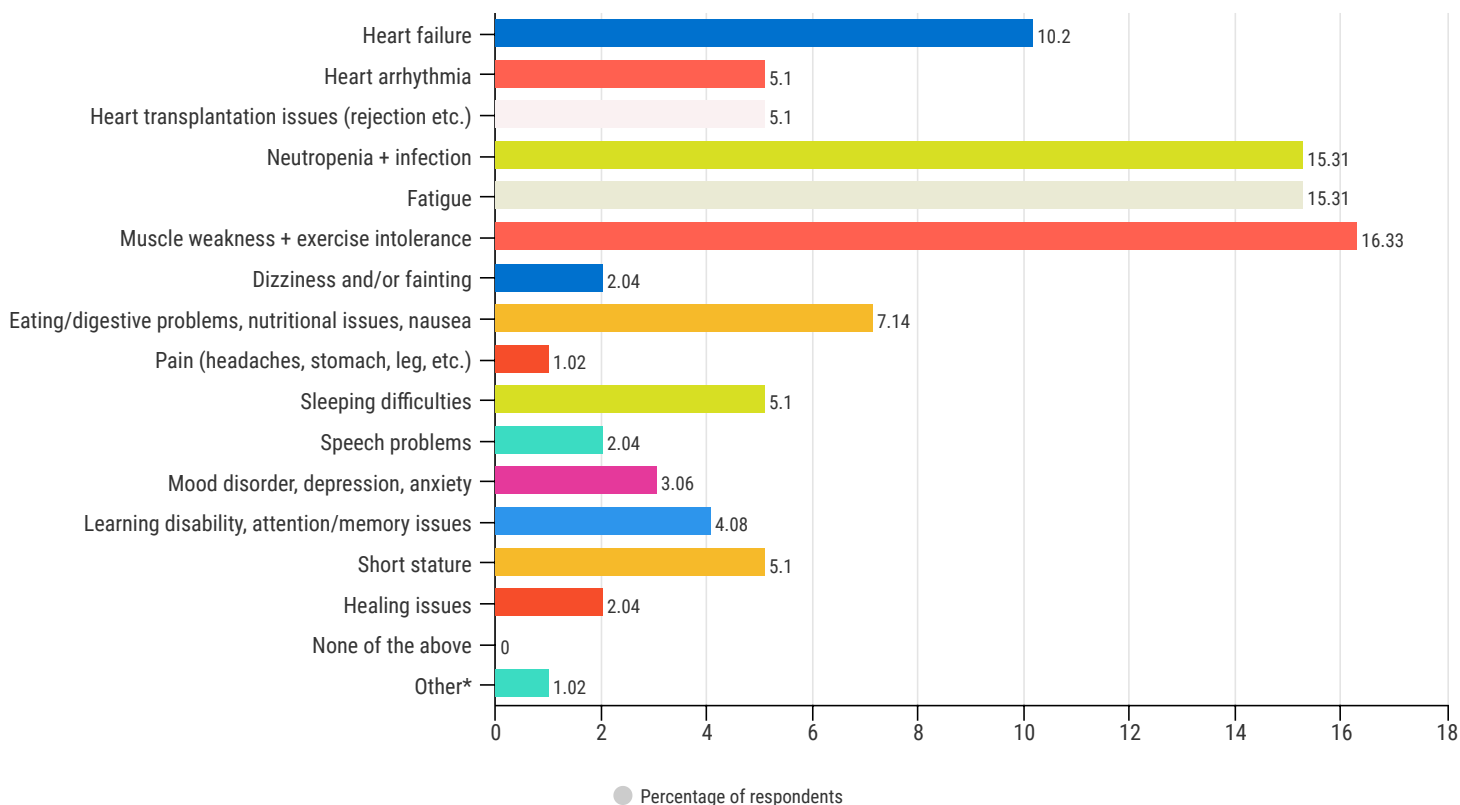
● Percentage of respondents

Answer	Count	Percent
0-1 year old	4	14.81%
2-5 years old	4	14.81%
6-11 years old	5	18.52%
12-15 years old	1	3.70%
16-19 years old	5	18.52%
20-29 years old	6	22.22%
30-39 years old	2	7.41%
40-49 years old	0	0.00%
50-59 years old	0	0.00%
60+ years old	0	0.00%
I am not sure	0	0.00%
<b>Total</b>	<b>27</b>	<b>100%</b>

Mean	Confidence Interval @ 95%	Standard Deviation	Standard Error
3.926	[3.172- 4.680]	1.999	0.385



## Currently, what are the symptom(s) that matter most to you/your loved one for whom you are responding (or in the last year of life, if the individual is deceased)? (SELECT UP TO FIVE)



\* Other: Inability to tolerate cardiac meds at the dose required to improve outcomes, actually detrimental to outcomes.



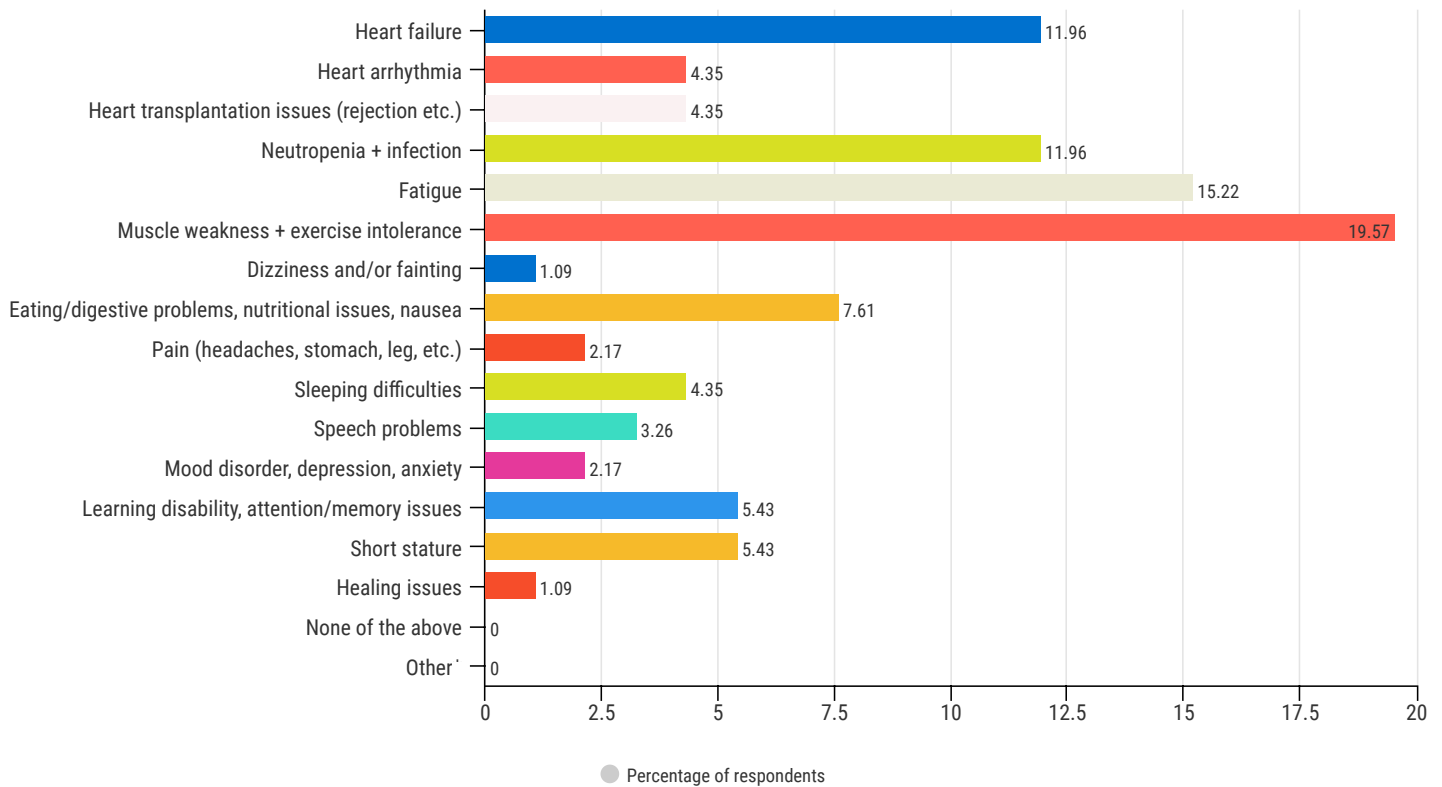


<b>Answer</b>	<b>Count</b>	<b>Percent</b>
Heart failure	10	10.20%
Heart arrhythmia	5	5.10%
Heart transplantation issues (rejection etc.)	5	5.10%
Neutropenia + infection	15	15.31%
Fatigue	15	15.31%
Muscle weakness + exercise intolerance	16	16.33%
Dizziness and/or fainting	2	2.04%
Eating problems, digestive problems, nutritional issues, nausea	7	7.14%
Pain (headaches, stomach, leg, etc.)	1	1.02%
Sleeping difficulties	5	5.10%
Speech problems	2	2.04%
Mood disorder, depression, anxiety	3	3.06%
Learning disability, attention issues, memory problems	4	4.08%
Short stature	5	5.10%
Healing issues	2	2.04%
None of the above	0	0.00%
Other: Inability to tolerate cardiac meds at the dose required to improve outcomes, actually detrimental to outcomes.	1	1.02%
<b>Total</b>	<b>98</b>	<b>100%</b>

<b>Mean</b>	<b>Confidence Interval @ 95%</b>	<b>Standard Deviation</b>	<b>Standard Error</b>
6.347	[5.565-7.129]	3.951	0.399



**Over your/your loved one's life, what are the symptom(s) that matter most to you/your loved one for whom you are responding (or in the last year of life, if the individual is deceased)? (SELECT UP TO FIVE)**



Answer	Count	Percent
Heart failure	11	11.96%
Heart arrhythmia	4	4.35%
Heart transplantation issues (rejection etc.)	4	4.35%
Neutropenia + infection	11	11.96%
Fatigue	14	15.22%
Muscle weakness + exercise intolerance	18	19.57%
Dizziness and/or fainting	1	1.09%
Eating problems, digestive problems, nutritional issues, nausea	7	7.61%
Pain (headaches, stomach, leg, etc.)	2	2.17%
Sleeping difficulties	4	4.35%
Speech problems	3	3.26%
Mood disorder, depression, anxiety	2	2.17%
Learning disability, attention issues, memory problems	5	5.43%
Short stature	5	5.43%
Healing issues	1	1.09%
None of the above	0	0.00%
Other	0	0.00%
Total	92	100%

Mean	Confidence Interval @ 95%	Standard Deviation	Standard Error
6.315	[5.535-7.096]	3.820	0.398



**Please name specific activities you/your loved one cannot do as WELL or as FULLY as you would like due to Barth syndrome. (Please respond about the last year of life, if the individual is deceased.)**

1. Does not have the energy to work full time
2. Simply walk around town. Go for hikes or bike rides. Participate in sports like his brother (soccer, martial arts). Play drums (he loves it but doesn't have the stamina to complete a song).
3. Feed and eat slow, to start walking
4. None
5. School days, exercise, keeping up with friends
6. To run
7. Studying, writing, eating
8. Steadiness on his feet, hyper-flexibility in joints cause him to fall when going up or down stairs.
9. He is unable to walk very far without becoming exhausted and that exhaustion can continue over several days. This can impact his ability to socialize with friends at university and participate in activities he would like to.
10. Skip, jump and going up and down the stairs, and speak fully.
11. Join in social events/days & nights out to concerts, etc., with friends/peers. Play sports, full days at school, planned events (due to fatigue) learning, some independence from adult help supervision
12. Play sports
13. Play sports, participate much in physical activities.
14. Heat intolerance. He gets hot really easily. He has to nap often so we cannot go out a lot.
15. Walk, sit, play
16. Spend a full day alone (at school, camp...) without being fed (enteral nutrition)
17. He can't go to school, often can't go out with friends because too tired
18. Walking, running, swimming, intimacy, drive long distances, dating, working, school/college.
19. Keeping a job and staying in touch with friends.

**Please list specific activities you/your loved CANNOT DO AT ALL due to Barth syndrome. (Please respond about the last year of life, if the individual is deceased.)**

1. Sports of any nature
2. Play with other kids at recess (he cries because he is not included or when included, he gets singled out) run, fun runs
3. Met developmental markers late
4. None
5. Most outdoor adventure activities
6. Walk long distances, to run, jump
7. Rugby, sports
8. Survive with a Barth syndrome-ravaged heart
9. Run, participate in sport. Have a part-time job whilst attending university. Have a career he would like – Chef.
10. Eat by mouth



11. My son said it is pretty much the same as above answer, so: Join in social events/days & nights out to concerts, etc., with friends/peers. Play sports, full days at school, planned events (due to fatigue) learning, some independence from adult help supervision
12. Can't play sports at a level that would allow him to play on the team and feel more like "one of the guys"
13. Is not able to walk long distances without assistance.
14. N/A
15. Talk
16. None
17. Ride a bike, do his homework alone, rest when sleeping
18. Lift heavy objects, ride a bike, be near sick individuals, etc
19. None that are important to me.

**How specifically does Barth syndrome affect you/your loved one on an average day? (Please respond about the last year of life, if the individual is deceased.)**

1. His day revolves around Barth ... cannot drive, works only part time, muscle weakness for walking, and heart issues for how far he can walk without being winded. Tired and needs to rest throughout the day.
2. Gets easily tired. Always monitored to ensure proper medicine/supplements intake. Have to plan ahead to get from point A to B.
3. Constant fear with constant infections and fevers anal sores, too
4. It really doesn't.
5. Fatigued to the point where I barely move in a day
6. Much
7. Meals are always hard times. I always feel worried about something bad affecting my son: severe infection, arrhythmia, heart failure. I feel sad my son cannot do the same things as his brothers (not the same sports, not the same school, not the same meals, not the same rhythm of life as a whole.
8. A lot. He worked really hard not to let it get to him. It was difficult, he was heroic in that respect but it wasn't easy for him. He didn't like to complain because complaints didn't make it better. He avoided thinking of himself as ill but as he once said, "Being in the hospital waiting for someone to die, so that I might live makes it impossible for me to escape the fact of just how sick I really am."
9. The fatigue has a huge impact and affects him to varying degrees daily. Hot weather makes this even worse. It makes it difficult to study and retain knowledge and participate in normal activities a teenager generally would. He has pain daily to varying degrees and also has a lot of trouble sleeping, which also further impacts fatigue and ability to perform or cope with daily activities. He also struggles with anxiety, which greatly affects his quality of life and ability to enjoy things.
10. It makes it to where he is having a hard time eating without having a g-tube; his learning is delayed to where he's having to go to therapies
11. Fatigue, fatigue. Low muscle tone. Affects his independence/social life/not many friends/I know he would love a girlfriend but he feels like this doesn't seem possible ... not sure if this gets him down. My son worries that his heart may stop while he is asleep and has told us this on many occasions, he worries that if this happens then "how would we know where to find him." This breaks my heart. I can



do all that I can helping with all the practicalities of his medical care, appointments, school, doctors, etc., but this, I cannot take away for him.

12. Limited abilities make for shorter outings, fatigue
13. Requires more time to prepare and administer medicines, need to allow more time for rest.
14. Little sleep because he doesn't sleep. Belly issues that's a daily battle. Always getting sick.
15. Could not explain what was wrong, always extremely tired, did not grow
16. Day interrupted by feeding times
17. We always have to manage a terrible fatigue and pain
18. Fatigue, overexertion, palpitations.
19. The fatigue requires me to give up on half the activities that are important to me, which lead to depression and loneliness. I also have to force myself to eat despite a complete absence of appetite and aversion to almost any kind of food, making every meal a struggle.

## **Has your/your loved one's disease changed over time? If so, how? Please give details.**

1. Of course. Small stature was an issue throughout his life until senior year in high school when he grew at a rapid rate. Each cardiac arrest without an explanation of why affects not only his heart, but his fear of living. Having a protruding stomach while you are still only in the 15th percentile for weight is also demoralizing. Dating, or should I say NOT dating is an issue. Still living with your parents because you cannot live on your own ... so many real-life obstacles.
2. Not noticeably
3. Heart improved appeared normal function on minute med so doctor took child off med and heart failed
4. Gotten more fatigued. And able to do less.
5. Over time the symptoms got worse
6. Not really
7. It killed him.
8. He appears to have less energy now than when he was younger.
9. No and it's been three years since the day we found out his disability
10. My son has had ups and down over the years with cardiac issues/infection/weight gain/low stature/back & leg pain and, of course, the every single day presence of fatigue.
11. His heart function has gotten better on medicines
12. When he was a baby he was in heart failure, after 6 was better but since he was 11 worse and while he's growing up is always exhausted
13. Transplant. Temporary cardiac function increase.
14. The symptoms themselves haven't changed much, but responsibilities increased as I grew older, making the fatigue much more prominent than early in life. And as a result, loneliness and depression became a much bigger issue as an adult than they were in childhood.



## **What worries you/your loved one most about your/your loved one's Barth syndrome? (Please respond about the last year of life, if the individual is deceased.)**

1. That another cardiac arrest will happen and the ICD will not be able to bring him back. Period.
2. He worries too much about things a 9-year-old should not worry about. He asks me every night to listen to his heart. Sometimes he says he doesn't want to die. We went for a trip to Italy this year and had to toss a coin in a fountain and make a wish. His brother wished for getting all the transformer toys. He wished for a cure to Barth.
3. Infections
4. Nothing
5. How much worse it will get with time
6. Neutropenia
7. Risk of sudden death, due to arrhythmia or severe infection
8. He didn't want a heart transplant because he knew there would be no treatment to cure rejection. He didn't want to die, either. So, he agreed to the transplant but he said, "The transplant is like being in death's waiting room. You're gonna die, it just takes longer till the reaper calls your name." Science can't move fast enough.
9. He worries about his future and ability to support himself and participate in things like a job and a social life.
10. That he will never get to eat right, die before he's 40 years old, or be able to do things that other kids can do
11. Heart function/arrhythmia/infection/fatigue
12. Not able to keep up with peers his age and having to deal with the stress of struggling medically.
13. The need for another heart transplant
14. I am afraid he isn't always going to be here. That we're going to lose him.
15. Death
16. Heart failure and infections
17. My husband and I are scared he could die, as his little brother, or become an adult that can't work or have a normal life
18. Death. Not accomplishing what I want out of life. Not finding an ideal life partner, never moving out of the parents' house, living unfulfilled.
19. The inability to keep up with society's increasing demands. I've gotten to a point where I hardly have any energy for what is important to me, and at this rate it will be a matter of time before I can't manage my healthcare and paperwork for disability benefits anymore, either.

## **Specifically, what are you/your loved one currently doing to help manage Barth syndrome conditions/symptoms? (Please respond about the last year of life, if the individual is deceased.)**

1. Keeping current on medications, doctors' visits, attending the conference and participating in Barth studies. In other words, "Doing the best we can with the tools we got." Constantly monitor medicine/supplement intake. Constantly talk to school/surrounding personnel to raise awareness and be his advocates.
2. Dig by mouth treating infections as they appeared used



3. Medication and exercise
4. Meds, reserving energy
5. I try to find pleasant activities, I talk to him, I ask his doctor for advice, I respect the scheme of the therapies
6. Regular cardiac follow-up, everyday life adaptations (computer at school, less walking, less sports ...), specific interventions for eating disorders, writing issues ...
7. His biggest issue was always cardiac-related. His heart got better and worse, better and worse throughout his life. Over the last year of his life it was like a vortex. He had to have a transplant to survive but he couldn't tolerate the standard dose of medications required to reach 1A status and I am convinced his metabolism fluctuated, which caused it to be very difficult to manage anticoagulation therapy.
8. He has a place at university where he can rest. He is allowed to miss lectures and access from home if needed but he loves the social aspect of university and hates to miss out. He has a disability sticker for his car so he can park close to where needed. Inducts with G-CSF twice weekly.
9. Having to take physical therapy, occupational therapy, developmental therapy, and speech therapy
10. Cardiac medications, G-CSF, physiotherapy, swimming, lifestyle choices with diet
11. Follow-up appointment with care team including cardiologist and KKI team at Kennedy Krieger.
12. Medications and supplement
13. Cardiac medicines for his heart failure and seeing multiple specialists
14. Medications, withdrawal from school
15. Medicine
16. We have some help for school, have a diet with much more proteins, have a therapy for neutropenia
17. Immunosuppressants for transplant, G-CSF, Levocarnitine.
18. Limiting my activities and taking antidepressants.

**How well do your/your loved one's current treatments/therapies work to manage the most significant symptoms of Barth syndrome? (Please respond about the last year of life, if the individual is deceased.)**

1. The ICD works, obviously. Other treatments and supplements are difficult to judge since you do not want to take the chance that something will happen without them.
2. Not well. He doesn't get sick too often but fatigue & muscle weakness, which is his primary barriers to a fulfilled life, have not improved.
3. Didn't
4. My current treatments manage my symptoms completely.
5. Fairly well. There is no real treatment for fatigue so ...
6. Pretty good
7. Pretty fine
8. Not well, antiarrhythmic drugs excited his proarrhythmic heart. The heart failure made him nauseated and the drugs to treat it worsened his nausea. He was hungry but he couldn't nourish himself because he would vomit. He was nearly 6 feet tall and went down to 113 pounds.
9. Neutropenia seems to be well managed at this stage and heart function appears to be stable however there is no real treatment or therapy for the fatigue which is the biggest issue.
10. He is almost done with physical therapy but the other therapies he's still behind on





11. They seem to be working okay (touch wood). Seems to be harder at the minute to keep physio in daily routine (think it may be age-related). Swimming helps my son's muscle pain and he always seems relaxed after it too.
12. Doing well with follow-up appointments and blood work.
13. Fairly well
14. His cardiac meds work great. We just need to figure out his sleeping and belly issues
15. Did not work
16. Well. Heart stable and no infections due to medicine.
17. G-CSF works very well Headache doesn't go away with medicines and sometimes melatonin helps for sleeping
18. As long as I take the meds regularly, it does its job. Depression changes that though.
19. Not nearly enough.

**What are the most significant downsides to your/your loved one's current therapies and exactly how do they affect your/your loved one's daily life? (Please respond about the last year of life, if the individual is deceased.)**

1. Honestly, there are no downsides as long as he remains with us.
2. We see no improvement. We see no worsening too but sometimes he has medicine intake fatigue. Why take all this if the quality of life seems to remain the same.
3. Stopped heart med
4. None
5. The fatigue and muscle weakness
6. injections are annoying
7. Time-consuming
8. The current therapy to treat a symptom exacerbates worsening of another.
9. Not having the energy to attend university impacts mentally and I teases depression and anxiety.
10. Therapies are helping him a lot better than before he started them. He's doing a lot better and improving very well.
11. My son is almost 18 and trying to keep him in his daily physio routine is becoming harder. He is doing his own G-CSF injections, his own medications, and I am currently trying to get him to deal with reordering his repeat prescriptions/dealing with receptionists at hospitals, etc. My son is currently transitioning from pediatric care to adult services at hospitals and because he sees so many doctors/specialists (7 different ones) he is finding this very overwhelming. He is finishing school at the same time (what is next for me, how will I cope out of the school system, etc.?) and all the change is too much for him to deal with at the same time (his own words) so I am trying to trickle the changes into his life so it's not too much at once.
12. Lots of time missed from school and work.
13. Not sure
14. It's time-consuming. Exhausting.
15. Did not work
16. None
17. When he is exhausted we can do nothing



18. Not being able to drink with friends, not being anywhere near a sick or coughing individual.  
Immunosuppressive meds might require me to have a liver transplant as well. I might require multiple heart transplants.
19. It takes up most of my limited energy, leaving little for things that make my life enjoyable.

**Describe the other non-medical aspects of Barth syndrome's impact on your/your loved one's life and your family members' lives. (Please include practical, financial, psychological and socio-economic impacts of Barth syndrome.)**

1. I may be repeating myself, but ... He cannot participate in life like most of his peers. He cannot live on his own for so many reasons ... muscle weakness for daily chores, transportation issues, independence for finances since he only works part time. He has indeed done amazingly well considering his circumstances, but would love to be able to participate in life more fully. Our family's financial life has been affected by the tremendous \$\$\$ spent on medical care to protect him, for "vacations" to conferences and outreaches and clinics that are not reimbursed. Loss of economic earning power for me, the mom, who had to quit her job to take care of him. Siblings sometimes had to take a back seat to the needs of their brother, yet they always seemed to understand. So many struggles to work through on a daily basis.
2. Practically, it takes planning (we researched and bought him an electric scooter to improve his independence). Financially, it is an endless list of medical bills. Medically, it is juggling and educating doctors about his condition. Psychologically, it is heavy but only when we get a break do we notice the near constant source of anxiety.
3. We had already lost one son and this was very hard on all of the family, the two girls, one 5 years older and one 18 months older, emotionally, financially. New to area and had no family nearby and no support system.
4. N/A
5. Only being able to work a few hours a week means money is always really tight.
6. We are often stressed because the unpredictable disease
7. Even though he is getting a disability check, which is helping a little, I'm having to stay at home instead of getting a job, and it's been very stressful ...
8. I've had to stop working to be able to take care of my son (medical appointments, missed school days due to fatigue or sickness ...). I have to cope with the idea arrhythmia, severe infection, or any life-threatening can occur any time.
9. Stresses to the family, differences of opinions in what should and should not be done.
10. He depends on government support whilst studying as he is unable to work and study. He does not have the energy to socialize after university and study due to fatigue and has to carefully choose what he participates in on weekends as it will impact him for the rest of the week. He needs to take time away from his studies for all of his doctor appointments, which causes further stress and anxiety. He would not be able to work in a physically demanding job and his career options are limited.
11. My son hates not being as independent as his friends/peers. It affects his day-to-day life, he loves sports and hates he cannot take part as much as he would like (he still goes along for the social aspect). He worries about getting/holding down a job/college. He watches his older brother go to university/have a busy social life/leaving to stay in another city and wants this for himself. He is



currently 17 years old and seems to resent his wheelchair at the minute, he seems frustrated with his fatigue and he relies on my for most of his social activities.

12. Lots of comments about his small stature, two years from a possible driver's license and he is still in a booster seat
13. Stress of having many appointments, taking time off work for those and stress of medical needs and rejection of heart.
14. It's been expensive paying for all his treatments and medicines. It's hard for me to work when he has bad days. It's hard to find a sitter because he's medically fragile.
15. Due to feeding problems sometimes difficult to be on the move
16. Psychological effects of this disease are really heavy, NOT ONLY FOR OUR FAMILY, but for all who love him. Often he is at home with family, his teen friends go away, by bike or playing sports. We can't work too much because he's always alone at home and become depressed.
17. Barth syndrome played a role in every choice I ever made and everything I did or did not experience: the kinds of food I enjoy, the people I met, the hobbies I picked, the study I chose, etc.

### **What factors do/will you take into account when making decisions about using a therapy or treatment? (Please respond about the last year of life, if the individual is deceased.)**

1. If it is safe, if it will improve his quality of life, then if we can afford it.
2. Ease of intake (painful, frequency, return). Psychological impact on him.
3. Risk/benefit
4. How it will affect my current medications.
5. Risking benefits against severity of negative side effects
6. The risks
7. How good the therapist is, the school they are with and most of all the cost
8. Efficiency, long-term risks, pain
9. Do the benefits outweigh the risks?
10. Side effects, risk/benefit, affordable availability
11. My son is open for trying new therapy/treatments.
12. Mom makes most of these decisions
13. The impact it will have on individual and commitment of time needed to complete.
14. If it will help him and will make him feel better we will do it
15. No dangerous down side effects
16. We evaluate side effects
17. Barth syndrome not only affects the body, but also the mind, personality, social environment, and much more. I would need to be reasonably sure a physical change would not break my body's compatibility with who I am, what I find important, and mental limitations.



**Assuming there is not a complete cure for Barth syndrome, what specific things would you look for in an ideal treatment? (Please respond about the last year of life, if the individual is deceased.)**

1. Improvement in muscle weakness and heart issues.
2. Fatigue and muscle weakness are number 1 for us, for now. Heart is, of course, vital as well.
3. Heart function and immune system
4. Fatigue and neutropenia
5. Help with the fatigue
6. Eliminate tiredness, restore cardiac function, resistance to infections
7. A cure that will cure everything that would take away everything associated with the syndrome
8. I would look for a treatment that would help my son to have a more normal life (less fatigue, less risks)
9. He would want to live his life without a transplant. He would want to live his life without an AICD. He would want to be a mechanic where he could repair engines, something he couldn't do with the AICD. He would want to have an MRI if he were in a car accident to check his brain without the AICD being detached from his heart.
10. Help with fatigue and pain and improve overall quality of life
11. Something to help fatigue.
12. Fatigue, heart function, and small stature
13. Something to help with fatigue and muscle weakness.
14. Something that can make him live a long, happy, healthy life
15. Improvement of feeding ability
16. Something that get down extreme fatigue
17. More energy to get through the day and accomplish what I find most important, as well as an improvement in mental health and social abilities, which all links together.

**What would you/your loved one be willing to do in order to try a new treatment? For example, would you travel? Would you agree to a hospital stay in the beginning? Would you be willing to undergo a procedure that requires anesthesia? Would you be willing to go to a doctor's office once a week to get the treatment? Would you be willing to have daily injections or regular blood work? Would you be willing to put up with some gastrointestinal distress to have the energy to get through a full day of school or work? What other kinds of things would you be willing to do and/or trade off?**

1. Most of these questions we have dealt with in the studies we all have participated in. Now that my son is working, the greatest issue is where it is and how long it will take. Working is what gives him purpose, and the scheduling of these things is of the utmost importance.
2. Travel - yes, hospital stay - tbd, procedure with anesthesia - tbd, doctor visit weekly - yes, daily injections - better 2, 3x weekly if possible to get a break here and there, gastro distress - unsure.
3. All of the above



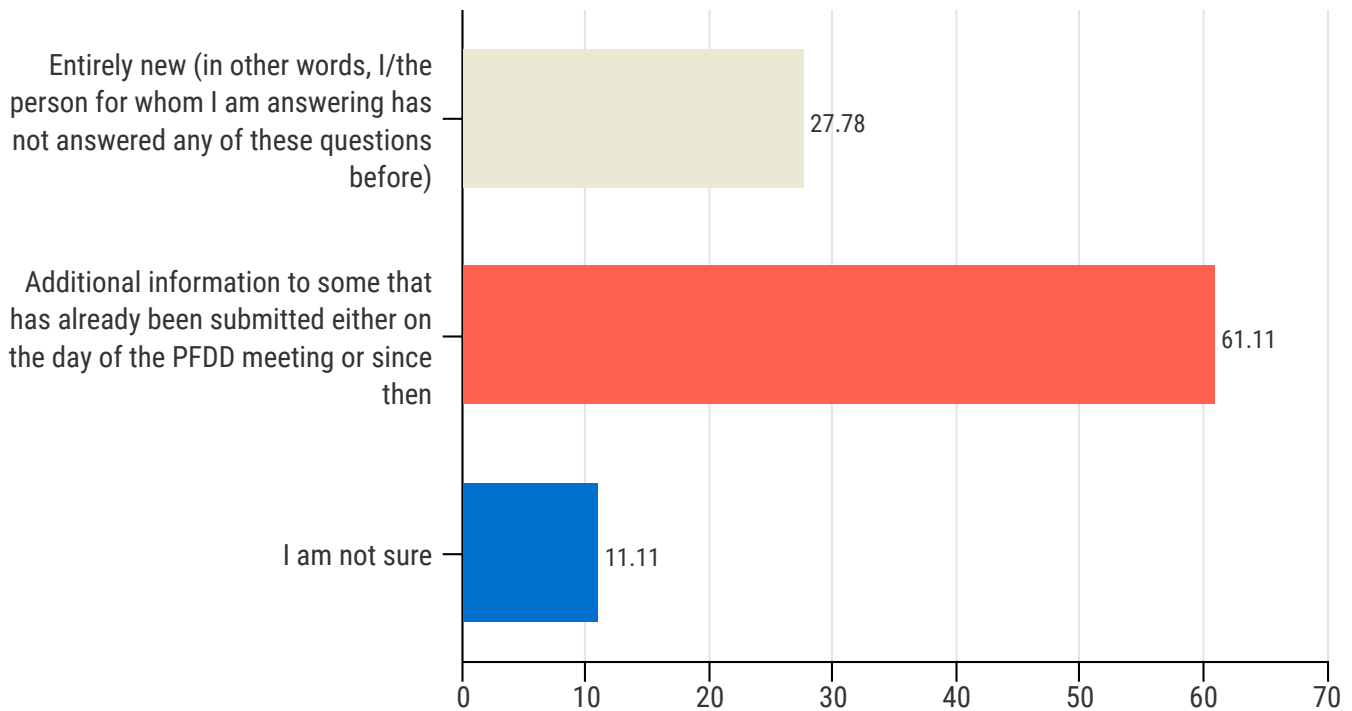
4. Anything
5. I'd travel and pretty much do any kind of procedure if I thought it would work
6. Yes
7. We would be willing to take a liquid drug anytime and travel as long as this drug didn't interact with his other meds and the distance was close to home.
8. I, as a mother, would agree to do as many things as possible, as long as it is not life-threatening, even if it is time-consuming or can be painful. I would also hesitate for a treatment that would be so time-consuming that my son wouldn't be able to follow a normal school rhythm.
9. In his life he was often the first to try an idea out before it was even put into a protocol. He tried anything that might improve outcomes. He once said, I participate in research because what I do today will make a difference after I am gone. I believe nothing would stop him from participating in research. He was painfully aware that Barth syndrome is extraordinarily rare. He knew he didn't have the luxury of denial that someone else could do it.
10. We would travel overseas and do what needed to be done.
11. I read the above statement to my son and he said yes to all of the above! Kinda sums up how much he wants help.
12. Not sure
13. Travel, go to appointments as needed, blood work.
14. Yes to all of the above. We'd do anything that would help me.
15. Everything except anesthesia (if safe to use)
16. Everything we can manage at the time
17. Most possible side effects of any treatment are part of my life without treatment already, so I'd be willing to accept almost any inconvenience if that leads to improvement afterwards.

## **Do you have anything else you would like to say about a possible treatment?**

1. Please pursue ASAP
2. Thank you
3. The young men need help with life decisions and moving toward independent living with financial support as needed
4. No
5. I hope it will work instead of giving bad side effects
6. It can't come soon enough.
7. I'm excited for the new studies and new treatments that could lead to a more normal life for him
8. We just need a treatment and a cure that's going to help our boys
9. Thanks to those who participated in the current trials!
10. I already mentioned this in other answers, but can't stress this enough: Barth syndrome influences every part of life. It affects what food you enjoy, what topics you grew interested in, what hobbies, education, and jobs you chose, who you became friends with, how confident you are in general and in specific areas, how important quantity of life is, what quality of life means, what you enjoy, and so much more. No consideration of treatment should stop at physical changes or even mental state. The impact on every aspect of life should be considered.



## This information in this questionnaire is:



Answer	Count	Percent
Entirely new (in other words, I/the person for whom I am answering has not answered any of these questions before)	5	27.78%
Additional information to some that has already been submitted either on the day of the PFDD meeting or since then	11	61.11%
I am not sure	2	11.11%
<b>Total</b>	<b>18</b>	<b>100%</b>

Mean	Confidence Interval @ 95%	Standard Deviation	Standard Error
1.833	[1.548-2.119]	0.618	0.146

