



BSF Beat

Saving lives through education, advances in treatment, and finding a cure for Barth syndrome.

News and updates from the Barth Syndrome Foundation

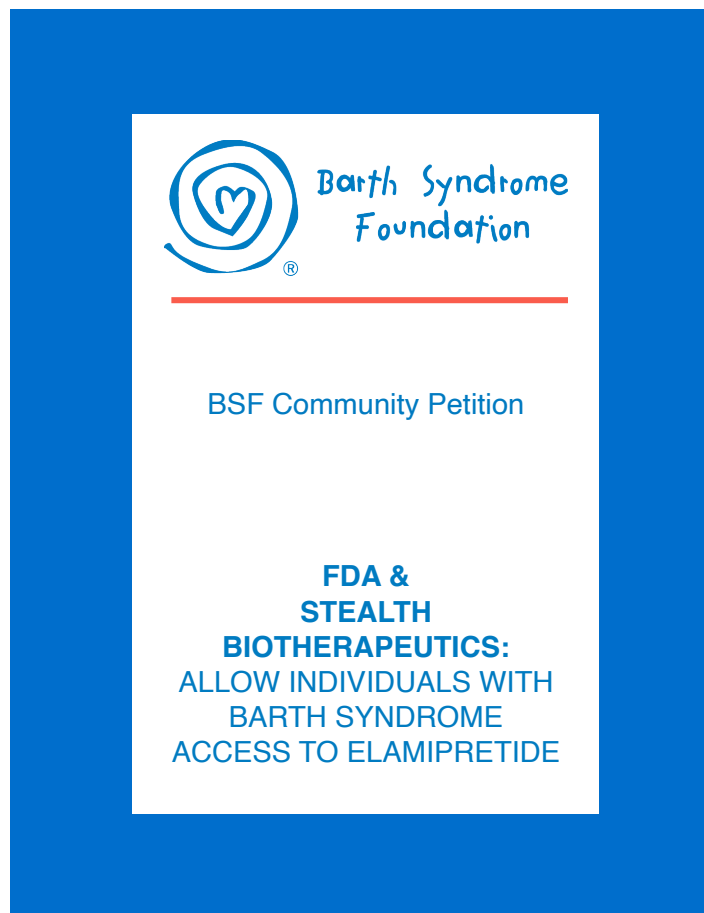
Winter 2021

BSF Urgently Appeals to FDA: Allow Access to Elamipretide

On November 17, 2020 BSF delivered the Elamipretide Community Petition to the FDA. It was signed by over 4200 supporters and accompanied by more than 730 written testimonials.

Elamipretide, produced by Stealth BioTherapeutics, is an experimental drug that has been shown to reduce debilitating fatigue and potentially improve important baseline health measures, including various heart components, in people with the ultra-rare disease Barth syndrome. Given the risk of life-threatening cardiac complications in this population, individuals with Barth syndrome cannot wait for additional studies of elamipretide before receiving access.

We are excited to share excerpts from the petition submission on the following pages. To view the full report, including all 730+ testimonials, please visit www.barthsyndrome.org/petition.



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Introduction

Barth Syndrome Foundation (BSF) and constituents support access to elamipretide to individuals with Barth syndrome. The enclosed citizens petition prompts action by FDA to urgently review this request.

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Advocating for Access to Elamipretide

A copy of the petition as provided in its entirety to BSF constituents, including background and rationale as published at barthsyndrome.org/petition.

3

Comments from the BSF Community

A compilation of qualitative comments from individuals living with Barth syndrome, parents, and caregivers of both living and deceased individuals, healthcare providers, researchers, and members of the community.

4

Signatures

Responses organized by first name and last initial to protect privacy.

BSF's mission

Barth Syndrome Foundation (BSF) is the only global network of families, healthcare providers, and researchers solely driven by the mission to save lives through education, advances in treatment, and finding a cure for Barth syndrome.

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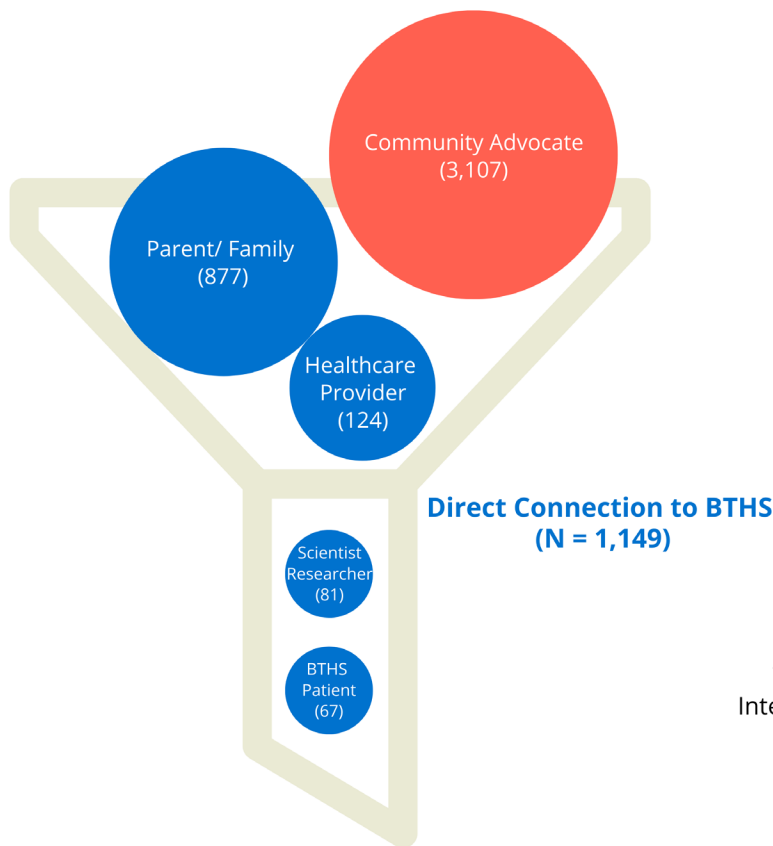
Introduction

4,256 unique signatures were gathered by Barth Syndrome Foundation (BSF) in September 2020 in an effort to demonstrate BSF community-wide support for allowing BTHS patients access to the drug elamipretide.

This petition was generated in response to FDA's request of Stealth BioTherapeutics (drug sponsor) to conduct additional clinical trials for the study of elamipretide in Barth syndrome (BTHS) prior to submitting a New Drug Application (NDA). This move would dramatically delay, if not close the door to, individuals' access to the potentially life-altering therapy, a drug that has already been proven to have a high safety profile.

Given the high death rate and rarity of BTHS as well as the positive safety profile of elamipretide, we are asking FDA and Stealth to grant access to elamipretide to BTHS patients as soon as possible.

All Respondents by Connection to BTHS (N = 4,256)

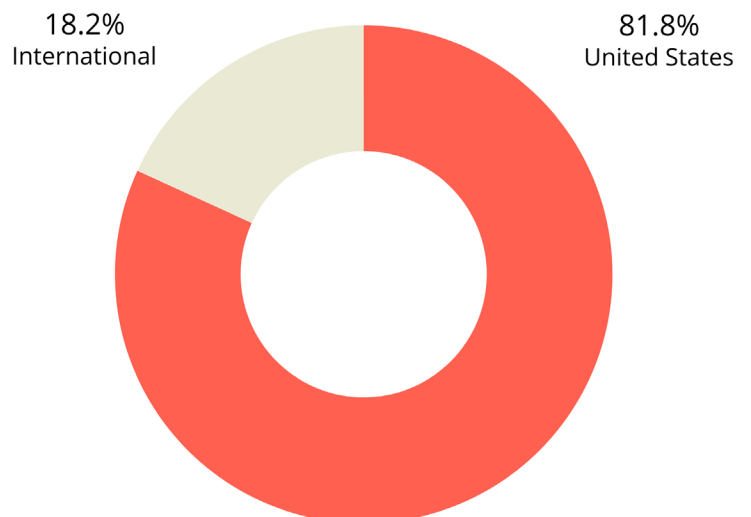


As of September 2020, 255 individuals were living with BTHS around the world (126 in the United States). BTHS patients over the age of 12 were invited to sign the petition and provide testimony, although some younger individuals opted to participate.

67 BTHS patients (51% of whom currently reside in the US) signed the petition asking for access to elamipretide.

In addition, almost 900 family members of BTHS patients, living and deceased, expressed support through the BSF-sponsored petition.

In which country do you currently reside?



The majority of responses (82%) were from residents of the United States, of which all 50 States were represented. International supporters were represented across 37 countries, demonstrating an overwhelmingly positive and global response to this request for access to elamipretide.

2

Advocating for Access to Elamipretide

The following is an exact copy of the information provided to the community via an electronically distributed petition. Between September 15 and 30, 2020, BSF published this information and gathered signatures at barthsyndrome.org/petition. Efforts were made to represent all information and views on which the petition relies.

FDA & STEALTH BIOTHERAPEUTICS: ALLOW INDIVIDUALS WITH BARTH SYNDROME ACCESS TO ELAMIPRETIDE

Elamipretide, produced by Stealth BioTherapeutics, is an experimental drug that has been shown to reduce debilitating fatigue and potentially improve important baseline health measures in people with the ultra-rare disease Barth syndrome. Given the risk of life-threatening cardiac complications in this population, individuals with Barth syndrome cannot wait for additional studies of elamipretide before receiving access.

FDA has repeatedly signaled the importance of incorporating the “patient voice” in drug development. This is especially critical in rare diseases. The 21st Century Cures Act requires sponsors to include and FDA to consider the patient perspective. The voice of affected individuals and organizational advocacy is critical in communicating to FDA the extreme unmet need in Barth syndrome. In 2018, the [externally-led Patient-Focused Drug Development meeting on Barth syndrome](#) revealed that 100% of patients experience fatigue, 90% (based on cardiomyopathy occurrence) have heart failure or other life-threatening cardiac complications related to their disease, and 100% of patients surveyed would like access to therapies that improve quality of life even if they do not reverse disease.

As of today, there are only 126 known affected living individuals in the United States. In a very small clinical trial like [TAZPOWER](#), it is very challenging to see compelling clinical data that reach statistical significance. The majority of trial participants experienced improvements in fatigue, strength, and quality of life. The patient voice becomes particularly critical in this setting. **We are asking FDA and Stealth to work together to provide access to elamipretide to people with Barth syndrome as soon as possible.**

Background

In the open-label extension portion of the Phase 2/3 TAZPOWER study, treatment with elamipretide resulted in a [27% increase in average cardiac stroke volume](#), or the amount of blood pumped by the heart's left ventricle per contraction. Most patients with Barth syndrome have underlying heart disease, often leading to heart failure and death. Even a modest improvement in heart function could potentially represent an opportunity for longer and improved quality of life for an individual with Barth syndrome.

People with Barth syndrome who were enrolled in the open-label extension of the TAZPOWER clinical trial for one year showed positive changes in functional assessments such as fatigue, muscle strength, and endurance. Compared to natural history information (data collected from patients not receiving an experimental treatment), patients receiving elamipretide showed an average improvement of 116.92 meters on their six-minute walk test compared to 1.73 meters for those in the natural history group over the same period of time. Improvements were also seen in muscle strength and sit-to-stand assessments. **Quality of life for people with Barth syndrome is of utmost importance and can be improved by access to therapies that increase the individual's strength and endurance as well as reduce fatigue.**

The trial also showed elamipretide is generally safe and well-tolerated, which builds upon Stealth's experience testing this experimental drug for other, more prevalent conditions.

Rationale

Barth syndrome is a serious and life-threatening genetic disorder, primarily affecting males. It is caused by a mutation in the *tafazzin* gene resulting in an inborn error of lipid metabolism. Cardinal characteristics of this multi-system disorder often include combinations and various degrees of cardiomyopathy, neutropenia, muscle weakness, growth delay, fatigue, and exercise intolerance. These symptoms limit the day-to-day quality of life for people with Barth syndrome, and often lead to life-threatening complications and early death. **In the last 12 months, the ultra-rare global Barth syndrome population has lost seven patients to complications of the disease. Given that there are currently 255 in the world living with this disease, this means that nearly 3% of the world's cohort has succumbed in the last year, predominantly due to cardiac-related causes.** Although improved diagnosis, symptom monitoring, and symptom management have improved the survival rate, heart disease (cardiomyopathy, sudden cardiac death, heart failure) remains the primary cause of premature death in the Barth syndrome population.

Given the results of the trial, Stealth BioTherapeutics and FDA must give patients with Barth syndrome, who currently have no other choice for treatment, access to elamipretide. FDA has emphasized the importance of the patient voice, especially for rare conditions without FDA-approved treatment options. As summarized in the [“Voice of the Patient: Barth Syndrome”](#) report, people with Barth syndrome experience compromised quality of life caused by fatigue and other symptoms. Affected individuals and families deserve the right to have access to elamipretide in order to potentially experience improvements as seen in the clinical trials.

Data from the clinical trial evaluating the use of elamipretide in Barth syndrome demonstrate meaningful potential benefit and low risk, particularly evidenced by people who participated in open-label extension and have used elamipretide for over one year. Individuals with Barth syndrome have been informed during the course of elamipretide clinical trials and are willing to accept the potential risks given the potential for benefit and the absence of any other FDA-approved therapies.

Therefore, we ask Stealth and FDA to address this issue with urgency by submitting and approving an NDA for elamipretide in Barth syndrome based on existing evidence from clinical trials.

Individuals with Barth syndrome have a reduced quality of life and many are dying. **We need treatment choices now.**

To view the full submission, including the 730+ testimonials, visit www.barthsyndrome.org/petition.

Gene Therapy Advancing, Challenges Ahead

Gene therapy has been a focus of BSF's research grant program for more than a decade. The potential use of gene therapy targeting Barth syndrome holds great promise for our patients, yet has significant scientific, financial, manufacturing and regulatory challenges that first must be overcome. BSF believes that collaboration across institutions is critical for bringing therapies from bench to bedside.

Two teams, the first is composed of Dr. Barry Byrne (University of Florida), Dr. Christy Pacak (University of Minnesota), and Dr. Todd Cade (Duke University), and a second team led by Dr. Bill Pu and his research fellow Dr. Suya Wang from Boston Children's Hospital are testaments to the dedication and commitment of researchers and clinicians invested in advancing this therapeutic strategy for Barth syndrome. Through our BSF Friday Chats and a Webinar last year, these contributors shared updates of their advancements in gene therapy.

Dr. Pu, Dr. Wang, and colleagues have worked to expand the tremendous body of pre-clinical work accomplished by Dr. Pacak, by testing the impact of gene replacement therapy in the Barth knockout mouse model. Dr. Pu's team's

2020 publication entitled "AAV Gene Therapy Prevents and Reverses Heart Failure in a Murine Knockout Model of Barth Syndrome" characterized the Barth knockout mouse, demonstrating that it is an ideal Barth animal model, given its similar manifestation of disease as affected individuals. Their expansive work also identified the following key insights and important variables to consider regarding gene therapy in Barth syndrome:

- A reduction of tafazzin (*TAZ*, the causative gene behind Barth syndrome) as well as total absence of the gene can be completely corrected by gene therapy in the Barth mouse model.
- Heart disease can be reversed to normal function, even in mice with established heart dysfunction.
- The dose of the gene therapy is critical to providing long-term benefit.

As shared during our October webinar, Dr. Byrne, Dr. Pacak and Dr. Cade have made significant strides towards a potential clinical application of gene therapy in individuals affected by Barth syndrome. Their approach involves using adeno-associated virus (AAV) vectors delivered into the bloodstream to



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Christy Pacak PhD
University of Minnesota



Todd Cade PT, PhD
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William T. Pu, MD
Boston Children's Hospital



Suya Wang
Boston Children's Hospital

introduce a new and working copy of the tafazzin gene. This potential therapy builds off similar successful approaches of gene replacement therapy in Leber congenital amaurosis (treated with Luxturna) and spinal muscular atrophy (treated with Zolgensma)

Dr. Byrne and colleagues believe that the approach of using gene therapy as a treatment for Barth syndrome will address both the cardiomyopathy and fatigue aspects of the disease. However, there are multiple complex challenges to consider, including the effectiveness of and ability to reach the targeted cells, immune-related safety issues, and both the scalability and availability of AAV manufacturing. Dr. Pacak's pre-clinical (animal model) studies focused on maximum safety and efficacy with a minimal dose using a AAV vector named rAAV9 via systemic intravenous delivery to the heart and muscle. Dr. Pacak and colleagues have performed a series of mouse studies examining the most effective vector as well based on which would work best in heart and muscle tissue. Overall, these researchers found correction or improvements in biological processes that are shown to be abnormal in Barth syndrome. As research progresses in cellular and animal models, efforts will continue to refine the maximal benefit of the therapy, balanced against the minimal dose possible.

A clinical trial assessing the safety and efficacy of gene therapy in people with Barth syndrome has not yet been conducted but is currently under consideration. Dr. Todd Cade and colleagues suggest the following possible parameters for a future study:

- Evaluating safety and effectiveness of two different systemic doses (high and low)
- Two year long, double-blind crossover Phase I/II clinical trial
- Participants ages 15-40 years old
- Trial initiation and follow-up done at University of Florida and Duke University, respectively
- Safety endpoints are a critical concern, including AAV delivery and heart function. Trial measurements of efficacy might include exercise tolerance via change in oxygen consumption and mitochondrial functions (both are reduced in Barth syndrome) and MLCL:CL ratio (which is abnormal in Barth syndrome)

Ultimately, the success of gene therapy in Barth syndrome depends on many factors including clinical trial readiness of our community, continued communication among our research and clinical champions, and effective engagement of commercial and governmental partners that are critical to the funding and oversight of a potentially pivotal trial in Barth syndrome. Alongside the intrepid preclinical efforts of both our gene therapy teams, BSF will continue to build upon the 20+ years of science that have led to this promising inflection point for Barth gene replacement therapy.

To watch the full recording of the October 2020 gene therapy webinar visit BSF's Vimeo page at vimeo.com/barthsyndrome.

BSF 2021 Conference Update

The usually every two year Barth Syndrome International Scientific, Medical, and Family Conference has been a lifeline for our global community, bringing together families and experts from all corners of the world for a week of unity, solidarity, and sharing. As you well know, COVID-19 required us to host a virtual scientific symposium in July 2020. Now, after careful consideration and based on input from both medical experts as well as our community, we have had to make the **very difficult decision to convert the July 2021 Conference into a virtual event as well.**

Like many of you, we remain concerned that travel poses too great of a risk for our

immune-compromised population, and almost all of our international families have indicated that they will not be able to travel.

Beyond the significant health concerns, we also recognize that many are financially struggling given the challenges of this past year. Rather than let another year go by, we are excited to announce that BSF will host a virtual event designed to include as many people as possible from around the world to join in our mission.

Let us continue to “stay positive but test negative.”

Organizational Values

BSF values our global community and exists, first and foremost, to serve the ongoing needs of our affected individuals and their families regardless of race, age, gender, transplant status, geography, socioeconomic means or religious beliefs. We also value the opportunity to collaborate with scientists and physicians around the world and extend this commitment to them as well. Reflective of this, The BSF Board voted to add “inclusion” to one of BSF’s important value statements: “We will ensure that BSF means: Credibility, Integrity, Inclusion, Professionalism, and Compassion.”

As we continue to focus on advancing research that will lead to treatments for Barth syndrome, we believe that deliberately

adding this concept to our organizational values statements heightens our ability to be sensitive, responsive and respectful while we work together toward our unified mission.

We also have taken a critical step toward putting this approach into practice by establishing an Inclusion Committee that will focus on this issue throughout our programs and activities. Board member BJ Develle, LCSW, has been named Chair of the Inclusion Committee. He is working to help frame and launch this recently envisioned group.

We welcome suggestions as to specific actions BSF can undertake to ensure a more inclusive organization, and we thank BJ for leading this important initiative.

BSF Core Values

Credibility • Integrity • Inclusion • Compassion • Professionalism

Family Focus: Meet Aiden



Eight-year-old Aiden is an avid fan of the Harry Potter book series and aspires to live at Hogwarts. When he is not wizarding, Aiden enjoys playing cricket and football. His mom sees him as very independent as he “likes to do his own thing.”

Aiden is often described as being “magnetic” as people seem to be drawn to him. It might be partly due to his sense of humor and his mom confirms his ability to “make us laugh.”

Even though Aiden is living with Barth syndrome, he doesn’t let himself be confined by what he can’t do. “Every day is hard for a range of reasons,” his mom says. “Sometimes you see the reactions of his body language when he can’t do the same things as his older brother.” But at the end of the day, Aiden isn’t afraid. Even at his young age, he has developed a keen ability to read his own signals and adapt to his own limits.

Aiden’s mom reflects “Regardless of whether you have a child with Barth syndrome or not, you constantly worry. Raising a child is a complex jigsaw and with Aiden, Barth syndrome is just another piece we are trying to put in place.”

You can meet more of our community by visiting Barth Syndrome Foundation website located at www.barthsyndrome.org



YARR
Leadership Academy

Application open Jan 1st, 2021

Hearusyarr.org

The YARR Leadership Academy, provided by the EveryLife Foundation, is a series of on-line courses offered to a select group of young adults in the rare disease community (ages 18-29). Academy students will learn about the roles and opportunities for patient representation in policy making, drug development and the regulatory process and the steps it takes to get there.

Application Deadline: February 15, 2021

To apply, visit: www.hearusyarr.org

Q&A with Dr. Brian Feingold

Q: My son who does not have Barth syndrome has been confirmed to have COVID-19. He did run a fever and have symptoms but is now asymptomatic. He was planning to come home for a visit. The government guidance is generic. I am concerned about him coming home for a visit which would expose his brother who has BTHS and has been isolating since February 2020. Do you have any specific advice?

A: Even if the individual with BTHS is not extremely clinically vulnerable (i.e., not in heart failure and has not had a transplant), some added precautions and considerations may be helpful in addition to government guidelines. General guidance is that anyone should isolate for 14 days after having direct contact with someone known to have had COVID. In some cases, exposed persons may be directed to stop quarantining 1) after 10 days but continue to watch for symptoms or 2) after 7 days with a negative COVID-19 test. Individuals with COVID-19 (i.e., positive COVID-19 test or a known exposure and symptoms consistent with COVID-19), must isolate for at least 10 days and at least 24 hours after last fever. Out of an abundance of caution at the end of the isolation for the exposed brother:

- All in the home could maintain distance and wear masks, even when alone in shared spaces while indoors
- Limit contact/exposure by not eating at the same table
- Ensure good handwashing
- Spend time outdoors

Plus, for the exposed brother

- Wash clothes and linens separately from others in the home at 60° C /140°F or above
- If possible, remain in a minimum number of rooms to minimize risk to others in household

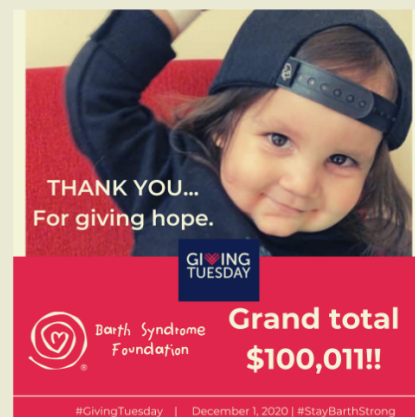
As always, it is very important to talk with the doctor who providing care for the individual who has Barth syndrome.

Dr. Brian Feingold is the Medical Director, Pediatric Heart Failure and Heart Transplant Programs, Children's Hospital of Pittsburgh, serves on the BSF Scientific and Medical Advisory Board and treats numerous patients with Barth syndrome.

GI[♥]INGTUESDAY 2020

BSF hits all-time record despite COVID-19!

We are so very proud and humbled by you, the global #BarthStrong BSF family!! The total funds raised on Giving Tuesday 2020 was over \$100,000, breaking every Giving Tuesday fundraising record of prior years! THANK YOU! Our gratitude goes out to every member of our community who helped to fundraise, our global affiliates, the Board of Directors and an anonymous donor who together provided a \$20,000 match, and this year's fundraising committee. Together we give hope to every person affected by Barth syndrome.



Volunteer Spotlight

Join us in honoring the individuals who tirelessly serve BSF behind the scenes in our new volunteer spotlight!

Lorna & Nigel

Please help us to recognize Nigel and Lorna from Barth Syndrome UK. Lorna and Nigel have been involved on the publications committee since 2005!

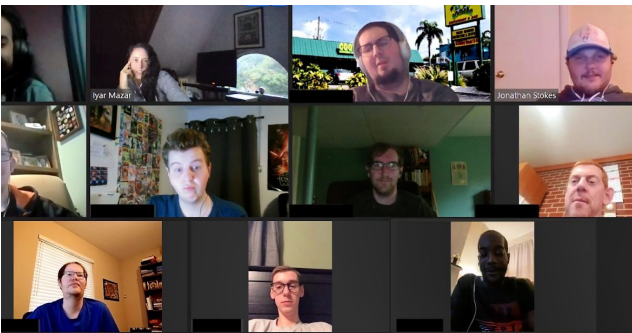
“The UK Barth syndrome family became our family. We are both retired now and we don’t do as much for Barth Syndrome Foundation but we have been moved by the Zoom meetings on Fridays. We admire the doctors and scientists and we are inspired by the tenacity of the parents,” said Lorna.



Lorna and Nigel

We appreciate you very much! Thank you for supporting BSF by sharing your time and talents for 15 years! #BarthStrong

Jon & Iyar

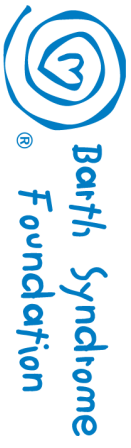


We would like to thank and recognize volunteers, Iyar Mazar, PhD and Jonathan Stokes, MBA!

Jon and Iyar were first introduced to our community when they were conducting patient-centered outcome research during the 2016 conference. At that point, they became a part of our Barth family.

Since then, they attended our 2018 conference as volunteers. Iyar’s Ph.D. dissertation from Boston College was about the chronic disease management of Barth syndrome. Then, Jon and Iyar led the charge to investigate the life experiences from the perspective of adults with Barth syndrome. They have been very generous and have contributed their expertise on patient-centered outcomes with numerous clinical researchers.

AND they have hosted bi-weekly calls for adults with Barth syndrome since early March of 2020. They have brought Barth syndrome to the attention of thought leaders in patient-centered research and are trusted allies to our cause.



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