

## Barth Syndrome, Arrhythmias, and Sudden Cardiac Death

Despite the documented and suspected cases of tragic sudden cardiac death due to arrhythmia experienced by our community, limited information is available about the risk factors that predispose an affected individual to these life-threatening events. Utilizing both the Barth Syndrome Patient Registry and on-site research projects conducted at our conferences, clinical champions like Dr. Carolyn Taylor (MUSC) and Dr. Randall Bryant (Sanger Heart & Vascular Institute) have tracked and published cases of arrhythmia and sudden cardiac death in affected individuals, pointing towards a risk associated between Barth syndrome, arrhythmias, and sudden cardiac death.

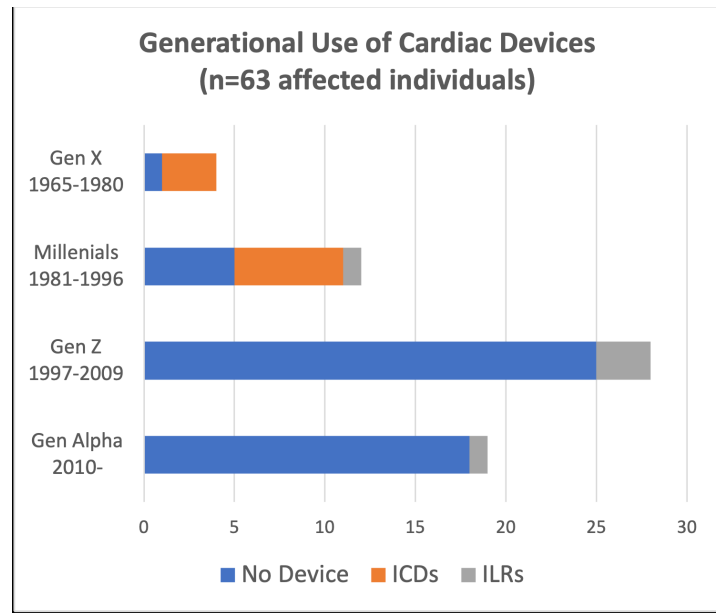
In recently published BSF-funded research, Dr. Bill Pu (BCH, SMAB member) and his research team documented and measured arrhythmias in the heart-specific TFAZZIN Knockout (CKO) mouse.

Dr. Pu reported that a subset of CKO mice presented with heart block, atrial tachycardia, and bidirectional ventricular tachycardia. To explore the mechanism behind these arrhythmias, Dr. Pu used induced pluripotent stem cells (iPS cells) to create heart cells (cardiomyocytes) and found that impaired calcium signaling and a subsequent decrease in the ability of Barth heart cells to contract contributed to this arrhythmia phenotype.

It was with this background and with the obvious unmet need in mind that BSF launched the Barth Heart Device Survey in February 2021 to better understand the use of devices such as internal cardiac defibrillators (ICDs) and implantable loop recorders (ILRs). The former serving to monitor and regulate heart rhythm when abnormal heartbeats are detected, and the latter conducts real-time, remote heart rhythm surveillance. With the participation

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of 63 affected individuals across the world, we have learned that nearly a quarter of respondents have some form of implanted cardiac device.

Nine individuals reported use of an ICD and generally were older affected individuals. The six reported users of ILRs, on the other hand, span affected individuals of ages 4-29 years old. Although age distribution differed in the two instances, interviews with families and affected individuals indicate that ICD and ILR use was either prescribed by a treating cardiologist or was a reaction to cases of sudden cardiac death by affected individuals in the community.

During our recently completed strategic plan, the BSF Board decided to prioritize our organizational efforts in several specific, well-considered areas in order to best advance our mission – one of which is improving clinical disease management. It is clear that arrhythmias are a significant and serious medical challenge faced by our community, and so we have selected this as our first clinical focus area to receive investment (meaning our time and money) during 2021. As a result, we have launched the BSF Arrhythmia Working Group, co-chaired by Dr. Brian Feingold

(U Pittsburgh, SMAB) and Dr. Colin Phoon (NYU), with members including Dr. Carolyn Taylor, Dr. Bill Pu, Dr. Reid Thompson (JHU/ KKI Barth Clinic), Dr. Reina Tan (NYU), and Dr. John Jefferies (UTHSC, SMAB). This all-star team of cardiologists and electrophysiologists will seek to develop a collaborative, multi-institutional effort to better understand and proactively address the unmet clinical need of arrhythmia risk in Barth syndrome.

**We heard you and now we need your continued participation to inform, guide, and drive this effort.**

Given the rarity of Barth syndrome and the geographical distribution of our community, we are issuing a call to action to our global community who have not yet, to participate in the multilingual Barth Heart Device Survey. By sharing your information and indicating your willingness to participate in research, the Arrhythmia Working Group can better determine the research approach that is both ideal and feasible to answer this unmet need. With your engagement, the entire Barth community can address this challenge together.

To participate, please visit: <https://qrco.de/bcNBux>



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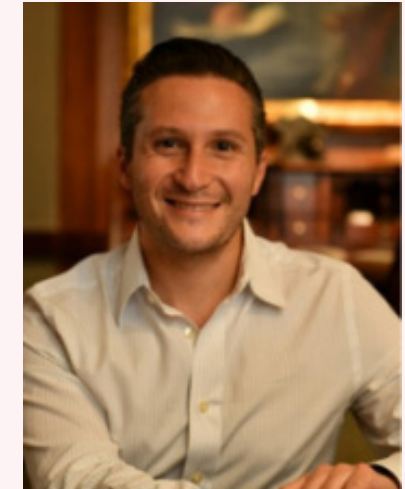
## COVID-19 Vaccine Antibody Response in Transplant Patients

Dr. Boyarsky joined a Barth Syndrome Foundation online forum on May 27th, 2021, to share published and preliminary results from his team's ongoing efforts at Johns Hopkins looking at the safety and immunogenicity (or how well an immune response is generated) of COVID vaccines in immunocompromised populations and solid organ transplant recipients.

This effort is of immense interest and value for the Barth and transplant communities as individuals with compromised immune systems were excluded in the mRNA vaccine trials. Furthermore, given the daily regimen of immune-suppressing drugs taken by our community of transplanted individuals, understanding the interplay of mRNA COVID vaccines and transplant status has long-term and real-time impact as we navigate our way through the pandemic. Dr. Boyarsky is an investigator in the National Vaccine Research Study for Transplant recipients being conducted by the Epidemiology Research Group in Organ Transplantation (ERGOT).

Under the mentorship of Dr. Dorry Segev, MD, PhD, Dr. Boyarsky and the Hopkins team had early hypothetical concerns that transplant recipients would not produce antibodies after getting the COVID vaccine. Utilizing social media to engage potential participants in December 2020, the team initiated a prospective study of solid organ transplant recipients in the US in order to evaluate safety and antibody response to the COVID vaccine, specifically monitoring local and systemic adverse effects, allergy, rejection, infections, and COVID-19 diagnosis.

Antibody testing is a surrogate measure of protection from COVID after getting the vaccine as it specifically tests for antibodies



Brian Boyarsky, MD, PhD

Dr. Boyarsky is a surgery resident at the Johns Hopkins University School of Medicine, Department of Surgery. He graduated with his medical degree at Rutgers Robert Wood Johnson Medical School and recently earned his PhD from the Johns Hopkins Bloomberg School of Public Health under the mentorship of Dorry L. Segev, MD, PhD.

to the COVID spike protein. The objective of the immune system after vaccination is to generate antibodies to the spike protein (this happens after natural infection as well). If you generate an antibody response, your antibodies will bind to the spike protein if the virus is introduced into the body thereby dampening and mitigating a potential infection.

In a novel approach not often used to facilitate a multi-center clinical study, social media was the primary driver in recruiting participants. Dr. Boyarsky and his colleagues successfully recruited study participants to provide data before and after vaccination

by mailing at-home blood collection kits or visiting local LabCorp sites. Using this safe and socially distanced method, antibody testing was conducted at baseline, between the first and second vaccination (in those who received Pfizer or Moderna) and then again at 1, 3, 6 and 12 months after the second dose.

Most transplant recipients voiced two primary concerns: is the vaccine safe, and is it effective? Dr. Boyarsky et al. first evaluated how safe vaccines were in this specific population, as published in *Transplantation* in April, 2021. From this study, most people had some sort of local reaction (redness, swelling) after the first dose, and increased systemic reactions (fatigue, fever, headache) after the second dose. No cases of COVID-19 occurred in the short interval following vaccination.

Immunogenicity, specifically measured by antibody response, of the first dose of the COVID-19 vaccine in transplanted individuals was described in the March 2021, *JAMA* publication. Dr. Boyarsky and his colleagues found vaccine antibody was detectable in only 20% of participants. It is surprising that these highly immunogenic vaccines that generate a robust immune response in healthy people provoke a dramatically decreased response in immunocompromised individuals.

Key determinants of a poor immune response:

- 10% of people who were on anti-metabolite medication developed no antibodies at all.
- Anti-metabolites are the most commonly prescribed immunosuppressive agents for transplant and include the commonly used drug mycophenolate (Cellcept). People on these agents had a 70% risk of developing decreased antibodies after the first dose.
- Older patients had a decreased risk for

developing antibodies  
Key determinants of a strong immune response:

- Receiving the Moderna shot resulted in greater likelihood of antibody response
- The further out from a transplantation, the better the immune response to vaccination

A subsequent *JAMA* publication in May 2021, described the average antibody response after the full vaccination series in transplant recipients.

Key findings include:

- Antibody was detectable in 57% of participants after the second dose (as compared to 100% in health people).
- The authors describe three phenotypes based on their data:
  - Non-responders, who have no immune response (43%),
  - Weak responders who have a little immune response, especially after the second dose, (40%)
  - Boosted responders, who respond positively to both doses (17%).
- Of the individuals shown to have impaired ability to generate a sufficiently robust immune response were patients on antimetabolite therapy. In particular, patients undergoing immune suppressive treatment with the antimetabolite belatacept were shown to have 94% reduction of response compared to an untreated individual.

Dr. Boyarsky et al further describe in another publication in *Transplantation* the effectiveness of antibody response in transplanted individuals who received the Johnson & Johnson single-dose vaccine. Comparing people who got the J&J shot to those who got an mRNA shot, those who got the J&J shot developed an even poorer response to vaccination. Only 20% of transplanted individuals who received the J&J vaccine developed antibodies compared to

56% of the mRNA group, and antibody levels were relatively low even among those who developed antibodies at all.

When evaluating immunogenicity in other immunocompromised populations, such as people with rheumatic and musculoskeletal diseases, the team found improvements compared to transplant patients. 74% of this group developed antibodies after the first dose. Consistent with findings from prior studies, anti-metabolites were still associated with decreased vaccine immune

response. Vaccines appear to be safe in these immunocompromised populations with antibody responses driven in large part by medications, specifically B-cell depleting agents that impact lymphocytes (rituximab and mycophenolate). Additional studies in teens and in children are forthcoming. The impact of this research described has influenced CDC guidelines and was featured in an NPR interview with Dr. Boyarsky's mentor, Dr. Dorry Segev.

[Watch the recording.](#)

## Webinar Q&A

### How are COVID vaccines working in transplanted individuals?

Anti-metabolite immunosuppression and older age are associated with decreased response to the vaccines; the Moderna vaccine and greater time since transplant are associated with an increased response.

### How should transplanted individuals use this information?

Get vaccinated and continue to practice caution similar to pre-vaccination. For individuals taking immunosuppressant medications, who have had transplant, and/or who have chronic immunosuppression, do not assume immunity after vaccination.

### How can the transplanted community use this information?

Despite the findings on a blunted immune response to the COVID-19 vaccine, Dr. Boyarsky and his colleagues strongly recommend that transplant patients and other immunocompromised populations still get vaccinated. They also strongly urge the social networks of these people to get vaccinated in order to provide some level of protection to their family members, friends, loved ones, etc.

### Should individuals test their own antibody levels?

The assays used in the study are approved but are largely used in research settings. Consequently, the recommendation from Johns Hopkins University, CDC and the national transplant organizations is to not get antibody tested after vaccination given we do not know what the exact antibody levels mean in an individual as opposed to looking at a large group of participants.

### What is the outlook for the transplanted community?

Additional research needs to be done evaluating booster doses, pausing immunosuppression therapies at the time vaccination, and observing longitudinal COVID infection rates in this population. While a 3rd dose is not readily available and cannot be given as part of this study, Boyarsky and his team are interested in observing individuals who do get a 3rd dose.

# Barth Syndrome Foundation and American Heart Association Collaborate

The Barth Syndrome Foundation (BSF) and the American Heart Association (AHA) have co-funded a first-ever, two-year postdoctoral fellowship to advance research around cardiac complications associated with Barth syndrome, a rare, life-threatening, mitochondrial disease. The AHA/BSF fellowship award goes to Dr. Nanami Senoo, a postdoctoral fellow and member of the Mitochondrial Phospholipid Research Center at Johns Hopkins University. Under the jointly funded fellowship, Dr. Senoo will explore the relationship between cardiolipin and the nucleotide transporter ANT1 and potential implications to individuals with Barth syndrome. This important collaboration between the AHA and BSF marks a strategic investment by BSF to broaden its impact by joining forces to accelerate progress through science and education.

Barth syndrome is a rare, X-linked, inborn error of metabolism characterized by cardiomyopathy, cardiolipin deficiency, musculoskeletal weakness, neutropenia, debilitating fatigue, growth delay, and hypoglycemia, among other clinical manifestations. The disease most commonly affects boys but has been reported in females and is associated with a genetic mutation in the TFAZZIN gene causing abnormal cardiolipin remodeling and impaired mitochondrial structure. As a result, over 70% of affected individuals with Barth syndrome present with cardiac complications. In fact, 17% of patients with Barth syndrome ultimately receive a heart transplant due to cardiac failure, and at least 13% are treated with internal pacemaker devices due to life-threatening arrhythmias. Advancing knowledge of cardiolipin's role in cardiomyopathies associated with Barth syndrome is one of several critical research pillars for BSF. In alignment with the broader collaborative

mission of AHA, cardiolipin abnormalities have been observed in other more common conditions including ischemia, congestive heart failure, and diabetes. "It is our goal that this effort advances Barth syndrome science while also serving as a collaborative template for other potential partners with shared clinical indications and research interests," says BSF's Director of Research Erik Lontok PhD.

Senoo will expand on the important role of cardiolipin in mitochondrial energy production by investigating the structural and mechanistic relationship between cardiolipin and the nucleotide transporter ANT1 in human cells. The AHA/BSF fellowship is designed to encourage early-career investigators to explore the underlying pathology of cardiomyopathy in Barth syndrome or involving cardiolipin. "As we serve an ultra-rare community heavily impacted by cardiomyopathy, this research collaboration is an opportunity to leverage the scale, expertise, and infrastructure of non-profit leaders like AHA," says Erik Lontok, "And Dr. Senoo's proposed work has the potential increase understanding of how cardiolipin functions in heart cells and answer whether ANT1 plays a role in Barth syndrome disease biology."

The fellowship was made possible by a newly launched funding program from BSF and the American Heart Association for investigator-initiated career development and knowledge discovery projects that directly involve Barth syndrome or cardiolipin research.

# Designing and Conducting a Clinical Trial for Barth Syndrome: the UK Experience

A recently published article from the University of Bristol (UK) CARDIOMAN clinical trial research team outlines the trial's overall protocol while highlighting its unique design with our affected individuals in mind.

To foster trial participation, the Bristol team addressed the geographical dispersion of our community by providing accommodation to families that lived far from the trial site, while responding to our community's voiced difficulty with pill-swallowing by commissioning the manufacturing of small tablets for the trial.

To conduct rigorous research, the Bristol team linked our affected individuals' past research participation and donated samples to the current trial, and importantly, will make accessible the anonymized dataset for future research uses.

Finally, to foster the best clinical care, the cardiologists and clinical care teams of heart transplanted individuals were consulted about study participation. In addition and of critical importance, both the participants and their local health care providers were provided with ways to unblind study medication in the case of an adverse event.

"The completion of such a challenging trial shows that careful multi-disciplinary planning, joint expertise of all team members, together with the unique and not often found engagement, enthusiasm and commitment of



**Dr. Guido Pieles**

Dr. Guido Pieles is a pediatric and adult congenital cardiologist with expertise in inherited cardiac conditions and sports and exercise cardiology.

the Barth families, patients and support group are key to patient centred high quality clinical research," says Dr. Guido Pieles, cardiologist at Bristol Heart Institute and the trial's principal investigator.

As our community awaits the published results the UK-based CARDIOMAN clinical trial in affected individuals with Barth syndrome, we are proud to support and showcase the collaborative outcome of the Bristol Trials Centre and Barth Syndrome UK.

## BSF Core Values

**Credibility • Integrity • Inclusion • Compassion • Professionalism**

# Advocacy: The BENEFIT Act

The U.S. Congress and the Food and Drug Administration (FDA) have made considerable progress in driving forward policies and procedures to ensure the patient perspective is considered by FDA reviewers evaluating candidate drugs and other medical products. As a result of numerous provisions of both the Prescription Drug User Fee Act (PDUFA) of 2012, Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012, and the 21st Century Cures Act in 2016, the FDA now has programs and policies in place to evaluate the benefits and risks of potential therapies and to gather and assess patient perspectives.

But while much progress has been made, some significant gaps remain. One such gap is the lack of any requirement in law today that the FDA include patient experience or patient-focused drug development (PFDD) data as a part of its risk-benefit framework. This means that the agency's signature tool for evaluating risk-benefit does not have to include data from the patient perspective that could be critical to informing the agency's evaluation and, ultimately, decision on whether or not to approve a product.

The Better Empowerment Now to Enhance Framework and Improve Treatments (BENEFIT) Act will amend the Food, Drug and Cosmetic Act (FDCA) to ensure that patient experience,

PFDD and related data – including information developed by a product sponsor or a third party such as a patient advocacy organization or academic institution – be considered as part of the risk-benefit assessment. This action will send an important signal to all stakeholders that patient experience and PFDD data will be fully incorporated into the agency's review process and will encourage such entities to develop scientifically rigorous and meaningful tools and data. The BENEFIT Act will also enhance an important transparency and accountability provision included in the 21st Century Cures Act by requiring the FDA to share how such patient experience and PFDD data was considered within the risk-benefit assessment for any approved therapies. This will provide additional learnings to all stakeholders, particularly patients, and help further refine and develop such tools going forward.

The nascent field of patient engagement in drug development is flourishing thanks to ongoing interest and focus by Congress. The BENEFIT Act will continue this evolution by filling a sizeable gap by ensuring such data is fully considered as part of the FDA's risk-benefit assessment for any new products.

**To learn more about the BENEFIT Act and other important legislation, visit:**  
[www.barthsyndrome.org/advocacy](http://www.barthsyndrome.org/advocacy)



SCAN ME

# Meet The Community: Luke



**How old are you now, Luke?**  
I'm fifteen.

**What is school like for you when you aren't on break for the summer?**  
I was homeschooled and really liked it but then I started attending a private school, and I really liked that. This past year I had to go back to being homeschooled due to COVID-19 and didn't like it as much. I'm hoping I can go back to the private school in the fall of 2021.

I really miss being around other people and having other people my age that I can talk with. I really haven't kept up with my friends through all of this.

**What have you done to socialize with others in place of school?**

I've attended the meetups that BSF offers. I have really enjoyed that a lot. It's been nice to connect with other people my age. It's also nice to connect with other people my age who have Barth syndrome.

**Have you met anyone who has Barth syndrome in person yet?**

I went to Baltimore to the Barth syndrome clinic. It was a long journey because we drove all the way from Memphis to Baltimore. I look forward to attending the conference in 2022.

**Do you have any hobbies?**

I play video games. I don't really play board games. I like to fidget with building things like K'NEX and jigsaw puzzles. I don't really enjoy reading. My sister loves reading. I don't know how she does it.

**Is there a place you enjoy going for entertainment?**

If I could go somewhere right now, I would really like to go to an arcade like Dave and Busters. I also enjoy a theme park that is nearby called Magic Springs. It's awesome. They have some cool roller coasters like the Gauntlet and the X Coaster. One day I would love to ride SAW. It's a roller coaster at Thorpe Park in England. It looks fun. They also have another roller coaster in England called the Smiler. It has 14 inversions!

**What are your favorite foods?**

I consider myself to be a foodie. I'm interested in all kinds of foods. I like Mexican food. Sometimes I like spicy foods, sometimes not. I love all kinds of food. It would be fun if we could all make a meal

# Meet the Community (cont.)

together because it seems like we all seem to have an interest in cooking, but we live too far away from each other.

## Do you bake?

No, but my mom does. She has her own baking business. We really like it when an order falls through because we get to eat the cakes and cookies that she made that didn't get picked up. She has a gift, that's for sure. I'm serious, you will not have a better cake than the ones my mom makes. They are out of this world.

## Did you see any sights while you were in Baltimore?

Yes, we stopped to see a cave on the way. I didn't like that so much. It wasn't bad going down, but it was hard coming back out. I just get exhausted when I walk too far. I must

stop. My legs won't move, my legs cramp and I get out of breath. For a long time, my parents thought I had asthma before I got the diagnosis of Barth syndrome last year.

We are hoping to come to the conference. We will probably stay in the camper. I will say that having a camper has made me appreciate how big my room is.

## What was it like for you when you received the Barth syndrome diagnosis?

It was kind of a shock to learn I had Barth syndrome because I had never heard about it before. I didn't know anything about it. It was also a relief to know what I had. The best part is I've met a lot of nice people that are a lot like me since the diagnosis. I didn't have that before the diagnosis.

# Zooming in the Sunshine



BSF, in partnership with Project Sunshine, is offering a unique opportunity to the Barth syndrome community. Project Sunshine's mission is simple: Bringing joy and play to pediatric patients. On July 26th, we launched the Project Sunshine Teleplay program for our younger affected individuals and siblings, with 15 youth in attendance. Teleplay offers engaging and educational virtual play in a group setting that is tailored to multiple age groups.

Activities include trivia, story-driven games, and imaginative cooperation. Project Sunshine recruits and trains volunteers – community members, college students, corporations, and youth – to deliver these activities. Their programs promote creative expression, socialization, and learning. Most of all, they let young patients act and feel like kids or teens during emotionally and physically challenging times.

Teleplay for the BSF community is every Thursday at 5:00pm EST, alternating weeks between affected individuals and siblings. To register for a session, visit the BSF calendar at [www.barthsyndrome.org/calendar](http://www.barthsyndrome.org/calendar)



SCAN ME

# Volunteer Spotlight

Please join us in honoring (and congratulating!) BSF's longtime volunteer, Megan King Branagh and her family (including their newest addition, Georgie)!

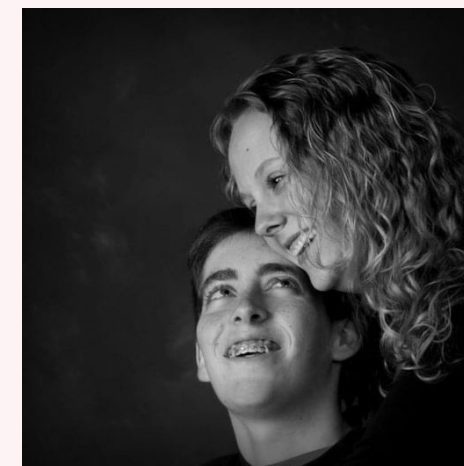
Megan began volunteering just 4 years ago in honor of her son, Henry who lives with Barth syndrome.



"Within the small community of a rare disease, there is no time to wait around for someone else to do it. As soon as we received our Barth diagnosis, I had a strong urge to do all that I could to make a difference, not only in Henry's life, but in all others affected. In volunteering for BSF, I have found that I truly believe in BSF's mission and respect the organization and those involved tremendously, which makes volunteering that much easier."

Megan serves on the BSF Board and the fundraising committee and hosts a grassroots fundraiser, Happy Heart Week each May. Like most of us, Megan misses the meaningful moments at conference.

Congratulations on your newest addition, and thank you Megan and family for all that you do for BSF!



"The families that I've gotten to know through BSF have become part of a larger extended family for me. And I've loved watching the younger siblings grow up and being like a big sister to them!"  
Meet Alanna Boozer, a valuable BSF volunteer!

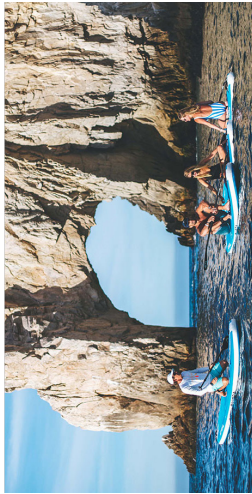
Alanna has volunteered with the Barth Syndrome Foundation in some capacity since its founding. She says, "I volunteer because I believe in the work that the Foundation is doing and because this organization has meant so much to me and to my family. My brothers may no longer directly benefit from this group, but I still do. I didn't know any other Barth siblings or families when I was growing up, which felt kind of isolating. Having these connections as an adult has really been priceless."

Thank you, Alanna, for your years of service and support of BSF!



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