THE JOHNS HOPKINS ARRHYTHMOGENIC CARDIOMYOPATHY (ARVC/ALVC/ACM) PRECISION MEDICINE CENTER OF EXCELLENCE

Summer 2024 *Volume 14, Issue 2*

WHAT'S INSIDE:

OUR GOALS

Established in 1999, the ARVC program has 3 main goals:

- **EDUCATION OF PATIENTS AND PHYSICIANS** (newsletter, annual conference, arvd.com, publications, presenting at national conferences.)
- **FACILITATE THE EVALUATION AND MANAGEMENT OF PATIENTS WITH KNOWN OR SUSPECTED ARVC** (cardiac evaluations, genetic testing, genetic counselor / electrophysiologist / heart failure consultations)
- **PROVIDE NEW KNOWLEDGE ABOUT ARVC** (collaborative research and publications)

SEMINAR REVIEW

Happy Summer from the Johns Hopkins ARVC Program!! We're excited to present updates since our last issue this past Winter. We are excited to share that we hosted our first hybrid seminar on April 27th, 2024, offering both an in-person program with an option to watch the presentations via livestream for those unable to travel. We had over 150 attendees join us in-person and an additional 230 viewed the livestream. We enjoyed seeing many old faces and it was great to meet so many new families. We, of course, reviewed ARVC diagnosis, genetics, and management, but had focused presentations on Desmoplakin Cardiomyopathy, heart failure and transplant, as well as featured presentations by Sam Sears and Andre LaGerche. Each of our research fellows also presented on the projects they've been working on. Once again, several industry representatives were in attendance to answer questions about their gene therapy focused trials. Many companies are interested in learning more about ARVC caused by PKP2 pathogenic variants and apply gene therapy techniques as a potential therapy.

The agenda was packed with presentations by the Johns Hopkins staff: Hugh Calkins, MD (The Johns Hopkins ARVC Program); Brittney Murray, MS (Back to Basics and Living Life with ARVC); Oliver Monfredi, MD (Understanding Your ICD); Andreas Barth, MD, PhD (Gene Therapy in ARVC); Nisha Gilotra, MD (Heart Failure in ARVC: Symptoms, Treatments and Trajectories); Steven Muller, MD (Family Screening for PKP2-associated ARVC); Babken Asatryan, MD, PhD (Evaluation of the Role of the 2010 TFC Family History Criterion for ARVC Diagnosis); Rick Carrick, MD, PhD (Gene-Specific Risk Score for DSP-Cardiomyopathy); Alessio Gasperetti, MD, PhD (Myocarditis in DSP-Cardiomyopathy); and Cindy James, PhD (Research Directions in ARVC); as well as two invited speakers: Sam Sears, PhD (ARVC 2024: Confronting Anxiety) and Andre LaGerche, MBBS, PhD (Same Genes, Different Beast: Athletes, Arrhythmias and Lessons to Learn).

The afternoon session offered research opportunities, a Question and Answer session, a Desmoplakin-specific small group discussion, as well as one for those under 30 years of age. Thank you to everyone who participated in our research studies! We collected over 40 blood samples for a particular research project.

Thank you to everyone who attended this year's seminar. It was amazing and so great to see everyone in-person. Many of the presentations will also be posted on our website in late July/early August, www.ARVD.com.

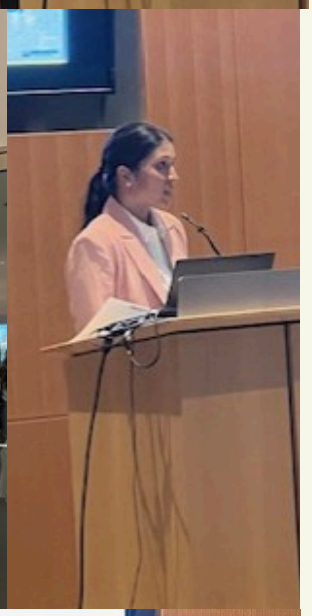
Watch on Demand here: **https://tinyurl.com/ARVC2024Seminar**

~ The ARVD/C Program
Hugh Calkins, MD
Cindy James, PhD
Brittney Murray, MS
Crystal Tichnell, MGC, RN

Family Seminar
SAVE THE DATE!!!
April 5th, 2025

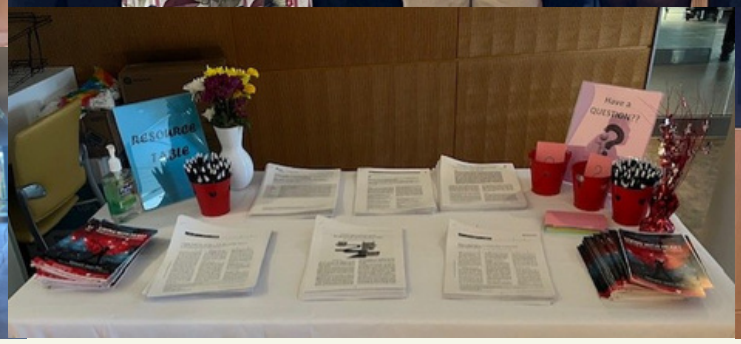





Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) Program
PATIENT AND FAMILY SEMINAR
THE JOHNS HOPKINS HOSPITAL
Meet, network, and learn the latest advances in ARVC



Courage Community
Courage Community ARVD.com

SADS FOUNDATION
SADS FOUNDATION
StopSADS.org



RESOURCE TABLE
Have a QUESTION??

Family Screening in PKP2

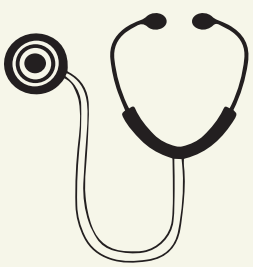
CLINICAL SERVICES AT JOHNS HOPKINS

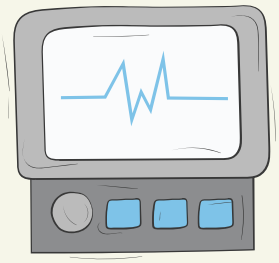
The Johns Hopkins Arrhythmogenic Cardiomyopathy Program provides a variety of clinical services. We see patients for second opinion consultations to discuss diagnosis and management, genetic counseling and testing, routine ICD management and family member screening. We can also arrange concurrent cardiac testing.

New patients are seen in consultation with Dr. Hugh Calkins and our clinical genetic counselor, Brittney Murray, to discuss test results, family history, and to provide guidance regarding further management. We see all of our patients for genetic counseling to discuss the diagnosis, the psychosocial impact of living with ARVD/C and with an ICD, as well as to discuss the benefits and limitations of appropriate genetic testing. In selected cases, we also offer catheter ablation as a treatment for difficult to manage ventricular tachycardia with Dr. Konstantinos Aronis and Dr. Jonathan Chrispin. Appointments with our heart failure specialist, Dr. Nisha Gilotra, can also be arranged. All appointments are billed to your health insurance.

With the COVID-19 pandemic becoming less of an impact, licensure waivers have ended. This means we are no longer able to offer telemedicine appointments with our physicians. However, there may be some flexibility with our genetic counseling ONLY visits to be able to continue to offer this option. Please reach out to Crystal to see if you are eligible for a telemedicine appointment based on your appointment needs and physical location. Remember, even if your condition is stable, you should be checking in at least once every two years with repeat cardiac evaluations. It is best to respond to early changes in your health, rather than react to an urgent situation.

To schedule an appointment, contact Crystal at ctichnell@jhmi.edu or 410-955-7292.

HEART RHYTHM 2024 UPDATE

Boston, Massachusetts

The Heart Rhythm (HRS) Society hosted its annual meeting in New Orleans this past May and is the largest gathering of heart rhythm professionals from around the world. Several members of our team presented on ARVC and are listed below. It was great to catch up with past fellows and collaborators as well.

- Babken Asatryan: ***Cardiovascular Genomics Boot Camp***
- Hugh Calkins: ***ECG Interpretation - ARVC***
- Richard Carrick: ***Improved diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC) using electrocardiographic (ECG) deep-learning (DL)***
- Alessio Gasperetti: ***Clinical Features and Outcomes of 815 Patients Harboring Desmoplakin Pathogenic Variants: Gene-specific Evaluation of a Distinct Clinical Entity***
- Alessio Gasperetti: ***Flecainide as an anti-arrhythmic in arrhythmogenic right ventricular cardiomyopathy (ARVC)***
- Alan Jacobsen: ***Exercise is not associated with clinical onset of cardiomyopathy or increased risk of sustained ventricular arrhythmias in patients with pathogenic desmoplakin (DSP) variants***
- Cynthia James: ***The Nuts and Bolts of Cardiogenetics session***
- Steven Muller: ***Gene-specific Plakophilin-2 Family Screening for Arrhythmogenic Right Ventricular Cardiomyopathy***
- Brittney Murray: ***Genetic Counseling and Selecting the Correct Panel--Is less more?***
- Brittney Murray: ***Who is Eligible for Gene Therapy?***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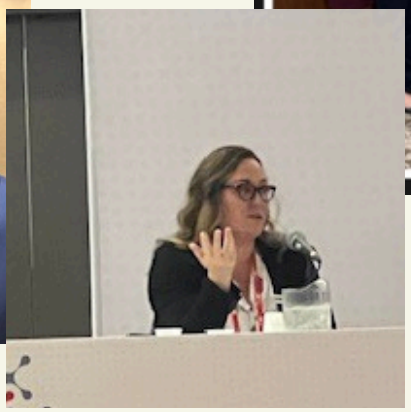
HEART RHYTHM

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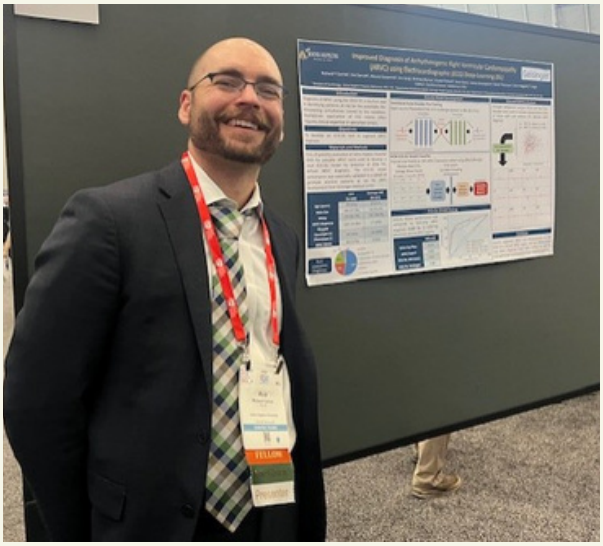
HEART RHYTHM


HRS 2024

Poster Presentations at HRS



Improved Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) using Electrocardiographic (ECG) Deep-Learning (DL)

Richard T Carrick, Eric Carruth, Alessio Gasperetti, Eric Sung, Brittney Murray, Crystal Tichnell, Sean Gaine, James Sampognaro, David Thiemann, Chris Haggerty, Hugh Calkins, Cynthia A James, Katherine C Wu

The goal of this project was to develop an ECG-DL tool to augment ARVC diagnosis. ECGs of patients evaluated at Johns Hopkins Hospital (JHH) for possible ARVC were used to develop a novel ECG-DL model for detection of 2010 TFC defined ARVC diagnosis. The ECG-DL model performance was externally validated in a cohort of genotype positive patients at risk for ARVC development from Geisinger Medical Center. In conclusion, ECG-DL augments ARVC ECG interpretation to the level of a clinical ARVC expert, and can differentiate true ARVC diagnosis from ARVC mimics as well as from genotype-positive/phenotype-negative patients.

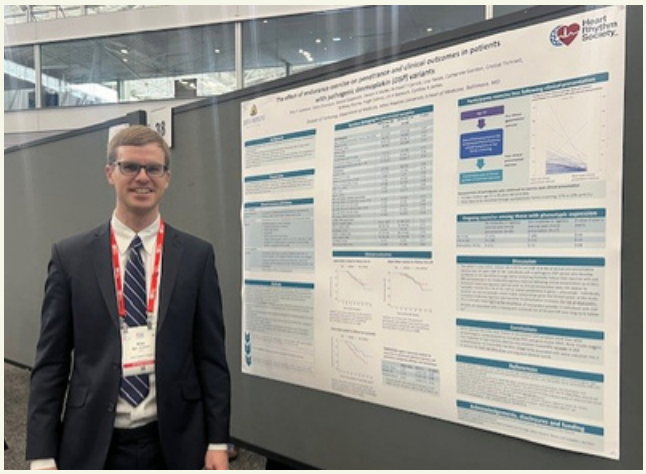
Desmoplakin, Exercise and Ventricular Arrhythmias

Alan Jacobsen, Katia Chiampas, Alessio Gasperetti, Lisa Yanek, Catherine Gordon, Crystal Tichnell, Brittney Murray, Hugh Calkins, Lili Barouch, Cythia James.

The goal of this study was to evaluate the role of exercise in those with a DSP mutation. Individuals with a DSP mutation (N=95) were interviewed about their physical activity. Lifetime moderate and vigorous physical exercise was expressed in metabolic equivalent hours per week (METhr/wk) and the relationship with sustained VA studied.

The median exercise dose until age of presentation was 27.3 METhr/Wk (interquartile range (IQR) 14.9-46.8) over 23.9 years (IQR 14.9-36.1). Seventy participants exhibited phenotypic penetrance at presentation, and 28 VA events occurred. By survival analysis, athletes were not at increased risk of VA compared with nonathletes (Figure, p=0.18). Myocardial injury, was more likely among athletes [HR 2.7 (95% CI 1.20-6.21)] and was associated with an elevated risk of both VA and HF thereafter.

Higher levels of endurance exercise may promote progression of DSP cardiomyopathy. This study aids shared decision-making discussions regarding exercise for individuals with pathogenic DSP variants, particularly among those without phenotypic expression.



STAFF UPDATES

Congratulations to Emily Graham, our genetic counseling assistant, and Catherine Gordon, our research program coordinator as they begin their new chapter pursuing their master's in genetic counseling. Both Emily and Catherine were with the ARVC program for 3 years and will be missed immensely! This Fall, Emily will be continuing her education at the JHU/NIH Genetic Counseling Program and Catherine will be at Thomas Jefferson University. We wish them both the best!

2024 International SADS Foundation Family Conference

Friday, November 8th and Saturday, November 9th, 2024
Lurie Children's Hospital
225 E Chicago Ave, Chicago, IL 60611

People living with SADS conditions, and their families, will have an opportunity to learn from the country's top medical experts, hear about the latest research, and connect with others on the same journey.

Healthcare Professionals: on Friday, November 8th there will be a one-day course for healthcare professionals that will focus on inherited arrhythmogenic diseases and cardiomyopathies that can cause sudden death.

Kids/Teens Program

- Kids, you can ask experts YOUR questions
- Meet other kids with a SADS condition (your siblings can also come)
- Games, activities, and lots of fun!

Registration rates:
Adults Early Registration* $125 (on or before Friday, Sept. 13)
Registration = $150

Kids/Teens (ages 8-17) Early Registration* $50 (on or before Friday, Sept. 13)
Registration = $75
**Family discount (2 adults + 2 kids): One kid free.

Become a SADS Monthly Sustainer and receive $25 off individual registration fees. Please contact us at 801-272-3023 or email erin@sads.org for additional details.

A limited number of financial scholarships are available. Please contact erin@sads.org for more information.

https://sads.org/get-involved/annual-conference/2024-international-conference/
for more information

RESEARCH OPPORTUNITIES

Clinical and Genetic Investigations of Right Ventricular Dysplasia (ARVD/C Registry)

This registry is the heart of our program and from which all of our research projects originate. This means eligibility for future clinical trials, including gene therapy, will require enrollment in our registry. You do not need to be a patient followed at Johns Hopkins to participate in our registry. Both children and adults either diagnosed with ARVC or a family member of someone diagnosed with ARVC are eligible to participate. Participation involves submission of past medical records and continued followup for at least 5 years (we will offer renewal for continued participation). A DNA sample may be collected for specific projects.

Reach out to Crystal at 410.502.7161 or ctichnell@jhmi.edu to join.

Seroprevalence Study of Pre-existing Antibodies against Adenovirus-Associated Virus Vector (AAV) in Patients with Plakophilin 2 (PKP2)-associated Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

This research study is sponsored by Tenaya Therapeutics, Inc. Eligible candidates will be invited to participate during their regular clinic appointment. The purpose of this study is to assess the prevalence of pre-existing antibodies against the AAV vector and to collect information about patients with PKP2 arrhythmogenic right ventricular cardiomyopathy (ARVC). Initial eligibility criteria include meeting definite task force criteria with a PKP2 pathogenic variant, being 18-65 years of age, and having a functioning implantable cardioverter-defibrillator (ICD). Participation involves donating a blood sample, completing quality of life questionnaires, and following up annually for 5 years. We will collect information from your existing medical records as well to help the sponsor learn about the natural history of ARVC.

A Cross-Sectional Observational Study to Assess Real-world Patient Characteristics, Clinical Course, and Treatment Patterns for Symptomatic Patients with Arrhythmogenic Cardiomyopathy (ACM) due To a Plakophilin-2 Pathogenic Variant (PKP2) [SNAPSHOT PKP2]

This research study is sponsored by LEXEO Therapeutics, Inc. Eligible candidates will be invited to participate during their regular clinic appointment. The is a 2-part observational research study: 1. A retrospective review of your medical records for the past 2 years and 2. A 1 year continuous prospective study where you will be asked to wear a 7-day heart monitor at the start and end of the study, as well as answer study questionnaires about your symptoms.

Stay Tuned for More Opportunities

FEATURED MANUSCRIPTS

Long-Term Arrhythmic Follow-Up and Risk Stratification of Patients With Desmoplakin-Associated Arrhythmogenic Right Ventricular Cardiomyopathy

JACC Adv. 2024 Feb 2;3(3):100832. doi: 10.1016/j.jacadv.2024.100832. eCollection 2024 Mar.

Alessio Gasperetti, Richard Carrick, Alexandros Protonotarios, Mikael Laredo, Iris van der Schaaf, Petros Syrris, Brittney Murray, Crystal Tichnell, Chiara Cappelletto, Marta Gigli, Kristen Medo, Peter Crabtree, Ardan M Saguner, Firat Duru, Robyn Hylind, Dominic Abrams, Neal K Lakdawala, Charles Massie, Julia Cadrin-Tourigny, Mattia Targetti, Iacopo Olivotto, Maddalena Graziosi, Moniek Cox, Elena Biagini, Philippe Charron, Michela Casella, Claudio Tondo, Momina Yazdani, James S Ware, Sanjay Prasad, Leonardo Calò, Eric Smith, Adam Helms, Sophie Hespe, Jodie Ingles, Harikrishna Tandri, Flavie Ader, Luisa Mestroni, Arthur Wilde, Marco Merlo, Estelle Gandjbakhch, Hugh Calkins, Anneline S J M Te Riele, J Peter van Tintelen, Perry Elliot, Cynthia A James

The purpose of this study was to characterize arrhythmic outcomes and to test the performance of the recently validated ARVC risk calculator in patients with DSP likely pathogenic/pathogenic variants fulfilling definite 2010 ARVC Task Force Criteria (DSP-TFC+).

Methods: DSP-TFC+ patients were enrolled from 20 institutions across 3 continents. Ventricular arrhythmias (VA), defined as a composite of sustained ventricular tachycardia (VT), appropriate implantable cardioverter defibrillator therapies, and ventricular fibrillation/sudden cardiac death events in follow-up, were reported as the primary outcome. We tested the performance of the ARVC risk calculator for VA prediction, reporting c-statistics.

Results: Among 252 DSP-TFC+ patients (age 39.6 ± 16.9 years, 35.3% male), 94 (37.3%) experienced VA over 44.5 [IQR: 19.6-78.3] months. Patients with left ventricle involvement (n = 194) were at higher VA risk (log-rank P = 0.0239). History of nonsustained VT (aHR 2.097; P = 0.004) showed the strongest association with VA occurrence during the first 5-year follow-up. Neither age (P = 0.723) nor male sex (P = 0.200) was associated with VAs at follow-up. In 204 patients without VA at diagnosis, incident VA rate was high (32.8%; 7.37%/y). The ARVC risk calculator performed poorly overall (c-statistic 0.604 [0.594-0.614]) and very poorly in patients with left ventricular disease (c-statistic 0.558 [0.556-0.560]).

Conclusions: DSP-TFC+ patients are at substantial risk for VAs. The ARVC risk calculator performs poorly in DSP-TFC+ patients suggesting need for a gene-specific risk algorithm. Meanwhile, DSP-TFC+ patients with nonsustained VT should be considered as high-risk.

Characterizing Decision-Making Surrounding Exercise in ARVC: Analysis of Decisional Conflict, Decisional Regret, and Shared Decision-Making

Circ Genom Precis Med. 2023 Dec;16(6):e004133. doi: 10.1161/CIRCGEN.123.004133. Epub 2023 Nov 28.

Jessica Sweeney, Crystal Tichnell, Susan Christian, Catherine Pendelton, Brittney Murray, Debra L Roter, Leila Jamal, Hugh Calkins, Cynthia A James

Background: Limiting high-intensity exercise is recommended for patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) due to its association with penetrance, arrhythmias, and structural progression. Guidelines recommend shared decision-making (SDM) for exercise level, but there is little evidence regarding its impact. Therefore, we sought to evaluate the extent and implications of SDM for exercise, decisional conflict, and decisional regret in patients with ARVC and at-risk relatives.

Methods: Adults diagnosed with ARVC or with positive genetic testing enrolled in the Johns Hopkins ARVC Registry were invited to complete a questionnaire that included exercise history and current exercise, SDM (SDM-Q-9), decisional conflict, and decisional regret.

Results: The response rate was 64.8%. Two-thirds of participants (68.0%, n=121) reported clinically significant decisional conflict regarding exercise at diagnosis/genetic testing (DCS [decisional conflict scale]≥25), and half (55.1%, n=98) in the past year. Prevalence of decisional regret was also high with 55.3% (n=99) reporting moderate to severe decisional regret (DRS [decisional regret scale]≥25). The extent of SDM was highly variable ranging from no (0) to perfect (100) SDM (mean, 59.6±25.0). Those diagnosed in adolescence (≤age 21) reported significantly more SDM (P=0.013). Importantly, SDM was associated with less decisional conflict (ß=-0.66, R2=0.567, P<0.01) and decisional regret (ß=-0.37, R2=0.180, P<0.001) and no difference in vigorous intensity aerobic exercise in the 6 months after diagnosis/genetic testing or the past year (P=0.56; P=0.34, respectively).

Conclusions: SDM is associated with lower decisional conflict and decisional regret; and no difference in postdiagnosis exercise. Our data thus support SDM as the preferred model for exercise discussions for ARVC.

ARVC PROGRAM INFO

ARVC Program Staff

Hugh Calkins, MD—Director
Konstantinos Aronis, MD—Ablation
Jonathan Chrispin, MD—Ablation
Nisha Gilotra, MD—Heart Failure
Caridad de la Uz, MD—Pediatrics
Stefan Zimmerman, MD—MR Imaging
Allison Hays, MD—Echo Imaging
Cynthia James, ScM, PhD—Genetic Counselor
Brittney Murray, MS—Genetic Counselor
Crystal Tichnell, MGC, RN—Genetic Counselor, Nurse
Anna Nelson—Genetic Counselor Assistant
Christal Holmes-Igwebike—Clinic Coordinator
Catherine Pendleton—Research Program Coordinator
Leonore Okwara – Research Program Manager
Alessio Gasperetti—Research Fellow
Babken Asatryan—Research Fellow
Steven Muller—Research Fellow

Contact Us

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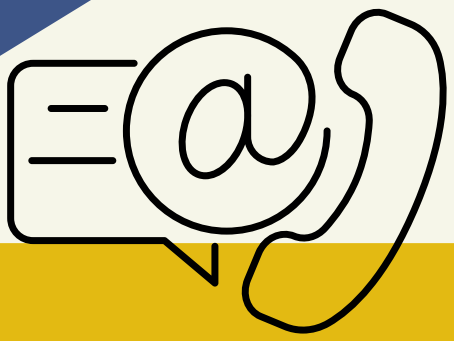
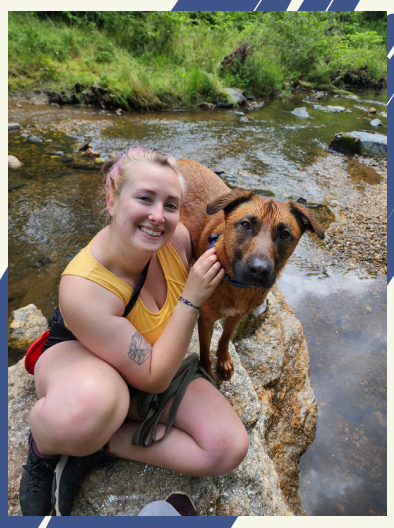
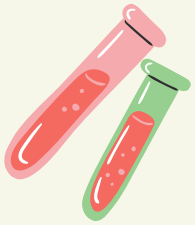


Meet Anna Nelson



Anna Nelson joined the team in June as our genetic counseling assistant, replacing Emily Graham. Anna attended NC State University and graduated with bachelor's degrees in both Genetics and Conservation Biology. She then worked as a research technician in the Veterinary Cardiac Genetics Lab at NC State's College of Veterinary Medicine. While at the vet school she conducted research on dogs and cats with various cardiac diseases including but not limited to ARVC, HCM and PDA, and ran a genetic testing service for breed specific variants. She then moved to Baltimore and worked as a Therapist Assistant at Maryland Addiction Recovery Center where she practiced crisis intervention and patient de-escalation in a clinical setting. She plans to receive her Master's in Genetic Counseling and is looking forward to all she will learn in her new position here at JHU!

Anna will be taking over for Emily Graham as of August 1; her email is anelso84@jh.edu, so update your address books!



Gene Therapy Clinical Trials

The first in human gene therapy clinical trials are currently enrolling. As you consider the question of whether you should participate, an even earlier question concerns whether you meet the strict entry criteria for the study. Gene therapy trials soon to be enrolling are relevant only to patients with a PKP2 pathogenic variant who have an ICD in place. There are many other inclusion/exclusion criteria as well that you will need to meet prior to being considered a candidate, and these may vary between trials. It is appropriate to weigh options between trials as you decide if participation is right for you.

Assuming you meet enrollment criteria the next question concerns whether you should participate. Participation in any study is a personal decision and participation in an early phase "first in man" gene therapy trial is a big decision. Before enrolling in a gene therapy trial, you should have a good understanding of the goals of the study and take into consideration what the expectations are of you, and what the risks and benefits of the study are before you agree to participate. Gene therapy trials will have strict protocols and it will be very important for you to be able to adhere to them. Participation is not for everyone, and that's okay. Each individual has different experiences/circumstances, including varying degrees of symptoms, medications and subsequent side effects, ICD shocks, catheter ablation procedures, etc. that play into how significantly ARVC has impacted their life. Each individual also has different tolerances for risk and different motivations for their decision to participate in the early phase gene therapy trial. In addition to learning about the risks and potential benefits of a clinical trial, other things to consider/questions you should ask include:

- Can I be screened for the clinical trial prior to traveling to an enrolling center?
- If I am interested and am a candidate for the clinical trial, can I review a copy of the consent form prior to traveling to an enrolling center?
- What experience does the enrolling center have in managing adult ARVC patients?
- What is expected of me as a participant?
- Are my travel and hotel expenses covered by the study?
- What are my out-of-pocket expenses to participate in the study?
- How long do I remain at the study site after infusion of the study drug?
- How many times do I need to travel to the enrolling center site for follow up?
- What tests and/or procedures do I need to undertake as a participant in the clinical trial?
- How long will I be in the study?
- Will I need to change my management to participate?
- What lifestyle changes do I need to consider?
- What are the risks of using Adeno-associated viral (AAV) vectors?
- What are the risks of participation in the trial?
- What are the potential benefits to me and to others for participating in the clinical trial?
- What happens if the company funding the clinical trial goes out of business while I am enrolled?
- Will I be able to continue to see my primary ARVC providers if I happen to have VT in the follow up phase or do I need to be seen at the study site where I enrolled in the clinical trial?
- Has this gene therapy company had experience with prior gene therapy trials for heart disease? If so, how did patients who received gene therapy do?

We hope this information is helpful as we navigate these new opportunities together. We look forward to our involvement as an enrolling center in the coming months.

Please visit ClinicalTrials.gov for a list of active clinical trials and locations.

Support of the Johns Hopkins ARVC Program Ensures Success

As a charitable, tax-exempt organization, Johns Hopkins Medicine relies on donations to make a difference in the lives of our patients. Supporters of Dr. Calkins and the team of experts in the ARVC Program are partners in the mission to provide exceptional personalized care, discover better ways to diagnose and treat our patients, and provide educational and training programs for medical professionals, patients, and families. Here are some of the ways that you can help:

Make a Personal Donation

Donations of all sizes, one-time or recurring, make a difference. There are a variety of ways to make a gift to support efforts in the ARVC Program:

- Make an outright gift of cash or securities
- Become a monthly donor
- Give in honor or in memory of a loved one
- Give through IRAs, wills and trusts
- Leverage workplace matching gift programs

To make a gift by credit card, visit our online giving form via the QR code

To make a gift by mail, please make a check payable to Johns Hopkins Medicine and indicate the "ARVC Program" on the memo line. Mail to:

Johns Hopkins University and Medicine
Attn: Heart and Vascular Institute
PO Box 49143
Baltimore, MD 21297-9143

https://secure.jhu.edu/form/heart
*Choose "**ARVC Program**" from the drop down menu*

Launch a Personal Fundraising Campaign

There are many opportunities to become involved in raising awareness and much-needed funds on behalf of the Johns Hopkins ARVC Program:

- Create an online giving page and leverage social media
- Ask friends to make contributions in lieu of gifts
- Host your own event or auction
- Plan a fundraising event in your community or school
- Contribute a portion of your company's sales

The Johns Hopkins Heart and Vascular Institute Development Office is here to help!
We welcome your questions, concerns, ideas, and feedback. Please contact Shannon Brockman, Associate Director of Development,
at 443-687-2947 or s.brokcman@jhumi.edu, for more information.