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

Winter 2024 *Volume 14, Issue 1*

New Year New Goals

Happy Holidays to you and your family! The Johns Hopkins ARVC Program wishes you a happy and healthy New Year! As we reflect on the past year, it is evident that the field is moving in the direction of novel treatments, including gene therapy for PKP2 type ARVC. Our program is working closely with a number of companies to refine protocols and submit for approval. It is important that you are up to date in our ARVC Registry as that is the database we will be screening for eligibility. If you have not signed a Johns Hopkins ARVC Registry consent form in the past 5 years, please reach out to Crystal at ctichnell@jhmi.edu.

IT'S TIME!!!

2024 SEMINAR

REGISTRATION IS OPEN

IN-PERSON AND LIVESTREAMED

RESEARCH OPPORTUNITIES FOR IN-PERSON ATTENDEES

DETAILS INSIDE

2024 ARVC SEMINAR

Presented by
The Johns Hopkins ARVD/C Program

You and your family members are invited to join us for our annual ARVD/C Seminar! This year the seminar will once again be held in-person, but the scientific presentations will also be livestreamed for those unable to join us in Baltimore. We hope you will consider joining in person to take advantage of the opportunity to meet other individuals and families, participate in research opportunities, and interact with industry, specifically gene therapy companies.

We are thrilled to have two invited guest speakers, Sam Sears, PhD, cardiac psychologist, and Andre La Gerche, MBBS, PhD, sports cardiologist. In addition, we will have presentations from our own Johns Hopkins faculty; Andreas Barth, MD, PhD; Nisha Gilotra, MD; Oliver Monfredi, MD; Cindy James, PhD; and Brittney Murray, MS. You won't want to miss this unique opportunity to meet and network with other families affected by ARVD/C and to learn the latest advances in the field. It will be exciting to share the collaborative efforts all around the world in solving the mysteries of ARVD/C.

Make plans to come into Baltimore early to attend a reception at the Hilton Garden Inn Friday evening (7pm-9pm). Heavy hors d'oeuvres will be served. This event is for patients and family members only. No industry representatives please.

Please register early! There is no registration fee for this seminar, but we continue to be mindful of our gathering capacity. You must register to attend.

WHEN: Saturday, April 27th, 2024 8:00am-5:00pm

COST: Registration is FREE. You just need to get here!

WHO: Patients and Families affected by ARVD/C, Healthcare Professionals

WHERE: Chevy Chase Conference Center Auditorium
Main level of Sheikh Zayed Tower
1800 Orleans Street
Baltimore, Maryland 21287

REGISTRATION: ALL participants must register! It is also helpful to list names of family members that will be attending with you so we can determine appropriate research opportunities. Register online by April 13th.

https://tinyurl.com/2024ARVCSeminar

Additional Information

HOTEL ACCOMMODATIONS – RESERVE EARLY!!!
Hotel rooms are available (limited) at the Hilton Garden Inn, Baltimore Inner Harbor (625 South President Street, Baltimore, Maryland 21202) at a special rate of $169/night plus tax until March 27th, 2024 or as long as they are available.

Hotel reservations can be made through the Hilton Garden Inn Central Reservations Line at 888-429-7482. The group name is Johns Hopkins ARVD/C and the group code is ARV. Reservations can also be made through the online booking link: https://www.hilton.com/en/attend-my-event/arvc-program-seminar/

The hotel front desk can be reached at 410-234-0999. Check-in 3pm / Check-out 11am. Self-Parking is available at a rate of $25 and valet $35 per day.

TRAVEL TIPS
The Baltimore/Washington International (BWI) Thurgood Marshall Airport is the closet international airport to Johns Hopkins (www.bwiairport.com). It is approximately 30 minutes from the seminar location.

Transportation from Hotel to Seminar – Uber and Lyft are recommended and is at your own expense. There is no bus transportation to and from the seminar.

PARKING AT THE SEMINAR
Parking is available at your own expense (max $15) in the Orleans Street Garage. There is a bridge that connects the garage to the main level of Sheikh Zayed Tower (4th floor).

SPECIAL EVENT
Join us for a Meet 'n Greet Reception, 7:00-9:00pm, on Friday, April 26th, 2024 in the Great American Grill at the Homewood Suites/Hilton Garden Inn. Please register for this event when you register for the seminar or contact Crystal. Patients and family members only. No industry representatives please.

CLINIC CONSULTATIONS – REQUEST YOUR APPOINTMENT NOW!!!
Dr. Hugh Calkins and the genetic counselors will be available Friday, April 26th and Monday, April 29th for consultations. Dr. Nisha Gilotra will also have a few clinic slots available. Diagnostic tests can also be arranged if necessary. We ask that if you live locally to please consider arranging your appointment at another time to allow new patients and patients traveling from a distance an opportunity to schedule. These appointments will be billed to your insurance. Please contact Crystal via email at ctichnell@jhmi.edu ASAP to schedule an appointment.

SHARE YOUR STORY
Looking for patient/family stories to share! If you are interested in sharing your story for others to read, please make sure your story and any photos you'd like to include can fit on an 8x10 page. Stories need to be submitted to Crystal by April 10th.

COVID-19
Masking is optional. We encourage self-testing prior to attending.

QUESTIONS
Contact Crystal Tichnell, MGC, RN at 410-502-7161 or ctichnell@jhmi.edu

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.

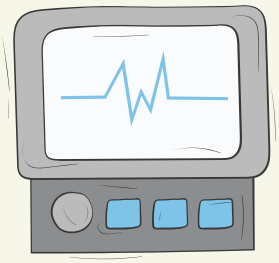
New patients are seen in consultation with Dr. Hugh Calkins and our clinical genetic counselor, Brittney Murray, to discuss test results, family history, and to provide guidance regarding further management. We see all of our patients for genetic counseling to discuss the diagnosis, the psychosocial 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. Appointments with our heart failure specialist, Dr. Nisha Gilotra, can also be arranged. All appointments are billed to your health insurance.

With the end of the COVID-19 state of emergency, licensure waivers have also ended. This means, per state laws, we are no longer able to offer telemedicine appointments with our physicians outside of Maryland. 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 410-502-7161.







Revising the Diagnostic Criteria

The initial diagnostic criteria were developed in 1994 by McKenna et al., providing a diagnostic standard for use in clinical research studies. These criteria incorporated structural, histological, electrocardiographic, arrhythmic, and familial features, each of which were designated as major or minor criteria. These criteria were highly specific but lacked sensitivity for early and familial disease. In 2010, the criteria were modified based on new knowledge and advances in genetics. These new criteria were a bit more quantitative leading to increased sensitivity and a better job correctly identifying patients who did have ARVC.

Over the years, it has become abundantly clear that ARVC or ACM may behave differently depending on the genetic variant. For example, PKP2 has classic T wave inversions, arrhythmias, and primarily right ventricular dysfunction. On the other hand, DSP tends to affect the left side of the heart and may have a normal ECG. Furthermore, TMEM43 is highly arrhythmic often leading to sudden death among males.

Therefore, the diagnostic criteria should not be "one size fits all".

An international effort lead by Drs. Firat Duru and Hugh Calkins will utilize the expertise of over 100 international leaders and in collaboration they will summarize each type of genetic ACM, propose more specific criteria for diagnosis, as well as specific management recommendations. This effort will help us to better understand disease progression, identify risk predictors and guide treatment based on one's genotype - a gene-first approach. It is anticipated that those that are determined to be gene elusive, or do not have a known genetic component, will continue to use the 2010 diagnostic criteria.

Groups have been organized and meetings have begun to address this growing need for updated, gene-specific criteria. We look forward to presenting our progress next year.

SADS FOUNDATION
SUDDEN ARRHYTHMIA DEATH SYNDROMES

The SADS (Sudden Arrhythmia Death Syndromes) Foundation led the first ever virtual Exerternally-Led Patient-Focused Drug Development Meeting (EL-PFDD) this past June 2023. This meeting provided the Food and Drug Administration (FDA) and other stakeholders (researchers, biopharma companies, healthcare providers, product developers, and federal regulatory partners) with the opportunity to hear directly from patients, their families, caregivers, and patient advocates about the symptoms that matter most to them, the impact the disease has on patients' daily lives, patients' experiences with currently available treatments, and patient's priorities for therapeutic outcomes. These inputs may also inform FDA's decisions and oversight both during drug development and their reviews of marketing applications for new therapies. Thank you to everyone who shared their stories to help make an impact on the FDA and researchers. You can watch the meeting here: **https://sads.org/research/get-involved/elpfdd/**

You can review **the *Voice of the Patient*** report here:https://sads.org/wp-content/uploads/2023/11/ARVC-VOP-report-Final.pdf. This report is publicly available and is provided to the FDA and to researchers developing new therapies for ARVC.

Upcoming Webinars sponsored by SADS

Presentation and Q&A on Sports and Exercise
January 9 @ 7:30 pm ET

with Michael Ackerman, MD, PhD and
Harikrishna Tandri, MBBS

Clinical Trials Webinar
January 17 @ 7:30 pm ET

With Dominic Abrams MBBS MD MBA
CoDirector – Center for Cardiovascular Genetics – Boston Children's Hospital
Associate Professor – Harvard Medical School.

REGISTER HERE:
https://sads.org/what-now/living-with-sads-webinars/

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.

Calling all Desmoplakin (DSP) Arrhythmogenic Cardiomyopathy Patients!!!

We have been working on several projects related to *DSP* type Arrhythmogenic Cardiomyopathy. Many papers are under way and will be submitted for publication soon. We are still working on exercise interviews and pregnancy questionnaires in this cohort of patients so if you are not yet in the Johns Hopkins ARVC Registry or haven't been invited to participate in an exercise phone interview or to completed the pregnancy questionnaire, please reach out to Crystal for more information. Thank you!

Stay Tuned for More Opportunities

FEATURED MANUSCRIPTS

Arrhythmic risk stratification in arrhythmogenic right ventricular cardiomyopathy

Europace. 2023 Nov 2;25(11):euad312. doi: 10.1093/europace/euad312.

Alessio Gasperetti, Cynthia A James, Richard T Carrick, Alexandros Protonotarios, Anneline S J M Te Riele, Julia Cadrin-Tourigny, Paolo Compagnucci, Firat Duru, Peter van Tintelen, Perry M Elliot, Hugh Calkins

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a heritable cardiomyopathy characterized by a predominantly arrhythmic presentation. It represents the leading cause of sudden cardiac death (SCD) among athletes and poses a significantly morbidity threat in the general population. As a causative treatment for ARVC is still not available, the placement of an internal cardioverter defibrillator represents the current cornerstone for SCD prevention in this setting. Thanks to international ARVC-dedicated efforts, significant steps have been achieved in recent years towards an individualized, patient-centered risk stratification approach. A novel risk calculator algorithm estimating the 5-year risk of arrhythmias of patients with ARVD has been introduced in clinical practice and subsequently validated. The purpose of this article is to summarize the body of evidence that has allowed the development of this tool and to discuss the best way to implement its use in the care of the individual patient.

This article is available http://www.ncbi.nlm.nih.gov/pmc/articles/PMC10674106/

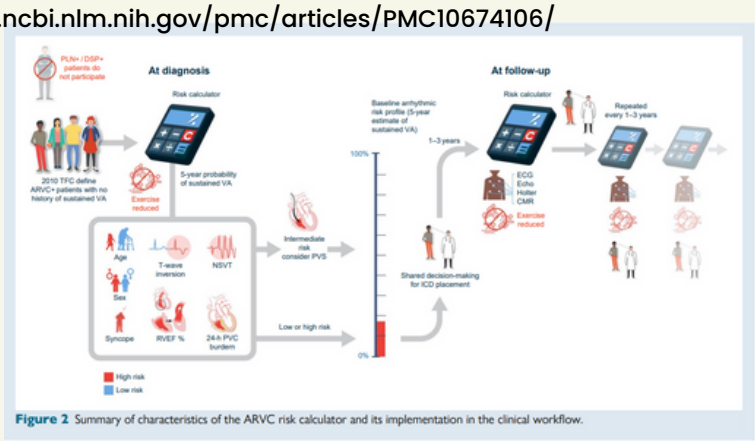


Figure 2 Summary of characteristics of the ARVC risk calculator and its implementation in the clinical workflow.

Exercise does not influence development of phenotype in PLN p.(Arg14del) cardiomyopathy

Neth Heart J. 2023 Aug;31(7-8):291-299. doi: 10.1007/s12471-023-01800-4. Epub 2023 Jul20.

Freyja H M van Lint, Fahima Hassanzada, Tom E Verstraelen, Weijia Wang, Laurens P Bosman, Paul A van der Zwaag, Toon Oomen, Hugh Calkins, Brittney Murray, Crystal Tichnell, Thais M A Beuren, Folkert W Asselbergs, Arjan Houweling, Maarten P van den Berg, Arthur A M Wilde, Cynthia A James, J Peter van Tintelen

Endurance and frequent exercise are associated with earlier onset of arrhythmogenic right ventricular cardiomyopathy (ARVC) and ventricular arrhythmias (VA) in desmosomal gene variant carriers. Individuals with the pathogenic c.40_42del; p.(Arg14del) variant in the *PLN* gene are frequently diagnosed with ARVC or dilated cardiomyopathy (DCM). The aim of this study was to evaluate the effect of exercise in *PLN* p.(Arg14del) carriers.

In total, 207 adult *PLN* p.(Arg14del) carriers [39.1% male; mean age 53+/- 15 years) were interviewed on their regular physical activity since the age of 10 years. The association of exercise with diagnosis of ARVC, DCM, sustained VA and hospitalization for heart failure (HF) was studied.

The 50% most and least active individuals had similar frequency of sustained VA and hospitalizations for HF. There was no relationship between exercise and survival free from (incident) VA, hospitalization for HF, diagnosis of ARVC or DCM during follow up. In multivariable analyses, exercise was not associated with sustained VA and HF hospitalizations during followup in this relatively not-active cohort.

In conclusion, there was no association between the amount of exercise and the susceptibility to develop ARVC, DCM, VA, or HF in *PLN* p.(Arg14del) carriers. This suggests unaffected *PLN* p.(Arg14del) carriers can safely perform mild-moderate exercise.

This article is available at https://www.ncbi.nlm.gov/pmc/articles/PMC10400740/

ARVC PROGRAM INFO

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Brittney Murray, MS—Genetic Counselor
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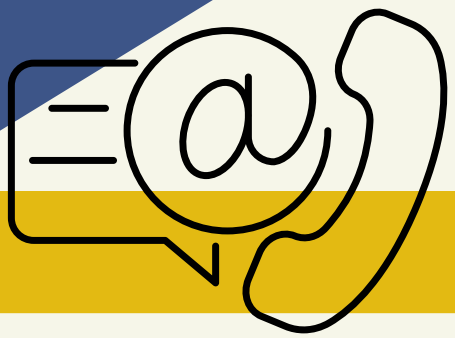
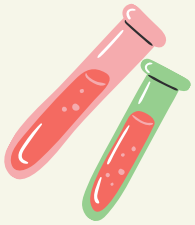


Meet Steven Muller

Steven Muller is a 3rd year PhD student from Utrecht, the Netherlands with a special interest in family screening in inherited cardiac diseases. Prior to his PhD trajectory, he worked as a first-year cardiology resident at the Jeroen Bosch Hospital in the Netherlands. He recently joined the Johns Hopkins ARVC group for 4 months as a research fellow to investigate family screening studies, specifically in relatives with a likely pathogenic/pathogenic variant and those who are from a gene elusive ARVC family. In his free time, he enjoys reading and exploring Baltimore and its surrounding cities. Steven has enjoyed his time with us so much that he has decided to extend his stay! We are so excited!



Gene Therapy Clinical Trials

The first in human gene therapy clinical trials are currently recruiting. 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 so far relevant only to patients with a PKP2 pathogenic variant who have an ICD in place. There are many other inclusion/exclusion criteria as well, which 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 study goals 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 an 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?
- Can I review a copy of the consent form prior to enrolling?
- 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?

Visit: **https://www.clinicaltrials.gov/** for a list of trials currently recruiting.

We hope this information is helpful as we navigate these new opportunities together.

JOHNS HOPKINS
MEDICINE

Your Support of the Johns Hopkins ARVC Program Ensures Our 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 our team of experts in the ARVC Program become part of our mission to provide exceptional personalized care and to find better ways to diagnose and treat our patients. Here are some of the ways that you can help:

Make a Personal Donation

Donations of all sizes, whether they're one-time or recurring, make a difference. There are a variety of ways to make a gift to support our 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 matching gifts through your workplace

To make a gift by credit card, visit our online giving form at https://secure.jhu.edu/form/heart

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

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

Launch a Personal Fundraising Campaign

There are many opportunities to become personally 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, Development Officer, at 443-287-7382 or s.brockman@jhmi.edu, for more information.