



RASopathies Study

Newsletter

Winter 2022-23

Division of Cancer Epidemiology and Genetics • Clinical Genetics Branch

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MESSAGE FROM THE RASOPATHIES STUDY TEAM

We are pleased to share the first newsletter for the RASopathies Study! This research study is designed and led by a team of experts from the Clinical Genetics Branch and Pediatric Oncology Branch – both of the National Cancer Institute, part of the National Institutes of Health. In this inaugural issue, we will highlight our research, discuss accomplishments during the study’s first year, introduce our research team, and more.

We would like to begin this issue by sharing our appreciation for you, our patients and

families. As we celebrate the first anniversary of the launch and recruitment of the RASopathies study, we want to express how grateful we are for your participation and look forward to our continued shared successes of this study.

We hope you enjoy this issue. Feel free to let us know what you think and share any feedback on what you’d like to see in the future!

Contact the study team at NCIRASopathies@mail.nih.gov or 1-800-518-8474.

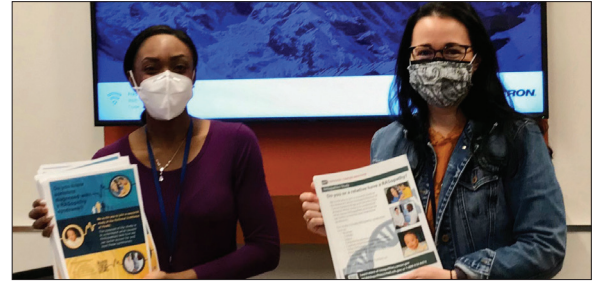
GOALS OF THE RASOPATHIES STUDY

The RASopathies Study seeks to learn more about the development of tumors in patients with a RASopathy. Our goals include:

- To better describe the medical conditions associated with RASopathies
- To better understand the risk of cancer that may be associated with certain RASopathies
- To describe the genetic causes of RASopathies more comprehensively
- To collect blood and tissue samples for use in RASopathy research
- To use data from the study to inform the clinical management of individuals with RASopathies
- To identify opportunities for clinical trials that may further improve the health of individuals with RASopathies

LAUNCHING THE RASOPATHIES STUDY

- **Initial approval from the NIH Institutional Review Board:** The RASopathies Study was opened for enrollment on May 7, 2021.
- **Online enrollment system:**
 - The study's online enrollment system officially went live on June 17, 2021.
 - The RASopathies Study is the first study in the Clinical Genetics Branch to have an entirely electronic enrollment process via a secure online study portal. Participants can also communicate with the study team via phone, secure e-mail, and/or mail.
 - The link to the study enrollment site is: <https://service.cancer.gov/myras>
- **Recruitment status:** So far, 74 people have completed the eligibility screener using the online enrollment system and 36 people have consented to participate. We welcomed our first participant to the Clinical Center in May 2022. We look forward to inviting more participants to the Clinical Center.
- **Recruitment efforts:**
 - We worked with both intramural and extramural investigators to launch this study. Internally, the study team worked with the NIH Office of Patient Recruitment to promote the study and to include the study information at the Patient Call Center. We also promoted the study across NCI social media platforms including Facebook, Instagram, and Twitter.
 - An email announcement was sent to the National Society of Genetic Counselors (NSGC) listserv in February 2022 to share information about the study with NSGC members who would be able to refer their patients to our study.
 - The study team also sent 144 mailings to local physicians to share information about the study in January 2022.
- **Presentations:** We have given two public presentations through our collaboration with the patient advocacy group, RASopathies Network, to describe and discuss our study. We will continue to engage those in the community who can help support our mission. Our goal was to enroll 100 participants by the one-year anniversary of the study opening and we are pleased with the progress we've made thus far.



Study Team Members preparing mailings to local physicians at the National Cancer Institute, Rockville, MD, January 2022
Pictured: Cecilia Higgs (left), and Gina Ney (right)

STUDY TEAM MEMBERS



Advancing RAS/RASopathies Therapies (ART) Kickoff Meeting, at the National Institutes of Health, February 2019

*Front row from left: Karlyne Reilly¹, Dominic Esposito¹, Megan Frone¹, Dawn Siegel², Lisa Schoyer³, Deborah Morrison¹, Beth Stronach³, Katherine Rauen⁴
Middle row from left: Jung Kim¹, Michael Sargen¹, Eric Legius⁵, Eva Dombi¹, Staci Martin¹, Bruce Gelb⁶, Marielle Yohe¹, Andrea Gross¹, Pam Wolters¹, Heather Thompson⁷, Paul Randazzo¹, Lisa Schill⁵
Back row from left: Scott Paul⁸, Brigitte Widemann¹, Joanne Derdak¹, Alex Pemov¹, Sharon Savage¹, Karen Gripp⁹, Dina Zand¹⁰, Douglas Stewart¹, Mignon Loh¹¹, Laryssa Huryn¹²*

¹ National Cancer Institute, ² Medical College of Wisconsin, ³ RASopathies Net, ⁴ UC Davis, ⁵ Leuven, ⁶ Mount Sinai, ⁷ California State University, Sacramento, ⁸ National Institutes of Health, ⁹ Nemours Children's, ¹⁰ U.S. Food and Drug Administration, ¹¹ Seattle Children's, ¹² National Eye Institute

Principal Investigator



Douglas Stewart, M.D., is a physician-scientist whose research focuses on characterizing familial cancer syndromes and developing new approaches to reduce the risk of cancer in families with these syndromes.

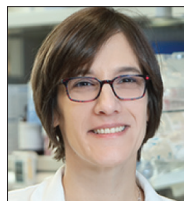
Lead Associate Investigators



Andrea M. Gross, M.D., is a pediatric oncologist who is interested in creating clinical trials to treat tumors and other types of cancers in people with rare genetic conditions that increase their risk for these issues.



Gina Ney, M.D., Ph.D., is a physician-scientist who is interested in understanding the connection between RAS mutations, cellular metabolism and energy production, and the processes that drive cells to change their identity.



Marielle E. Yohe, M.D., Ph.D., is a physician-scientist who studies how RAS mutations disrupt normal signals within a cell, in rhabdomyosarcoma and neuroblastoma.

Advancing RASopathies Research: A Conversation with Drs. Gina Ney and Douglas Stewart

In this interview, the lead investigators of the RASopathies study discuss the goals of the study and reflect upon its inaugural year.

Read the full article:
<https://dceg.cancer.gov/news-events/news/2022/rasopathies-conversation>

Lead Medical Advisors



Sharon A. Savage, M.D., is a medical advisor for the RASopathies study and supervises all genetic studies in the Clinical Genetics Branch.



Brigitte C. Widemann, M.D., is a medical advisor for the RASopathies study whose interests are in developing and discovering anticancer drugs that target and treat childhood cancers and genetic conditions that can lead to cancers or other tumors, such as neurofibromatosis type 1 (NF1).

Clinical Team

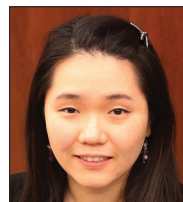


Margarita Aryavand, CAPT., U.S.P.H.S., M.S.N., C.R.N.P., is a board-certified Family Nurse Practitioner and a Commissioned Officer and Captain in the US Public Health Service. She is the lead clinician on the RASopathies study.



Megan Frone, M.S., C.G.C., is a genetic counselor who provides genetic education and counseling to study participants.

Genetics and Bioinformatics Physicians and Scientists



Jung Kim, Ph.D., is a staff scientist who focuses on understanding the genetics and biology that make people more susceptible to cancer.



Esteban Astiazaran Symonds, M.D., is a recent clinical fellow who investigates novel genetic approaches used to study Noonan syndrome and RASopathies. He is now a clinical geneticist at the University of Arizona, Tucson.

STUDY TEAM MEMBERS... cont'd



Alexander Pemov, Ph.D., is a molecular biologist who studies how changes in RASopathy genes may (or may not) lead to cancer.

Study Managers



Cecilia Higgs, M.H.S., is a Program Manager in the Clinical Genetics Branch. She leads the study management aspects of the RASopathies study and manages submissions to the Institutional Review Board.



Renee Bremer, M.S., is an Epidemiology Program Analyst in the Clinical Genetics Branch. She leads the development of the online enrollment system and ensures that technical issues are addressed.

Study Support



Maureen Risch, R.N., B.S.N., is a research nurse on the RASopathies study.



Stephanie Steinbart, R.N., M.P.H., is a research and referral nurse for the RASopathies study.



Neve Brennan, B.A., is a research assistant on the RASopathies study.

Please visit the RASopathies website
<https://www.rasopathies.cancer.gov>
to find out more about the key study team members
and their roles in the study.

UPDATES, COLLABORATIONS, AND NEW PROTOCOL DEVELOPMENTS

Advancing RAS/RASopathies Therapies (ART)

The RASopathies study is part of a larger initiative at the NCI aimed at developing new therapies for patients with RASopathies called ART (Advancing RAS/RASopathies Therapies). The laboratory-based efforts related to ART, the ARTbench, are being conducted through a collaboration between the labs of Marielle Yohe and Deborah Morrison of the NCI as well as the NCI RAS Initiative (<https://www.cancer.gov/research/key-initiatives/ras>).

Update from the ARTbench

In the lab, we are focused on two main projects:

1. We are studying how variants in RASopathy genes found in our patients cause human

disease. We have started evaluating variants in the RAS and RAF genes, but plan to study other RASopathy genes as well.

2. We are testing the efficacy of newly developed RAS/MAPK pathway inhibitors in mouse models of RASopathies. Many of these inhibitors were developed to treat patients with cancer but could also be effective in patients with RASopathies. We have started our experiments with the mouse model of Costello syndrome developed by a team of scientists and doctors led by Dr. Aoki at the Tohoku University School of Medicine. We are also developing mouse models of Noonan syndrome caused by NRAS and SOS1.

Please stay tuned for more updates from the ARTbench!

New Study for Caregivers of Children with a RASopathy

The Pediatric Oncology Branch has launched a new study to find out if Acceptance and Commitment Therapy (ACT) can help caregivers of children with a RASopathy better cope with parenting stress. ACT is a skills-based therapeutic approach that has been found to be helpful for parents of children with other chronic illnesses and disabilities. If you are a caregiver/parent of a child (younger

than 18 years) with a RASopathy and the child lives with you at least 50% of the time, you are eligible to participate. The study involves three telehealth sessions with an ACT coach, watching videos, and completing questionnaires. The entire study will be virtual so you will **not** have to travel to the NIH. Participants are paid to thank them for their time. If you are interested, please contact Dr. Atara Siegel at 240-858-7113 or atara.siegel@nih.gov or Dr. Nour Al Ghriwati at 240-760-6039 or nour.alghriwati@nih.gov.

RECENT PRESENTATIONS AND PUBLICATIONS

Presentations

Advancing RAS/RASopathies Therapies (ART)

Gina M Ney, Andrea Gross, and Marielle E Yohe, on behalf of the NCI RASopathies Team:

Margarita Aryavand, Renee C Bremer, Megan N Frone, Cecilia Higgs, Sharon A Savage, Douglas R Stewart, Brigitte C Widemann

Advancing RAS/RASopathies Therapies (ART) and RAS Initiative Collaboration, November 2021

A main goal of NCI is to understand how RAS biology causes disease, both when present at birth (as in RASopathies) and when it occurs later in life in only one tissue (such as cancer). This presentation highlighted the intersection of RASopathies, and cancer and our teams met and discussed how to work together to solve challenging RAS-related medical problems.

Clinical, Genetic, and Epidemiologic Study of Children and Adults with RASopathies

Gina M Ney, on behalf of the NCI RASopathies Team:
Margarita Aryavand, Renee C Bremer, Megan N Frone, Andrea Gross, Cecilia Higgs, Sharon A Savage, Douglas R Stewart, Brigitte C Widemann, Marielle E Yohe

RASopathiesNet Webinar, February 27, 2022

This webinar can be viewed online at: <https://youtu.be/sp8hQriFhJA>

Supported by patient advocates and family networks at RASopathiesNet, we discussed the details of the RASopathies Natural History Study with the RASopathies community. It was a chance for individuals to ask questions about the study and to hear about what the study is trying to achieve.

The ART of Medicine: Advancing RAS/RASopathy Therapies at the NCI

Gina M Ney, Marielle E Yohe, and Andrea M Gross on behalf of the NCI RASopathies Team:

Margarita Aryavand, Renee C Bremer, Megan N Frone, Cecilia Higgs, Sharon A Savage, Douglas R Stewart, and Brigitte C Widemann

Pediatric Oncology Branch Seminar, March 10, 2022

The RASopathies Natural History Study is a collaboration between two branches at NCI: the Pediatric Oncology Branch and the Clinical Genetics Branch. This unique project and its goals were discussed during the meeting.

Publications

Advancing RAS/RASopathy therapies: An NCI-sponsored intramural and extramural collaboration for the study of RASopathies.

Gross AM, Frone M, Gripp KW, Gelb BD, Schoyer L, Schill L, Stronach B, Biesecker LG, Esposito D, Hernandez ER, Legius E, Loh ML, Martin S, Morrison DK, Rauen KA, Wolters PL, Zand D, McCormick F, Savage SA, Stewart DR, Widemann BC, Yohe ME. *Am J Med Genet A*. 2020

This paper provided a summary of the Advancing RAS/RASopathy Therapies (ART) Kickoff Meeting held at the National Institutes of Health in February 2019. It includes a review of how one defines a RASopathy, as well as how we envisioned the development of the pre-clinical research, clinical trial, and population genomics aspects of the ART project.

COVID-19

There are no specific recommendations regarding COVID-19 vaccination for individuals with RASopathies. Individuals with RASopathies should follow the CDC guidelines for COVID-19 vaccination for the general population. However, immune deficiencies can be seen in RASopathies and patients with a RASopathy who have been diagnosed with an immune deficiency may be eligible for the vaccine trial described below.

Study on COVID-19 Vaccine Response in Persons with Immune Deficiencies

A study at the NIH is looking at the response to the COVID-19 vaccine in persons with immune deficiencies. If you are interested, please see <https://clinicaltrials.gov/ct2/show/NCT04852276> or email NIAIDCovidVaccineStudy@niaid.nih.gov

Additional COVID-19 Resources

What people with cancer should know:
<https://www.cancer.gov/coronavirus>

Get the latest public health information from CDC:
<https://www.coronavirus.gov>

Get the latest research information from NIH:
<https://www.nih.gov/coronavirus>

**Thank you for participating in
our RASopathies study!
The strength of our study is in
our participants.**