Science and Medical Programs

TSC Alliance Research Programs

The TSC Alliance stimulates, coordinates, and drives research toward a cure for TSC while improving the lives of those affected. Since 1984, the **TSC Alliance has invested more than $39 million into TSC research projects**:

- $20.9 million in research grants
- $5.5 million into the Natural History Database and Biosample Repository
- $11.6 million into the Preclinical Research Consortium
- $1.8 million into the Clinical Research Consortium

Innovative Research

Research Grants Program - Through the TSC Alliance research grants program, applications can be submitted for postdoctoral fellowships or research grants. Since 2020, research grants have been limited to early-stage investigators as defined by the National Institutes of Health (NIH). Grants are reviewed in a three-step process: (1) all grant applications are reviewed by a committee comprised of scientists knowledgeable about the topic area for scientific merit and of adults affected by TSC for potential impact on the lives of those affected by TSC; (2) the Science and Medical Committee of the Board of Directors evaluates the grant review committee's recommendations and the relevance of the applications to the TSC Alliance's funding priorities; and (3) the Board of Directors then reviews the recommendations of the Science and Medical Committee and makes final approval for funding. For a complete list of currently funded projects and an archive of past awardees, please visit tscalliance.org/researchers/grants-funding/.

Thanks to a recent gift from the Ramesh and Kalpana Bhatia Family Foundation, the TSC Alliance has created Anya's Accelerator to focus on furthering translational research on TAND. As a result of this gift, the TSC Alliance hosted an Innovation Workshop in April 2023, which focused on identifying biomarkers and predictors of specific aspects of TAND through collaborative and inclusive analysis of existing biosamples and data via metabolomic, genetic (RNA-seq), or other methods. We had an attendance of 30 TSC experts ranging from scientists, clinicians, researchers, community members, industry, and NIH. After this innovative workshop, we began plotting a course to identify fluid-based biomarkers to improve clinical trials and clinical care associated with TAND. Our goal is to develop a panel(s) of markers to help predict risk and progression, as well as treatment responses for TAND manifestations, similar to diabetes blood-markers A1c and glucose used in disease management and

treatment response. These blood-based markers will be identified through protein expression and WGS and metabolomics, RNA and epigenetics analysis.
We initiated the identification of blood-based markers, beginning with the 84 samples:

- Protein analysis using 11K protein assay at SomaLogic (completed in 2024.
- Whole Genome Sequencing at TGen (completed in 2024).
- Establishing scope of work for RNA sequencing, as well as to explore other biomarkers including DNA epigenetics for early 2025.

In 2025, we will begin the Anya's Accelerator Patient-Reported Outcome Measure (PROM) Project, led in collaboration with Agnies van Eeghen, MD, PhD of UMC Amsterdam. Her project will focus on the harmonization of PRO measures used both in standard of care and clinical trials to standardize the assessment of symptoms under the TAND umbrella. With the guidance of the Anya's Accelerator PRO Steering Committee, this three-year project will also lead to the first TSC-PROM validated in adults and children.

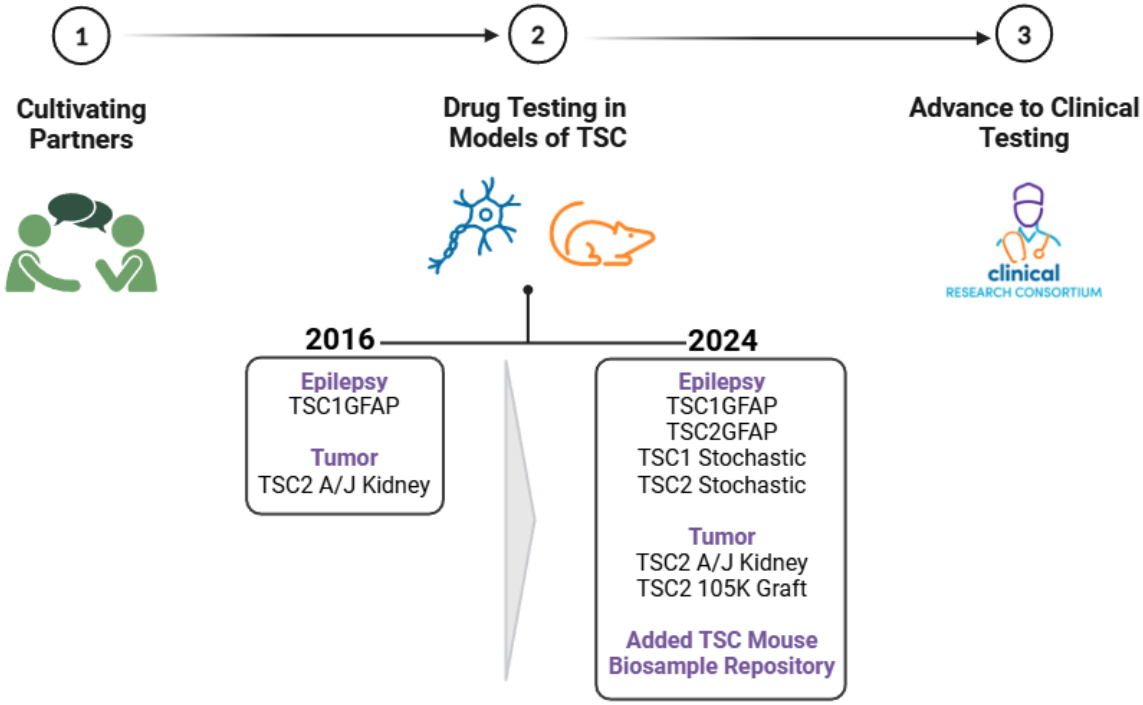
Since the updated TSC Consensus Guidelines on the surveillance and management of TSC were last published (2021) a strong organizational and community focus has been on the utilization of evidence-based data to help influence and guide clinical care. With the generous support of the Samuels Family Foundation, we launched a Reproductive and Perinatal Health Initiative to identify gaps in TSC care related to social determinants of health, as well as women's and fetal health, ultimately leading to the first set of guidelines for this crucial area of care.
In March 2024, the TSC Alliance hosted a Reproductive and Perinatal Health (RPH) Workshop in Memphis, Tennessee. The workshop gathered more than 25 TSC and LAM experts and stakeholders to discuss present and future clinical recommendations for women with TSC and/or LAM who become pregnant. Outcomes included:

- the development of a survey to gather community perspectives on pregnancy and TSC,
- drafting a call-to-action and risk stratification manuscript to be submitted for publication, and
- identifying potential collaborators with existing pregnancy databases to gather more clinical evidence towards establishing clinical guidelines.

Research Conferences - The TSC Alliance sponsors a research conference every two years.
The TSC Alliance will host our biennial International TSC Research Conference June 26-28, 2025. The conference will be held at the North Bethesda Marriott Hotel and Conference center, and the theme for the conference is "Engage, Accelerate, Transform." The conference features an all-star organizing committee, a combination of new and established TSC researchers invited to present their work, and a poster session for sharing data and encouraging engagement among scientists. An Early-Career Researcher Symposium will help trainees and researchers launching their careers to learn from each other and from more experienced investigators.

Preclinical Consortium
Translational research takes early discoveries and facilitates its entry into clinical care through coordinated and directed research to evaluate the effectiveness and safety of candidate therapeutics. A key component of this research is conducted in the TSC Preclinical Consortium, which encourages collaboration between a multidisciplinary team of researchers, including clinical researchers. The consortium facilitates drug testing in cell and animal models of TSC. Those compounds that prove efficacious and safe are referred to the TSC Clinical Research Consortium to consider for clinical testing. A goal of the Preclinical Consortium is to advance at least two candidate compounds into clinical trials by the end of 2025.

Through donations from the community and collaboration with industry, *TSC2* models of tumors and *TSC1* epilepsy models have been established suitable for drug testing (screening). In 2025, the Consortium continues to pursue potential TAND-relevant models and is currently finishing the first *in vivo* characterization studies of potential LAM models in collaboration with the LAM Foundation.



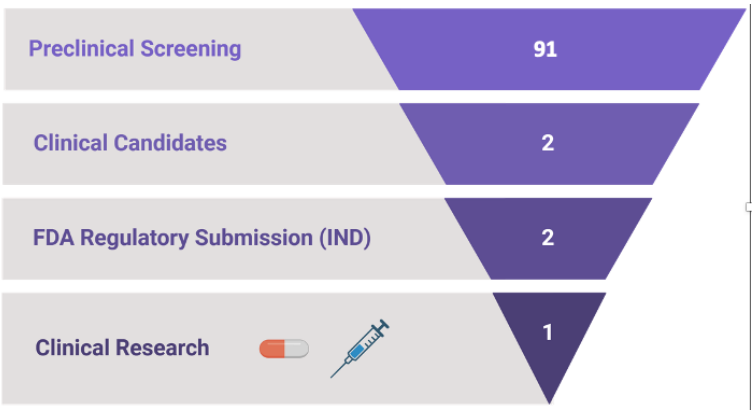
Experiments are carried out at partnering research institutions, including contract research laboratories, to ensure consistency in testing, data acquisition and interpretation. Epilepsy studies are conducted at PsychoGenics (US), and the tumor graft model is conducted at Porsolt (France). The TSC Alliance partners with the Van Andel Research Institute, a non-profit research organization, to maintain separate colonies of our models.

These resources are vital to the consortium for TSC research and recruiting industry and academic partners to TSC. The consortium continues to add new members with a goal to increase the diversity of mechanisms and likelihood for some of the technology to advance to clinical testing.

The Preclinical Consortium ended 2024 with 10 active industry partners, increasing the total number to 24 industry partners since 2016. The consortium tested nine unique compounds in 2024, raising the total tested to 91 since 2016. Many compounds will enter preclinical testing, though only some will advance to clinical testing due to lack of efficacy and safety.

Excitingly, there are partners seeking clinical trials for their compounds in 2025-2026. Two have or are conducting “FDA-enabling studies” required to establish the safety of the drugs and one partner is

on the cusp of launching a Phase 2 trial in TSC-associated refractory epilepsy. With time and continued investment, more of the 91 tested compounds will likely move forward into FDA-enabling studies, INDs, and clinical trials.



The team continues to capitalize on the momentum to advance candidate compounds to clinical testing. The horizon for preclinical research in 2025 is bright. Looking forward, in just the first few weeks of 2025 we have already contracted studies with two companies to evaluate their drugs in preclinical models and are actively cultivating two new industry members.

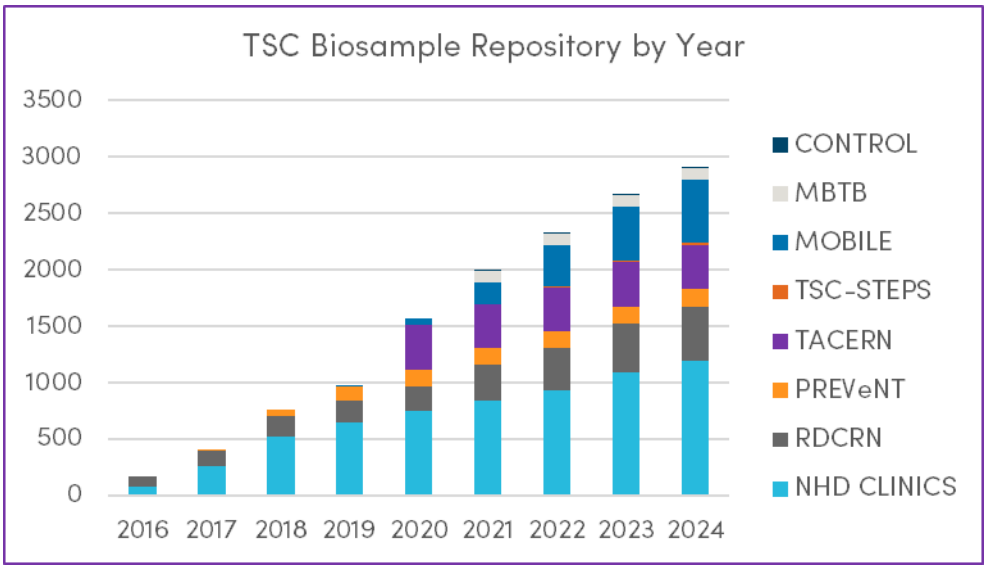
Since 2016, donors such as Drs. Bonnie and Jonathan Rothberg & Family and the Gerry and Bill Cowlin Foundation have helped establish and grow the consortium diversity and capacity for drug testing. This allows us to work with academic collaborators to nominate novel mechanisms for screening as well as collaborate on post-study analysis of tissues for important markers and signals.

The team is working hard to increase donations that support the TSC Preclinical Consortium. This funding allows us to increase the diversity of TSC models and assays, attract new investigators and industry partners, and for testing compound nominations made by investigators.

TSC Biosample Repository and Natural History Database

The TSC Alliance built the TSC Biosample Repository to accelerate research into why TSC is so variable among individuals and how we might determine which individuals respond better or poorly to certain treatments. Samples in the repository are linked to detailed clinical data in our TSC Natural History Database and are available to qualified researchers worldwide. As of December 1, 2024, the Natural History Database contained 2,780 participants enrolled across 22 TSC clinic sites or by the TSC Alliance.

Samples are housed at and distributed from the Van Andel Institute in Grand Rapids, Michigan, under control of the TSC Alliance. Research projects utilizing biosamples are expected to lead to new hypotheses regarding biomarkers, mechanisms for new treatment approaches, risk factors, or genetic modifiers. These discoveries could make clinical trials more efficient and lead to drug development or new directions of research and larger projects funded by the National Institutes of Health (NIH), Department of Defense's Tuberous Sclerosis Complex Research Program (TSCRP), or other sources.



Key: NHD: Natural History Database; RDCRN: Rare Disease Clinical Research Network (NIH-funded research network of the Developmental Synaptopathies Consortium (DSC) including a focus on TSC); PREVeNT: Preventing Epilepsy Using Vigabatrin in Infants with Tuberous Sclerosis Complex trial; TACERN: Tuberous Sclerosis Complex Autism Center of Excellence Network Early Biomarkers of Autism in Infants with TSC; TSC-STEPS: Stopping TSC Onset and Progression 2B: Sirolimus TSC Epilepsy Prevention Study; Mobile: mobile samples from the Waxlax Biosample Collection Initiative; MBTB: Maryland Brain and Tissue Bank samples; Control: non-TSC samples.

The Biosample Repository continues to add diversity in types of samples. Ultimately, this valuable resource will help lead the way for predictive and personalized care. As of December 1, 2024, the Biosample Repository has acquired 2,904 blood, buccal (cheek) swab, or tissue samples. Our mobile phlebotomy initiative, with generous support from Lorne Waxlax, enables anyone with TSC to participate in the Biosample Repository regardless of where they receive medical care. To date, we have acquired 557 blood samples via mobile phlebotomy. We are excited to enable our constituents to participate from anywhere in the US or Canada.

Since inception, portions of 3,370 samples have been distributed to 50 distinct researchers for 59 distinct projects. TSC Alliance also sponsors funding of scientifically reviewed applications for Biosample Seed Grants to increase the utilization of our current inventory and advance scientific discoveries.

Whole Genome Sequencing (WGS) - Because TSC affects everyone differently, many researchers have hypothesized the existence of “modifier genes” outside of the *TSC1* and *TSC2* genes that could modify disease progression or severity. Studies to search for modifier genes require hundreds to thousands of DNA samples from unique individuals and costly sequencing of each person’s DNA. WGS is a type of next-generation sequencing and is currently the most comprehensive method to characterize a person’s full genetic code. The main difference between standard sequencing methods and WGS is the amount of data generated. WGS is very high throughput. Whereas traditional sequencing may sequence a single DNA fragment at a time, WGS can process hundreds to thousands of fragments at one time. Additionally, WGS has an improved ability to detect DNA changes that occur infrequently or that may not be able to be detected via traditional methods, thus

allowing researchers to discover new DNA changes (also called variants). WGS is an important step toward understanding the relationship between genetic variants and their impact on disease. Rather than having many researchers at different institutions undertake this type of sequencing, the TSC Alliance can accelerate this process by coordinating and funding WGS on hundreds of DNA samples and sharing those data with multiple researchers.

Genetic results are one of the most requested pieces of data from the Natural History Database. We have completed or have in-progress WGS on 191 samples and plan to grow this project to complete WGS on 500 samples and offer the data to TSC researchers to better understand the variability observed in people affected by TSC, which may lead to predictive and personalized care.

This initiative also supports clinical validation of variants found via WGS in either the *TSC1* or *TSC2* gene at Ambry Genetics, so genetic results can be offered back to participants along with a genetic counseling session free of charge to the family to help them better understand their unique TSC diagnosis and provide valuable information for future decision making such as family planning. Our current genetic counseling partner is Kate Richardson, MS, CGC, at University of Texas Health Science Center at Houston.

Self-Report Portal - In December 2021, the TSC Alliance added the TSC Self-Report Portal (SRP) to the TSC Natural History Database. This portal permits the collection of patient-reported outcomes (PROs). PROs are a report of the patients' perspectives about the impact of disease and treatment on their health status, for example quality of life and symptoms, without the interpretation of a clinician or anyone else. Through the SRP, the TSC Alliance is collecting information on how TSC affects individuals and families, which will complement medical data in the Natural History Database. The purpose of this initiative is to help the TSC Alliance and TSC researchers better understand the perspective of those affected by TSC to develop tools to measure improvement in areas most important to the TSC community. Eventually, these measurements can be used to identify endpoints for clinical trials and evidence-based guidelines for treatment.

One of the most impactful aspects of TSC on the quality of life for people living with TSC is TAND—TSC-associated neuropsychiatric disorders. Through collaboration with the TANDem project (Empowering Families through Technology: a mobile-health project to reduce the TAND identification and treatment gap), the self-quantified TAND checklist (TAND-SQ) has been incorporated into the SRP, and 83 individuals have completed the TAND-SQ in the SRP to date. The TSC Alliance is helping the TANDem project team validate the utility of the TAND-SQ for future use in a mobile application. (You can read more about the TANDem project at tandconsortium.org/about/). For many TAND symptoms, there are currently no objective outcome measurements or a way to quantify severity. This initiative is designed to help us better understand TAND and how to treat it by learning directly from those affected by TSC or their caregivers. In 2023, a second questionnaire was added focusing on TAND and epilepsy from the caregiver perspective to complement the patient perspective.

Clinical Research Consortium

In 2012, the TSC Alliance helped create the TSC Clinical Research Consortium in partnership with investigators running clinical studies to ensure clinical research in TSC is as efficient and effective as possible. Since then, TSC Clinical Research Consortium investigators have been awarded more than $39 million by the NIH and Food and Drug Administration (FDA) through competitive grant processes. TSC Alliance personnel serve on the leadership team for the consortium, actively track enrollment, and raise community awareness to help identify potential participants for clinical studies. The TSC

Alliance also provides supplemental financial support to accelerate or expand NIH-funded studies and collects blood samples from participants in selected studies.

In 2020, the TSC Alliance provided $200,000 supplemental funding for TSC-STEPS (Stopping TSC Onset and Progression 2B: Sirolimus TSC Epilepsy Prevention Study), which is ongoing. The TSC Alliance continues to educate the community about this pivotal trial. Twenty-eight infants have been enrolled to date and twenty-three biospecimens collected for the TSC BSR. For more information, please search for NCT05104983 at clinicaltrials.gov.

The TSC Alliance has continued providing supplemental funding and collecting blood samples for the Developmental Synaptopathies Consortium (DSC), an NIH-funded project which includes studies of TSC and the related rare disorders Phelan-McDermid Syndrome and PTEN Hamartoma Syndrome. These three rare diseases seem to affect certain shared pathways influencing the development of synapses, or brain connections. This study's goal is to learn more about children and young adults who have TSC and autism spectrum disorder and/or intellectual disability. Researchers are trying to find earlier signs of these disorders and find effective treatments and interventions. In 2024, the TSC Alliance awarded an additional 12 months of funding, $163,737 in total, to support collection of additional data and biosamples from August 2024 through July 2025.

In 2025 we are initiating an expanded clinical research network with TSC Alliance serving as a central hub for patient-focused clinical research. Benefits of doing so include participation by a broader group of recognized TSC Clinics, clinicians and researchers; inclusion of the diversity of TSC manifestations impacting multiple organ systems throughout a lifetime; and improved awareness and access of individuals with TSC to clinical studies by collaborating with additional sites across the country and working with global partners.
The expanded network will provide advice on clinical research projects originating from TSC Preclinical Consortium projects and industry partners. By using a membership model similar to the Preclinical Consortium, which is free of charge to academic members, we can generate revenue from industry members. Revenue can be in the form of a membership fee to gain access to infrastructure and experience, payments for specific services rendered, and milestone payments, royalties or equity to provide future revenue as projects advance toward regulatory approval. The expanded network will leverage the many lessons learned from the existing Clinical Research Consortium. Some learnings include best practices for designing patient-centered clinical study protocols, selection of outcome measures, harmonization of data collection, analysis, and more.

International TSC Clinical Consensus Guidelines

In August 2021, two new publications were published in *Pediatric Neurology*, "*Updated International TSC Diagnostic Criteria and Surveillance and Management Recommendations"* and *"Beyond the Guidelines: How We Can Improve Healthcare for People with TSC Around the world*." The new papers are available from https://www.tscalliance.org/healthcare-professionals/key-medical-publications/ and provide the first significant updates to the international guidelines since 2013 because of new medications and advances in treatments. To address the changes, a working group led by Darcy A. Krueger, MD, PhD, of Cincinnati Children's Hospital Medical Center, and Hope Northrup, MD, McGovern Medical School, University of Texas Health Science Center at Houston, included 80 participants from 16 countries. We anticipate making the next update after the 2026 TSC World Conference.

TSC Centers of Excellence and TSC Clinics

In 2023, we launched an updated clinic application and as of 2024 all our recognized clinics and Centers of Excellence (COEs) have completed the application.

We currently recognize **73 clinics** including **18 COEs** and **15 international clinics**

In 2025, we will launch a new designation for Affiliated Providers, which are TSC providers of different specialties that see patients outside of our currently recognized clinics and COEs. We hope to expand this internationally in the future and have started a querying process of our domestic clinics to get an idea of to whom we can refer international patients for quality care.

As a part of our strategic plan, we are working alongside clinicians and clinic staff to begin the process of building Transition of Care guides, which would serve as an outline for clinics to follow while transitioning patients from pediatric care into adult care. We plan to implement the use of these guides in recognized TSC clinics by 2028 to ensure that each has a strong transition plan. The TSC community has reported this transitional period as a difficult time for TSC families, and our hope is to utilize these guides to alleviate some of the stress associated with the transition from pediatric to adult care.

TSC Navigator
In 2024, the TSC Alliance launched our redesigned and improved website, incorporating TSC Navigator with a streamlined design that has improved accessibility to families and individuals in need. Since 2021, TSC Navigator has served as an easy-to-use, interactive online tool to help guide individuals and families through the complexities of TSC across the lifespan, proactively manage their care and live their fullest lives. Thanks to the new design, users can navigate directly to the most relevant sections based on their age of diagnosis. Since the launch of our improved website, TSC Navigator has had more than 59,223 views.
Community-Focused Research and Clinical Development Priorities – The TSC Alliance convened an externally-led patient-focused drug development meeting (PFDD) with the FDA at the Hyatt Regency on Capitol Hill in Washington, DC, on June 21, 2017. This session provided the opportunity for individuals affected by TSC and caregivers of dependent adults or children with TSC to communicate their perspectives on living with TSC to help the FDA understand the context in which regulatory decisions are made for new drugs. The TSC Alliance submitted the *Voice of the Patient* report resulting from this meeting to the FDA in October 2017. The report and recordings of the meeting are available at tscalliance.org/pfdd.

International Scientific Advisory Board (ISAB) – The TSC Alliance science and medical program is advised by a group of distinguished and dedicated TSC researchers. These individuals serve a three-year term and are nominated and approved by members of the Science & Medical Committee. The ISAB plays an important role planning conferences, advising on research priorities and strategy, and reviewing proposals for funding of research by the TSC Alliance.

Professional Advisory Board (PAB) – The Professional Advisory Board is comprised of healthcare professionals with expertise in the various clinical manifestations of TSC. These individuals serve a renewable three-year uncompensated term and are nominated by the Science and Medical Committee. The PAB serves as a vital resource for medical expertise to develop and review health-related information provided by the TSC Alliance.

TSC1/2 Variation Database – The TSC1/2 Variation Database was developed by the late Dr. Sue Povey and Dr. Rosemary Ekong at University College London. This database serves as a resource for clinicians, molecular diagnostic laboratories and researchers worldwide. Though the TSC Alliance funding for this project has completed, the database is still maintained as a clinical and research resource.

Exhibits at Professional Society Meetings – TSC Alliance staff exhibit at or attend selected in-person professional society meetings with the goal of providing information about TSC to conference participants and educating health care professionals and researchers about TSC. The largest TSC Alliance presence is at the American Epilepsy Society annual meeting, which has the largest attendance of neurologists and bench researchers working on TSC; it also attracts international clinicians and researchers. When drafting the annual budget, TSC Alliance staff look for opportunities to engage with attendees at various specialty meetings including autism, nephrology, dermatology, neuroscience or cancer research, pediatrics, and advanced practice providers (nurse practitioners and physician assistants).

Partnerships with other nonprofit organizations – The TSC Alliance works with other non-profit organizations with common interests to help bolster research and support efforts across a wide span of activities. One such partnership is the Epilepsy Leadership Council, a coalition that focuses on epilepsy research, care, services, education, and advocacy efforts.

Two public-private partnerships involving the TSC Alliance are the Interagency Collaborative to Advance Research in Epilepsy (ICARE) and the Interagency Autism Coordinating Committee (IACC), both of which include nonprofit and patient advocacy groups and federal government representatives from the National Institutes of Health, Centers for Disease Control, and other relevant agencies.

The LAM Foundation and TSC Alliance co-hosted the 2021 international research conference virtually. Each year the organizations share information on grant applications to consider whether co-funding of research grants is an opportunity, which we have done multiple times in the past. The organizations have also collaborated to include individuals with sporadic LAM in the TSC Natural History Database COVID-19 sub study.

As a leading rare disease patient advocacy organization, TSC Alliance is often asked by umbrella rare disease organizations, including Global Genes, the Milken Institute, and the Chan-Zuckerberg Initiative, to share our experiences with new, smaller organizations. This also benefits the TSC Alliance by introducing us to new industry partners and other larger non-profits, which has led to new collaborations.

The TSC Alliance gains insight and provides our voice by partnering with like organizations in overall efforts to increase awareness of rare diseases like TSC. The TSC Alliance is a member of the Rare Epilepsies Network, a project which developed a joint registry of individuals affected by rare diseases that cause epilepsy, and AGENDA (Alliance for Genetic Etiologies of Neurodevelopmental Disorders and Autism), a partnership of research and advocacy organizations focused on improving outcomes of individuals with all forms of autism by fostering a genetics-first approach to autism science. We partner with the Child Neurology Foundation and other organizations as Governance Committee members of the Infantile Spasms Action Network to sponsor Infantile Spasms Awareness Week annually during the first week of December and were founding members of the Seizure Action Plan Coalition along with the Dravet Syndrome Foundation and LGS Foundation. We are proud members of the National Organization of Rare Diseases (NORD), Research!America and the Health Research

Alliance. Additionally, the TSC Alliance frequently meets with other rare disease organizations to provide insights and guidance into research program development and management.

Other Sources of TSC Research Funding available – This money goes directly to researchers, not to or through the TSC Alliance.

- Tuberous Sclerosis Complex Research Program (TSCRP) of the Congressionally Directed Medical Research Program (CDMRP) administered by the Department of Defense (DOD) has supported $105 million in TSC research since 2002.
- National Institutes of Health (NIH) funding has supported approximately $412 million in TSC research since 2002. The TSC Alliance has conversations annually with senior personnel in the following institutes and offices at NIH: NCATS (including the Office of Rare Disease Research), NIAMS, NHLBI, NCI, NIDDK, NINDS, NICHD, and NIMH. Additionally, program officers from these institutes meet bi-annually with TSC Alliance staff and TSCRP staff in a "Trans-NIH meeting" to share TSC research being supported by each organization and to discuss ways in which they can work together to stimulate and support TSC research initiatives. In March 2015, NINDS, TSC Alliance, and TSCRP led a workshop of clinical, basic, and industry researchers to update the 10-year Research Plan for TSC. The outcomes of this workshop continue to influence the priorities for investment of precious research dollars by the TSC Alliance, NIH, and TSCRP.
- There are several non-profit organizations that also support TSC-related research grant awards. They include The LAM Foundation, AES, CURE Epilepsy, the PKD Foundation, and Autism Speaks.