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Rare Disease

Patient Perspective

The role of the TSC Alliance in advancing therapy development: a patient organization perspective

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***Abstract*:** Tuberous sclerosis complex (TSC) is a genetic disease leading to malformations, or tubers, in the cerebral cortex and growth of tumors, most frequently in the brain, heart, kidneys, skin, and lungs. Changes in the brain caused by TSC usually have the biggest negative impact on quality of life. Approximately 85% of individuals with TSC have epilepsy, and TSC-associated neuropsychiatric disorders (TAND) affect nearly all individuals with TSC in some way. TSC Alliance's research strategy is built upon both funding and catalyzing research. Through grants, the organization provides funding directly to researchers through a competitive application process. The organization has also built a set of resources available to researchers worldwide, including a Natural History Database, Biosample Repository, and Preclinical Consortium. These resources catalyze research because they are available to qualified academic or industry researchers around the world, enabling an almost unlimited number of scientists to access data and resources to enable and accelerate research on TSC. This research strategy continues to be shaped by the needs and priorities of the TSC community, working toward a future where everyone affected by TSC can live their fullest lives.

Plain language summary

The role of the TSC Alliance in advancing therapy development: a patient organization perspective

Finding a new treatment for any disease is a long and expensive process, and it can be even more challenging for a rare disease such as tuberous sclerosis complex (TSC). To encourage research on TSC and speed up the process developing new treatments, the TSC Alliance established a research strategy based upon the priorities of people living with TSC. TSC community members best know how the disease negatively affects their lives. Equally importantly, the TSC community is a necessary partner for any researcher or company who wants to bring forward a potential new treatment. The TSC Alliance awards research grants to individual researchers who are at early stages of their careers. We also collaborate with many researchers and healthcare providers, and with the TSC community, to build shared resources. These resources include data from medical records and biological samples, such as blood and tissue samples, which are shared with researchers around the world for a wide range of projects related to TSC. We also collaborate with researchers from academic laboratories and the pharmaceutical or biotech industry to test potential new drugs or other therapies in animals, which is required before new therapies can be tested in humans. Before and during human testing in clinical trials, we help researchers design a trial that is both meaningful to the

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TSC community and not overly burdensome to participants. As new therapies become available, the TSC Alliance educates the TSC community and advocates for patient access to new therapies. Over time, as more is learned about how best to monitor and treat people with TSC, the organization convenes a conference of TSC experts to update clinical consensus guidelines to guide improved treatment of this rare disease.

Keywords: patient-centered research, patient engagement, research strategy, TSC Alliance, translational research, tuberous sclerosis complex

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Introduction

The TSC Alliance is an internationally recognized nonprofit that strives to do everything it takes to improve the lives of people with tuberous sclerosis complex (TSC). Founded in 1974 by four mothers of children with TSC, the TSC Alliance quickly became the leading source of support and hope for those affected by the disease. In our first 50 years, we have made incredible progress in raising awareness, accelerating research discoveries, and creating support systems around the world. We will not stop until every person with TSC can realize their fullest potential – no matter how complex the journey is to get there.

Based upon an incidence rate of roughly 1:6000 live births,[1] we estimate approximately 50,000 people in the United States and one million worldwide have TSC. Determining a precise prevalence is challenging because TSC is highly variable in the way it impacts different individuals, which can lead to delayed diagnosis or misdiagnosis. Some people live with few symptoms while others need continual, life-long support.

TSC is a genetic disease leading to malformations, or tubers, in the cerebral cortex and growth of hamartomas, or tumors, in many organs.[2] Tumors occur most commonly in the brain, heart, kidneys, skin, eyes, and lungs. Changes in the brain caused by TSC usually have the biggest negative impact on quality of life. Approximately 85% of individuals with TSC have seizures, which are often refractory to treatment.[3] Neuropsychiatric issues including autism, developmental delay, intellectual disability, behavioral challenges, anxiety, and many other issues, are encompassed by the umbrella term of TSC-Associated Neuropsychiatric Disorders (TAND),[4] Aspects of TAND are often the most impactful aspect of the disease,[5] yet a large treatment gap remains.[6]

Many TSC manifestations are similar to those of more common diseases, such as epilepsy, cancer, and autism. Additionally, the genes causing TSC regulate the activity of the mechanistic target of rapamycin (mTOR), which is involved in cancer, immunology, aging, and more.[2] The more we understand about TSC, the more we will understand about other diseases. For these reasons, we consider TSC a 'linchpin' disease. We hope and expect that advancements in TSC research will contribute to improved treatments for autism, epilepsy, and cancer – diseases that affect nearly 27 million people in the United States alone.[7–9]

TSC research strategy

Stimulating research on a rare disease

Since the TSC Alliance awarded its first research grant in 1984, the organization has put more than $37 million toward supporting and driving TSC research. Little was known about TSC genetics and biology in the 1980s and early 1990s, so the TSC Alliance funded a variety of research grants to stimulate basic and translational research and to attract and retain new researchers in the TSC field. By all accounts, the grant program was extremely successful. Funded investigators included key contributors to discovering the *TSC1* and *TSC2* genes that cause the disease, scientists who learned how the proteins encoded by *TSC1* and *TSC2* regulate the activity of mTOR, and researchers who would be involved in early

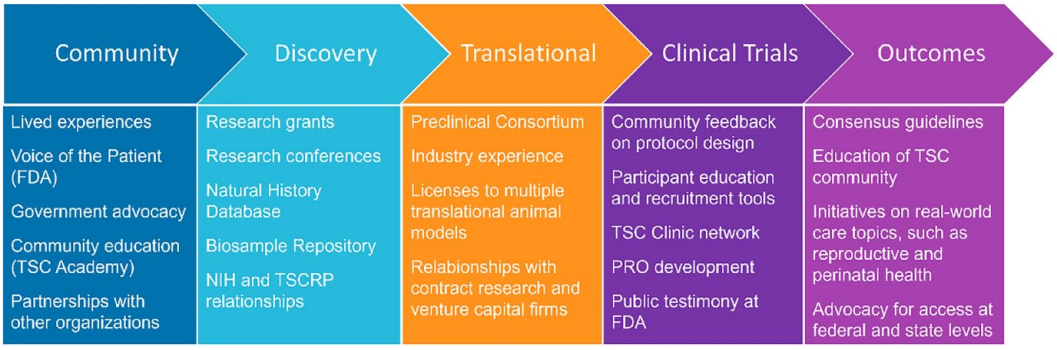

Figure 1. Key capabilities, programs, and relationships built by the TSC Alliance to help accelerate development of new therapies for TSC.
TSC, tuberous sclerosis complex.

clinical trials of mTOR inhibitors to treat various aspects of TSC.[10–12] Several of today's leaders in TSC research say their first research grant was one from the TSC Alliance.

The discovery of the genes responsible for TSC in the 1990s and their link to mTOR activity in the early 2000s were quickly followed by a surge of interest in clinical trials. From 2005 onward the TSC Alliance has grown its research, advocacy, and educational programs to ensure the TSC community is engaged in research at all levels (Figure 1). Together with an unprecedented variety of external partners, the TSC Alliance is working tirelessly toward a future where everyone affected by TSC can live their fullest lives.

TSC community

The TSC community of adults living with TSC and family members of children or dependent adults with TSC are best poised to describe the community's unmet clinical needs. Community members share their insights in a variety of ways, including TSC Alliance constituent surveys, advisory boards, and testimony at United States Food and Drug Administration (FDA) advisory committee hearings. In 2017 the TSC Alliance sponsored a patient-focused drug development meeting (PFDD) with the FDA. The purpose of this meeting was for community members to describe directly to the FDA the impacts of TSC on individuals' daily lives, what types of treatment benefits make the most impact on people's lives, and to share perspectives on how well available therapies are (or are not) working. The resulting Voice of the Patient report captures key messages from the testimony and includes results of an international drug development survey distributed prior to the PFDD meeting.[5] Furthermore, the report includes a framework for the FDA to include in its risk-benefit analysis when considering future therapy approvals.

Development of new therapies for TSC cannot advance without participation of the TSC community. Beyond the obvious need for participation in clinical trials, individuals with TSC contribute their medical history, blood, and tissue samples for discovery and translational research. Community members also advocate for state and federal research funding, including an annual March on Capitol Hill to garner Congressional support for the Tuberous Sclerosis Complex Research Program (TSCRP), which from 2002 to 2023 has appropriated $113 million to fund competitive grants to TSC researchers worldwide.[13] To educate the TSC community about TSC genetics, research, and government advocacy, the TSC Alliance produces TSC Academy, a freely available online learning system to enable them to be confident messengers about the importance of funding and participating in research.[14] The TSC Alliance also partners with other nonprofit organizations to raise awareness of unmet needs, particularly in the areas of epilepsy, autism, lymphangioleiomyomatosis (LAM), and reproductive and perinatal care. Moreover, the TSC Alliance collaborates worldwide through Global Alliances and TSC International (TSCi).[15]

Figure 2. TSC Alliance has begun funding a third generation of TSC researchers.
TSC, tuberous sclerosis complex.

Discovery research

Current therapies are not yet sufficient to enable everyone with TSC to live their fullest lives. Thus, the need remains for continued basic discovery research. As the National Institutes of Health (NIH) and TSCRP fund many times the number of research grants the TSC Alliance could afford, especially to established investigators, the TSC Alliance research grants are instead focused on attracting and retaining innovative early-career investigators in TSC research around the world. Through this critical funding, early investigators can develop the data necessary for sustainable funding through the NIH, TSCRP, and other sources. Equally important, the TSC Alliance creates a long-lasting relationship with the investigator, who also becomes an advocate for the TSC community and helps train more researchers who have an interest in TSC. We are excited to have begun funding a third generation of TSC Alliance-funded researchers: that is, young scientists working in the laboratory of a researcher who was previously funded by TSC Alliance and who, in turn, was trained in a laboratory that had received TSC Alliance funding (Figure 2).

Relationships among a larger number of investigators are built and strengthened through a biennial international research conference hosted by TSC Alliance.[16] Attendees and invited speakers are intentionally diverse, encompassing basic, clinical, and industry researchers working in TSC or related disorders. Senior investigators, early-career researchers, and trainees are included to germinate new collaborations, and the NIH and TSCRP are active participants in the conversations. In 2002 and 2015 the NIH sponsored strategic research workshops, including expert TSC clinicians and researchers, TSC community members, program officers from multiple NIH institutes and centers, and, in 2015, TSCRP programmatic staff and pharmaceutical industry researchers.[17] Additionally, the TSC Alliance meets annually with those agencies to ensure types of research funded by these three organizations are synergistic and not duplicative.

Because NIH and TSCRP funding of TSC research grants has increased over the last 20 years, the TSC Alliance has chosen, rather than funding grants to a few additional researchers, to invest much of its financial resources to build and sustain patient-centered resources to share with all researchers. Two such resources are the TSC Natural History Database and the TSC Biosample Repository, which are tightly integrated.

An understanding of natural history is important for designing clinical trials and generating hypotheses for research questions. In 2005, Dr. Steven Sparagana at Texas Scottish Rite Hospital for Children received an award from the TSCRP for a natural history study of TSC, and he chose to partner with the TSC Alliance to establish the TSC Natural History Database.[18] This ensured that the database would be sustainable after initial funding was exhausted. Because it is owned by the community it serves, the database is still operating and growing today thanks to support from donors and corporate partners.

The TSC Natural History Database captures clinical data to document the impact of the disease on each person's health over the lifespan. More than 2600 people with TSC are currently enrolled in this project, and enrollment remains open. The TSC Alliance provides funding to participating clinics to perform data entry, monitors the integrity of the database, and makes data available to investigators to answer specific research questions and identify potential participants for clinical studies. Additionally, to broaden the geographical diversity of participants, qualified TSC Alliance staff can remotely consent participants and enter data into the database without the participant needing to visit 1 of 22 participating TSC clinics. In 2021, a self-report portal was

added to the database to capture patient- or caregiver-reported outcomes which are linked to the clinical data. Data from the self-report portal promises to greatly enhance the value of the Natural History Database by capturing patient-reported outcome (PRO) measures for the impact of TSC on daily living.

Building further upon the Natural History Database, in 2015 the TSC Alliance established the TSC Biosample Repository. Biosamples are collected from individuals with TSC who agree to contribute blood or tissue samples, such as remnant surgical tissue, and medical data for research purposes. Blood is collected at most of the Natural History Database clinic sites, or the TSC Alliance can consent individuals remotely and send a mobile phlebotomist to their home. The Biosample Repository also includes blood collected as part of certain clinical trials. Samples are owned by the TSC Alliance on behalf of the TSC community, and samples are stored at the Van Andel Institute in Grand Rapids, Michigan. Each biosample is linked to detailed clinical data in the TSC Natural History Database. Samples and data are available to qualified researchers worldwide, and a steering committee comprised of external researchers and TSC community members reviews applications for access to data and biosamples. At least 20 papers have been published utilizing natural history data and/or biosamples from these resources, providing insight into risk factors for developing drug-resistant epilepsy,[19] demonstrating that individuals with dark skin were less likely to be diagnosed in infancy compared to people with light skin,[20] and identifying potential new drug targets.[21]

The TSC Alliance's whole-genome sequencing (WGS) initiative using DNA from blood samples in our biosample repository began in 2021 with a goal of eventually generating WGS data to be shared with researchers from at least 500 individuals with TSC. This initiative also supports clinical validation of variants found *via* WGS in either the *TSC1* or *TSC2* gene, enabling genetic results to be offered back to participants along with a free genetic counseling session to the family to help them better understand their unique TSC diagnosis and provide valuable information for future decision making, such as family planning. This is one way of directly sharing the benefits of research back to those who make research possible – the TSC community.

Translational research

Translational research strives to build upon early discoveries and translate them into clinical care options. This critical research facilitates the process from ideas into new or repurposed treatments by evaluating the effectiveness and safety of candidate therapies. The TSC Alliance launched the TSC Preclinical Consortium in 2016 to help advance more drug candidates into clinical testing. To achieve this end, the Preclinical Consortium provides the infrastructure to foster collaboration between academia and pharmaceutical industry researchers and access to resources to help facilitate development of new therapies for TSC.[22] Two of us (SLR and DJA) together have more than 35 years of experience in the pharmaceutical and/or device industry, enabling TSC Alliance to engage in robust and meaningful conversations with all stakeholders in this space.

The TSC Preclinical Consortium is a collaboration between a multidisciplinary team of researchers and industry partners. The Preclinical Consortium invites academic and industry researchers to submit compound nominations to continue to refresh the drug discovery pipeline based on the latest data and novel ideas. Nominations are peer-reviewed by consortium members and prioritized by the Preclinical Consortium Steering Committee for funding by the TSC Alliance. If the TSC Alliance funds the study, the data are shared with the consortium for transparency and stimulation of additional hypotheses.

Partnership with pharmaceutical companies is an important aspect of the consortium, as these organizations have the infrastructure to efficiently move preclinical research findings to clinical testing and eventually commercial distribution. The TSC Alliance holds licenses to several animal models enabling the organization to allow for-profit companies to utilize these models. This avoids the need for each company to negotiate with each institution that owns a given model, which is often a lengthy process. To retain ownership and confidentiality of their data, companies usually choose to pay the full costs of their studies plus license fees and overhead costs to the TSC

Alliance. Companies may join and leave the consortium on an annual basis. The consortium has had 22 unique company members from 2016 through 2023. Two industry partners are conducting FDA-enabling studies required to establish the safety of the drugs and one additional partner is preparing an investigational new drug application to begin clinical trials. The opportunity to interact with industry researchers has helped the TSC Alliance develop relationships with many contract research organizations and venture capital funds. Active relationships in this space enable the TSC Alliance to bring together potential partners who may not otherwise have crossed paths.

The consortium tested 82 compounds from 2016 through 2023, including industry-sponsored therapies and compounds nominated by academic investigators. Although many candidate therapeutics enter preclinical testing, only some will advance to clinical testing for various reasons, such as lack of efficacy, unacceptable safety, or business decisions by industry sponsors. In addition to our existing epilepsy and tumor mouse models, the consortium actively reconstitutes additional models for drug testing at the Van Andel Institute to have a more robust representation of TSC manifestations. With PsychoGenics, Inc., we validated one *Tsc1* behavior model (with autism-like features) and are in the process of validating two *Tsc2* additional epilepsy models and a *Tsc2* behavioral/epilepsy model. Also, a model relevant to LAM is in development in collaboration with The LAM Foundation. These models are vital to the Consortium for recruiting industry and academic partners to TSC research.

Clinical trials

For TSC, as for any rare disease, it is critical that every clinical trial is designed and executed for success. Regardless of whether a therapy may be effective or not, without a successful trial, we will likely never find out. The TSC Alliance is a critical point of contact between clinical trial sponsors and the needs and priorities of the TSC community. The organization can provide community feedback on protocol designs at a very early stage to ensure a trial is designed with endpoints to meet the highest priority needs of the community while having inclusion and exclusion criteria and study visit schedules that do not hinder participation by the very population the sponsor wishes to help.

Another critical role for the TSC Alliance is to educate the TSC community on the importance of participating in clinical trials, the roles community members can have in relation to trials, and the questions potential participants should ask when considering specific trials. We provide information and materials on our website, educate our volunteer community leaders, and spread the word using social media, webinars, in-person educational meetings, and more.

In 2012 the TSC Alliance partnered with a group of TSC Clinics on a series of NIH- and FDA-funded clinical studies.[23–25] These sites came together with the goal of running multiple clinical studies over time among a small group of sites to more efficiently initiate and complete clinical trials, building on shared infrastructure and lessons learned from previous iterations. The TSC Clinical Research Consortium has been very active and productive, including prospective natural history studies on the development of epilepsy and autism in infants. The TSC Alliance is now in the first stage of building a broader TSC Clinical Research Consortium model to expand beyond pediatric neurology trials and facilitate clinical studies to address the needs of adults living with TSC and individuals of all ages in need of clinical trials to address manifestations of TSC in organs beyond the brain.

The TSC Alliance has also partnered with academic investigators and companies to develop and test PRO measures. For example, the TSC Alliance, in collaboration with the TAND Consortium in the TANDem Project, is helping validate the TAND self-quantified checklist (TAND-SQ) through the Natural History Database's self-report portal. The intent is to use a validated TAND-SQ in a mobile application, and ultimately as a tool to determine if a particular drug or therapy is effective in treating aspects of TAND. Recently, a second questionnaire was added focusing on TAND and epilepsy from the caregiver's perspective to complement the patient's perspective. For many TAND symptoms, there are no existing 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.

Finally, when clinical trials reveal a new beneficial therapeutic approach, the TSC Alliance can provide input to the FDA on the importance of the unmet medical need that may be addressed by a new therapy. To define guardrails for interactions with industry and regulators, the TSC Alliance has adopted policies for corporate relations and for organizational participation in FDA hearings and meetings. These policies prohibit taking a stance for or against any particular product while enabling the organization to represent the needs of the TSC community with respect to unmet medical needs, relevant endpoints, etc. The expertise, resources, and relationships available to the TSC Alliance are available to help any sponsor or researcher with an interest in helping change outcomes for individuals living with TSC.

Impacting outcomes

The products of research are beneficial only when they are accessible to the people who need them. Access can be impaired at many levels, such as misdiagnosis or delayed diagnosis, lack of a healthcare provider's knowledge of current treatment standards, lack of evidence to choose among various therapies in a specific situation, payer processes and denials, socioeconomic barriers, and more.

While outstanding TSC Clinics and Centers of Excellence exist across the country, not everyone with TSC has the ability to obtain regular care at one of those clinics. As with any rare disease, only a small percentage of healthcare professionals outside such specialty clinics will have encountered a person with TSC. Even many of those who have had a TSC patient will not be familiar with current standards of care. Fortunately, consensus guidelines for the diagnosis, surveillance, and management of TSC exist. The TSC Alliance has sponsored clinical consensus conferences when there have been inflection points impacting standards of care to convene international experts in all aspects of TSC. These conferences led to the publication of updated consensus guidelines, the most recent of which were published in 2021.[2]

To help these guidelines reach healthcare providers who need them, the TSC Alliance reaches out at conferences, through professional publications, and continuing medical education providers. Additionally, the TSC Alliance educates the TSC community about the existence and importance of consensus guidelines and encourages them to share a copy of the guidelines with their own providers.

In many cases, insufficient evidence exists to support a consensus recommendation with high confidence. To help identify and fill such gaps, the TSC Alliance has recently taken the lead on important quality improvement initiatives in collaboration with TSC Clinics and the TSC community. Following discussions on women's health at the 2022 World TSC Conference, the TSC Alliance 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 the aim is to lead the development of frameworks to identify, develop, and adopt consensus guidelines by defining predictive risks through prospective and longitudinal evidence-based data collection to better inform guidelines and community education.

The TSC Alliance also advocates for access to approved therapies with payers, including at the state and federal government if needed. To empower community members to advocate for themselves, the TSC Alliance developed the TSC Navigator, an online resource to help people learn about various aspects of the TSC journey based on where each person is at on his or her journey. The TSC Navigator serves as a cross-functional tool for community members, physicians, and researchers. Participants have the opportunity to connect directly with TSC Alliance staff to help prioritize needs and receive education tailored to their unique situations. This program fosters optimized individual and caregiver insight, enhances access to specialists in TSC, and cultivates engagement and support. In tandem with our TSC Navigator program, our Clinic Ambassador Program provides additional support for designated TSC Clinics, with a specific focus on underrepresented and rural areas. Volunteers from the TSC community, serving as representatives of both the TSC Alliance and the

designated clinics, play a crucial role in offering peer-to-peer support to individuals and caregivers. They assist in navigating the challenges associated with this diagnosis and serve as integral members of the internal clinic support team, ensuring the patient and caregiver voice is represented in every care-coordination meeting.

Culture of collaboration

Collaboration permeates the TSC community at every level, throughout every program.[26] First and foremost, the TSC Alliance is committed to conveying the voice of the TSC community to create meaningful research outcomes. Collaboration continues with industry and academia on programs that deliver results to the TSC community. The TSC Alliance builds relationships with federal agencies, nonprofit organizations, and for-profit companies to accelerate development of innovative therapies and ensure access when they are approved. Our work will not end until, together, we have created a future where everyone affected by TSC can live their fullest lives.

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Ethics approval and consent to participate

No applicable.

Consent for publication

Not applicable.

Author contributions

Steven L. Roberds: Conceptualization; Methodology; Project administration; Resources; Supervision; Writing – original draft.

Zoë Fuchs: Data curation; Investigation; Methodology; Validation; Visualization; Writing – review & editing.

Elizabeth M. Cassidy: Data curation; Methodology; Project administration; Validation; Writing – review & editing.

Samantha Metzger: Data curation; Methodology; Validation; Visualization; Writing – review & editing.

Ayat Abi: Data curation; Investigation; Methodology; Writing – review & editing.

Ashley J. Pounders: Conceptualization; Investigation; Methodology; Resources; Writing – review & editing.

Dean J. Aguiar: Conceptualization; Investigation; Methodology; Resources; Writing – review & editing.

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Appendix

Abbreviations

FDA	Food and Drug Administration
IND	investigational new drug application
LAM	lymphangioleiomyomatosis
mTOR	mechanistic target of rapamycin
NIH	National Institutes of Health
PFDD	patient-focused drug development
PRO	patient-reported outcome
TAND	TSC-associated neuropsychiatric disorders
TAND-SQ	TAND self-quantified checklist
TSC	tuberous sclerosis complex
TSCi	TSC International
TSCRP	Tuberous Sclerosis Complex Research Program
WGS	whole genome sequencing

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