cureCADASIL Strategic Plan

2024-2026

"Never doubt that a small group of thoughtful committed individuals can change the world. In fact, it's the only thing that ever has." – Margaret Mead

A MESSAGE FROM LEADERSHIP

In 2012, a group of CADASIL families met, passionate to make an impact on their disease. From this meeting, the CADASIL Association (a.k.a. cureCADASIL) was formed. Since its founding, cureCADASIL has been a patient advocacy organization managed by and solely in the interests of patients, families, and caregivers. We have grown and matured, continuing to build a solid organizational foundation from which we have developed initiatives to support our "CARE platforms" of Communications, Advocacy, Research, and Education. Our initiatives were chosen to make a meaningful impact while building our organization to be positioned to take on the next level of initiatives that will move us closer to our community's vision for finding a cure for CADASIL.

We listened to the community and heard the sense of urgency to identify disease-modifying therapeutics. Our three-year strategic plan focuses on rapid and complete enrollment of on-going patient history studies; in-depth assessment, and prioritization of research that cureCADASIL will fund; and fundraising campaigns to support the priorities most vital to the patient community. We are excited to share our plan and calls to action with our CADASIL families, researchers, clinicians, donors, and volunteers.

We are deeply grateful to everyone who has supported us on this journey. We still have a lot of work to do together. Please consider donating, fundraising, attending a community or educational event, joining a study, or volunteering to help us accomplish the actions laid out in this strategic plan.

Thank you!

Bertram Kasiske President	**Jane Gunther** Science Officer	**Debra Robinson** Treasurer
Pedro de Lencastre Secretary	**Sandra Talbird** Trustee	**Vinita Bahl** Trustee

INTRODUCTION

In 1991 multiple members of a large French family were first reported to have a disease that included strokes, migraine, dementia, seizures, and leukoencephalopathy.[1] Genetic studies traced the disorder to chromosome 19, and an appreciation of the unique abnormalities of intracerebral arteries led to the newly described disease's name.[2] Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is caused by a mutation in the NOTCH3 gene. Although rare, it is the most common monogenic cause of strokes and vascular dementia. It has been reported to affect 2-4 persons per 100,000 adults.[3-6] The prevalence of gene mutations known to cause CADASIL has been found to be higher in more recent studies, however it is possible that not all of these gene mutations caused CADASIL.[7,8] There are no known treatments to prevent, cure or slow the progression of CADASIL.

CureCADASIL (https://curecadasil.org/) was founded in April 2012 as a patient-advocacy organization and cureCADASIL is a 501(c) non-profit organization under federal law of the United States. The Board of Trustees is currently made up of six volunteers who all have CADASIL, and/or family members or close personal relations with the disorder.

In 2020, the Board adopted the Castleman Disease Collaborative Network model focused on patient-centric research as a patient-led organization committed to advancing CADASIL research through uniting patients, researchers, and clinicians to find a cure for CADASIL.[9.10]

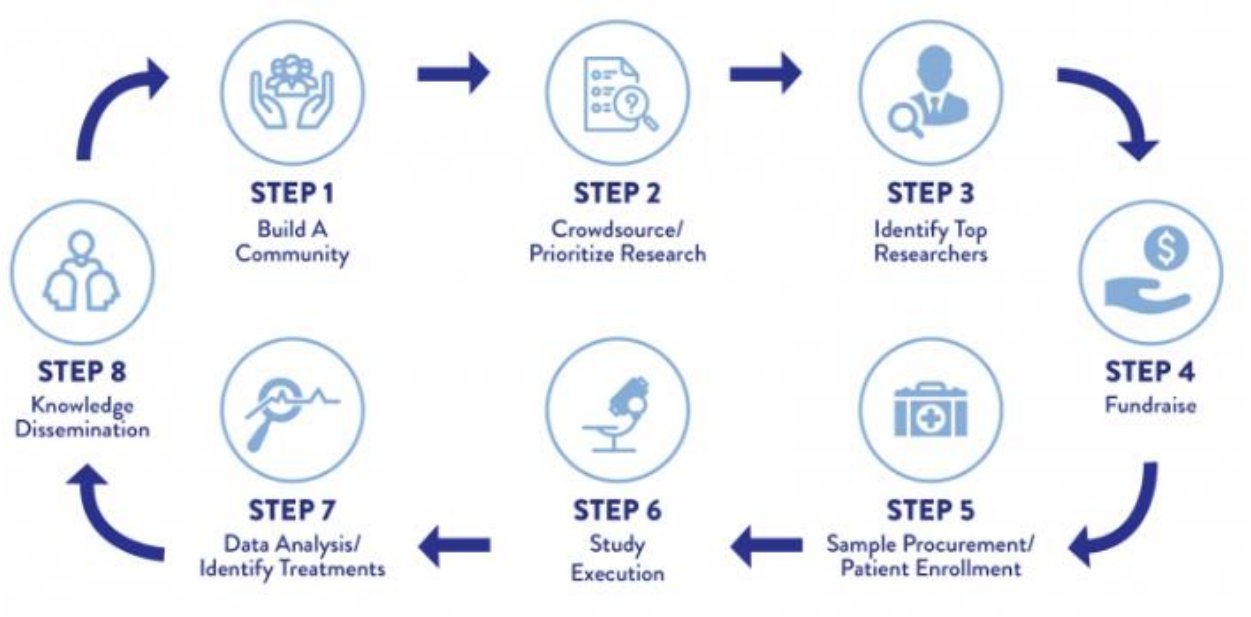

Figure 1. Castleman Disease Collaborative Network model, used with permission. (https://cdcn.org/about-us/our-approach/)

METHODS

The Board worked with a Strategic Planning Facilitator that led to the development of our 3-year strategic objectives and identification and prioritization of the major goals. In the process, we also revised our Vision and Mission statements. Our strategic plan was approved by the cureCADASIL Board of Trustees on March 6, 2024.

WHO WE ARE

OUR VISION:

A world without CADASIL.

OUR MISSION:

CureCADASIL is a patient-led organization committed to advancing CADASIL research through uniting patients, researchers, and clinicians to find a cure for CADASIL.

OUR CORE VALUES:

We leverage our core values of collaboration, community, inclusion, integrity, and optimism to work on behalf of the patients and their families living with CADASIL.

COLLABORATION. We highly value collaborations with researchers, clinicians, and other collaborators, recognizing the collective strength in advancing our shared mission.

COMMUNITY. We actively engage with the diverse CADASIL community, fostering connections among patients, family members, caregivers, researchers, clinicians, and all other stakeholders invested in discovering treatments and ultimately finding a cure for CADASIL. Together, we are dedicated to making a meaningful difference in the lives of those affected by this disease.

INCLUSION. We embrace diversity across all geographic regions and ethnic backgrounds affected by CADASIL. While acknowledging that socioeconomics can influence access to CADASIL diagnosis and care, we are committed to inclusivity, striving to overcome barriers and ensure all patients and families receive the support that they need.

INTEGRITY. Our commitment to ethical conduct is unwavering. We pledge honesty and transparency, upholding these values in all interactions within our community.

OPTIMISM. We embrace the power of hope and are dedicated to fostering optimism by relentlessly pursuing research & drug development to realize a world without CADASIL.

CURECADASIL MILESTONES

A UNIQUE ICD-10 CODE for CADASIL

In July 2018, through the collaborative effort of cureCADASIL, its Scientific Advisory Board, CADASIL researchers, specialists, and the CADASIL patient community, the National Center for Health Statistics designated a specific ICD-10 diagnostic code for CADASIL. The decision was based, in part, on a proposal developed by cureCADASIL and presented by Dr. Swati Sathe to the Centers for Disease Control and Prevention ICD-10 Coordination and Maintenance Committee at a public meeting on March 8, 2017.

The ICD-10 diagnosis code for CADASIL is an important milestone for epidemiologic research to determine prevalence, morbidity and mortality; recruitment of patients for clinical trials; outcomes of clinical interventions; and protocols for care.

MILLION DOLLAR BIKE RIDE FUNDRAISING FOR RESEARCH

Since 2019 cureCADASIL has participated in the University of Pennsylvania School of Medicine Orphan Disease Center Million Dollar Bike Ride (MDBR) research fundraising initiative, raising a total of $512,792.[11] In 2023, Team CADASIL raised $109,806. This grant was awarded to Helena Karlström, Karolinska Institutet, Sweden, for "Immunotherapy and improved diagnosis and prognosis of the small vessel disease CADASIL". She was selected from among several applicants by an independent team of expert reviewers under the administration of the Orphan Disease Center. Annually, researchers present their results supported by the CADASIL community's funding through the MDBR.[12]

CHAN ZUCKERBERG INITIATIVE (CZI) GRANT INITIATED

In November 2022, cureCADASIL was awarded a Patient-Partnered Collaborations for Rare Neurodegenerative Disease Grant award, partnered with Fanny Elahi, MD, PhD, at the Icahn School of Medicine, Mount Sinai, New York.[13]

The patient engagement and research plans were initiated in January 2023. The award is for $2,000,000 over four years, with $400,000 going to cureCADASIL-led activities. The funding enables us to build communication and education capabilities to better engage patients, clinicians, and researchers. It also helps us to support Dr. Elahi's natural history study and basic research to understand the mechanisms of disease.

PATIENT-INVESTIGATOR MEETING

In June 2023, cureCADASIL held a conference bringing together the patient community and key clinical and basic researchers in a half-day Patient-Investigator meeting as part of the United Leukodystrophy Foundation's annual Family Conference. These investigators are working on target discovery and leading the NIH-funded patient history

studies in the US. They presented their research updates and participated in an open panel discussion with patients and family members.[14]

RECRUITING FOR OBSERVATIONAL STUDIES IN THE US

There are currently three major, natural history studies taking place in the US with over 200 patients enrolled. These studies are critical for the discovery of unique biomarkers that will help in the understanding of the mechanisms of disease and provide information necessary for the design of future therapeutic trials.

- CADASIL Consortium,
- CZI PPC Grant – cure CADASIL
- National Heart Lung Blood Institute's observational study of CADASIL.

CureCADASIL and the patient community are committed to collaborating with the investigators to enroll patients and family members in these studies. CureCADASIL has been conducting webinars, social media postings and actively recruiting patients and family members to increase participation. It is imperative that we increase enrollment in these studies. To achieve enrollment goals, we have assembled a social media and marketing team to improve outreach and engagement with our patient community.

CHALLENGES

CADASIL is caused by a single mutation of the NOTCH3 gene on chromosome 19, but more than 200 distinct pathogenic mutations have been reported.[15] As noted above, it is not known why the prevalence of mutations that can cause CADASIL is greater than the actual prevalence of the disease itself.

Although awareness of CADASIL is growing, its diagnosis is often delayed, especially in patients with limited access to healthcare. In addition, CADASIL may be misdiagnosed, for example as multiple sclerosis.

Individuals can show variability in the nature, severity and age of onset of symptoms, as well as the rate of disease progression. Research suggests that variability is due to the position of the mutation on the NOTCH3 gene. But environmental factors may also influence disease manifestations.[8,16]

Characteristic features have been observed by magnetic resonance imaging in patients with CADASIL, and efforts are being made to identify reliable imaging and blood biomarkers. The

accumulation of granular osmiophilic material (GOM) in blood vessel walls is also a characteristic feature associated with CADASIL. However, the role of GOM in the pathogenesis of CADASIL is unclear.[17]

The pathogenesis of CADASIL continues to be studied by cell culture, animal models and clinical observation. Major hypotheses have included abnormal NOTCH3 signaling, toxic aggregation of mutated Notch3 protein, vascular dysfunction, and involvement of the immune system.[17] It is important for cureCADASIL to support research in these different areas.

Information from studies of the natural history of CADASIL are critical for the design of therapeutic trials. CADASIL researchers depend on patients and family members to identify demographic, genetic, environmental, and other factors that correlate with disease progression and outcomes. Natural history studies also foster the identification of biomarkers that predict disease outcomes and response to therapy. The importance of natural history studies cannot be overstated.

There are no known therapies that prevent or slow the progression of CADASIL. Addressing vascular risk factors, such as hypertension and tobacco use, may mitigate disease severity.[16] But only a concerted research effort will yield effective disease-modifying treatments.

To meet these challenges, cureCADASIL supports natural history and other research studies in collaboration with investigators, fundraising for their research and importantly, recruiting patients to participate in studies. These efforts will help bring us closer to identifying and testing therapeutic candidates in clinical trials.

STRATEGIC OBJECTIVES

ACCELERATE RESEARCH

By collaborating with our advisors, we will identify key areas of research that will deepen our understanding of CADASIL. This approach will guide strategic collaborations that accelerate research and maximize our impact on efforts to find treatments that slow disease progression. To achieve this, cureCADASIL identified the following as key strategies: 1) community engagement (patients, clinicians, and researchers), 2) funding, 3) scientific synergies, and 4) broader awareness of CADASIL.

STRATEGIC OBJECTIVES:

1. Continue to seek out, collaborate, and fund diverse research that reflects many biological pathways including vascular dysfunction, misfolded proteins, the immune system, and RNA- or DNA-modifying therapeutics.
2. Focus resources to support the natural history studies that are the critical first steps of obtaining the data necessary to design clinical trials.
3. Partner with our advisors (Patient & scientific) and external collaborators to develop a prioritization model that will enable an iterative process to select promising research projects most vital to the patient community.
4. Identify research partners to focus on drug repurposing to advance this research through the drug development process.
5. Unite experts to understand possible paths forward for gene therapy.
6. Communicate research advancements to the community and gain alignment on opportunities requiring funding.

INCREASE REVENUE

We aim to increase revenue by mobilizing our communities, engaging individual donors, corporations, and organizations to accelerate progress and maximize the impact of our mission. We will make investments in research that will improve our understanding of CADASIL and identify treatments, steward our donations wisely and keep a tight rein on expenses.

STRATEGIC OBJECTIVES:

1. Generate $50,000 in annual revenue through initiative-taking engagement with individual donors.
2. Establish robust collaborations with industry partners to garner support for research and educational endeavors.

Enhance Community Communications and Engagement

We will provide resources for our community of patients, caregivers, families, clinicians, and researchers to learn about CADASIL, ongoing research, and opportunities.

Strategic Objectives:

1. Make it easier for our community to access critical information about CADASIL disease, and facilitate the participation in research studies, a patient registry, natural history studies, and provision of samples for researchers studying CADASIL.
2. Continue to communicate research advancements to the community.
3. Connect our community through in-person and virtual patient-investigator conference, outreach events, and research updates via webinars.
4. Include our Community Advisory Group in opportunities to help steer and support our mission.

Advocate for Our Community

We are forming relationships and utilizing resources within the rare disease community to make our voice heard, attract support, and focus on our cause.

Strategic Objectives:

1. Generate external interest in our community by sharing patient stories, updates on research and the science of CADASIL.
2. Stay involved in drug development and regulatory processes when we believe it will make a difference.
3. Promote the interest of our community at rare disease conferences and with state and federal legislators.

Build an Effective and Stainable Patient-Led Advocacy Organization

We aim to transition from the current all-volunteer organizational model to one that incorporates sufficient professional management. This will enable volunteers and Board

members to focus on their strengths in providing patient education, leading research projects, conducting fundraising campaigns, and influencing data management.

STRATEGIC OBJECTIVES:

1. Secure grants to facilitate the expansion of organizational infrastructure to enable the recruitment of skilled, paid professional personnel.
2. Expand the Board as needed to grow cureCADASIL.
3. Recruit volunteers to work on projects and events that enhance community communications, patient engagement, and advocacy.

ABBREVIATIONS

CADASIL, Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy;
CDCN, Castleman Disease Collaborative Network;
CDMG, CADASIL Disease Modeling Group;
CZI, Chan-Zuckerberg Initiative;
GOM, granular osmiophilic material;
MDBR, Million Dollar Bike Ride;
PCORI, Patient-Centered Outcomes Research Institute;
RDCA-DAP, Rare Disease Cures Accelerator- Data Analytics Platform;
SAB, Scientific Advisory Board;
SMART; **S**pecific, **M**easurable, **A**chievable, **R**elevant, **T**ime-bound

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APPENDIX

Strategic Plan: Accelerate Research

2024-2026 Strategic Objectives	2024-2026 SMART Goal Priorities
1. Continue to seek out, collaborate, and fund diverse research that reflects many biological pathways including vascular dysfunction, misfolded proteins, the immune system, and RNA- or DNA-modifying therapeutics. **2.** Focus resources to support the natural history studies that are the critical first steps of obtaining the data necessary to design clinical trials. **3.** Partner with our advisors (patient & scientific) and external collaborators to develop a prioritization model that will enable an iterative process to select promising research projects most vital to the patient community. **4.** Identify research partners to focus on drug repurposing to advance this research through the drug development process. **5.** Unite experts to understand possible paths forward for gene therapy. **6.** Communicate research advancements to the community and gain alignment on opportunities requiring funding.	• Initiate projects in Q1 2024 to conduct CZI research, education, and communication plans. • Fulfill the terms of the CZI grant with Dr. Elahi and continue to collaborate on study enrollment to secure the second round of funding in Q4 2024. • Facilitate creation of a development plan for data-sharing between the US natural history studies by the end of Q2 2024 and thereby reduce data collection burden on patients that encourages participation. • Identify research funding needs and opportunities not met by other sources (e.g. MDBR) by the end of Q2 every year and consider fundraising campaigns. • CZI-CDCN Drug Repurposing Roadmap: – Initiate the Prep Stage: Identifying potential drugs and target pathways with research advisors and consultants by end of Q4 2024. – Initiate Early stage: secure funding, secure research team, test existing drugs in nonclinical models, collect any existing patient data by Q4 2025. – Initiate Clinical Stage by recruiting patients for clinical trials, executing clinical trials stages I, II, III by Q4 2026 • Help CDMG develop specific aims, and new members to achieve those aims, annually. • Establish an active SAB and new charter by the end of Q2 2024, in order to advise a research strategy and recruit new members as needed. • Establish a Natural History Study on a new, sustainable platform by Q4 2024; transfer current registry by Q4 2025; and conduct an enrollment

	campaign to increase registry participants by at least 10% by Q4 2026. ● Establish a plan to maximize potential collaborations with RDCA-DAP by Q4 2024.

Strategic Plan: Increase Revenue	
2024 – 2026 Strategic Objectives	**2024-2026 SMART Goal Priorities**
1. Generate $50,000 in annual revenue through initiative-taking engagement with individual donors. **2.** Establish robust collaborations with industry partners to garner support for research and educational endeavors.	● Achieve revenue targets for 2024 of $40,000; 2025 of $50,000; and 2026 of $50,000. ● Achieve MDBR fundraising goals for 2024 of $110,000; 2025 of $120,000; and 2026 of 130,000. ● Draft 3-year fundraising plan by Q3 2024. ● Identify and apply for at least 1 federal or private research grant(s) by Q4 2025. ● Increase community support for research by converting 50 donors to recurring annual-giving, conducting contact meetings with 10 high- tier donors, and roll-out new fundraising tools by end of Q4 2025.

Strategic Plan: Enhance Community Communications and Engagement	
2024 – 2026 Strategic Objectives	**2024-2026 SMART Goal Priorities**
1. Make it easier for our community to access critical information about CADASIL disease, and facilitate the participation in research studies, a patient registry, natural history studies, and provision of samples for researchers studying CADASIL. **2.** Continue to communicate research advancements to the community. **3.** Connect our community through in-person and virtual patient-investigator conference, outreach events, and research updates via webinars. **4.** Include our Community Advisory Group in opportunities to help steer and support our mission.	● Each quarter 2024-2025, host an open office zoom meeting for community relationship building and to better understand the patient/family experience. Provide a report to the Board on insights gained to improve communication and engagement. ● Develop a communication strategy and initiate it by the end of Q2 2024. A social media team will update the communication strategy based on previous years' metrics reports and initiate it by the end of Q1 2025 and Q1 2026. ● Enhance and update the cureCADASIL website, including new patient stories and videos per Board approved plan by end of Q2 2024. Develop a new content plan for the website and execute by Q4 2024. Evaluate needs for enhancement and update of the website in Q1 of 2025 and Q1 2026 to plan for any needed work for the year. ● Launch a quarterly podcast aimed at education and advocacy by Q1 2026. ● Continue educating our community about research and advocacy opportunities via quarterly newsletters. Develop and disseminate our 2024 annual report on our website and via social media.

Strategic Plan: Advocate for Our Community	
2024 – 2026 Strategic Objectives	**2024-2026 SMART Goal Priorities**
1. Generate external interest in our community by sharing patient stories, updates on research and the science of CADASIL. **2.** Stay involved in drug development and regulatory processes when we believe it will make a difference. **3.** Promote the interest of our community at rare disease conferences and with state and federal legislators.	● Commit to providing comments on and support regulatory guidance and legislation that impact rare diseases. ● As researchers and drug developers pursue new avenues of research, cureCADASIL will continue to collaborate with policymakers and the FDA to represent the patient perspective.

Strategic Plan: Build an Effective and Sustainable Patient-Led Advocacy Organization	
2024 – 2026 Strategic Objectives	**2024-2026 SMART Goal Priorities**
1. Secure grants to facilitate the expansion of organizational infrastructure to enable the recruitment of skilled, paid professional personnel. **2.** Expand the Board as needed to grow cureCADASIL. **3.** Recruit volunteers to work on projects and events that enhance community communications, patient engagement, and advocacy.	● Identify capacity building grant (e.g., PCORI) 2024 application deadlines and grant requirements. Apply for the grant by the end of 2025. ● Recruit volunteers for social media, marketing, content writing, fundraising, operations/ project coordination, volunteer staff support, and policy news by the end of 2024. Expand the Board by 1 member in 2024 and 1 member in 2025. ● Define a plan and secure funding to hire an Executive Director and Fundraising/Development Manager by the end of 2026.