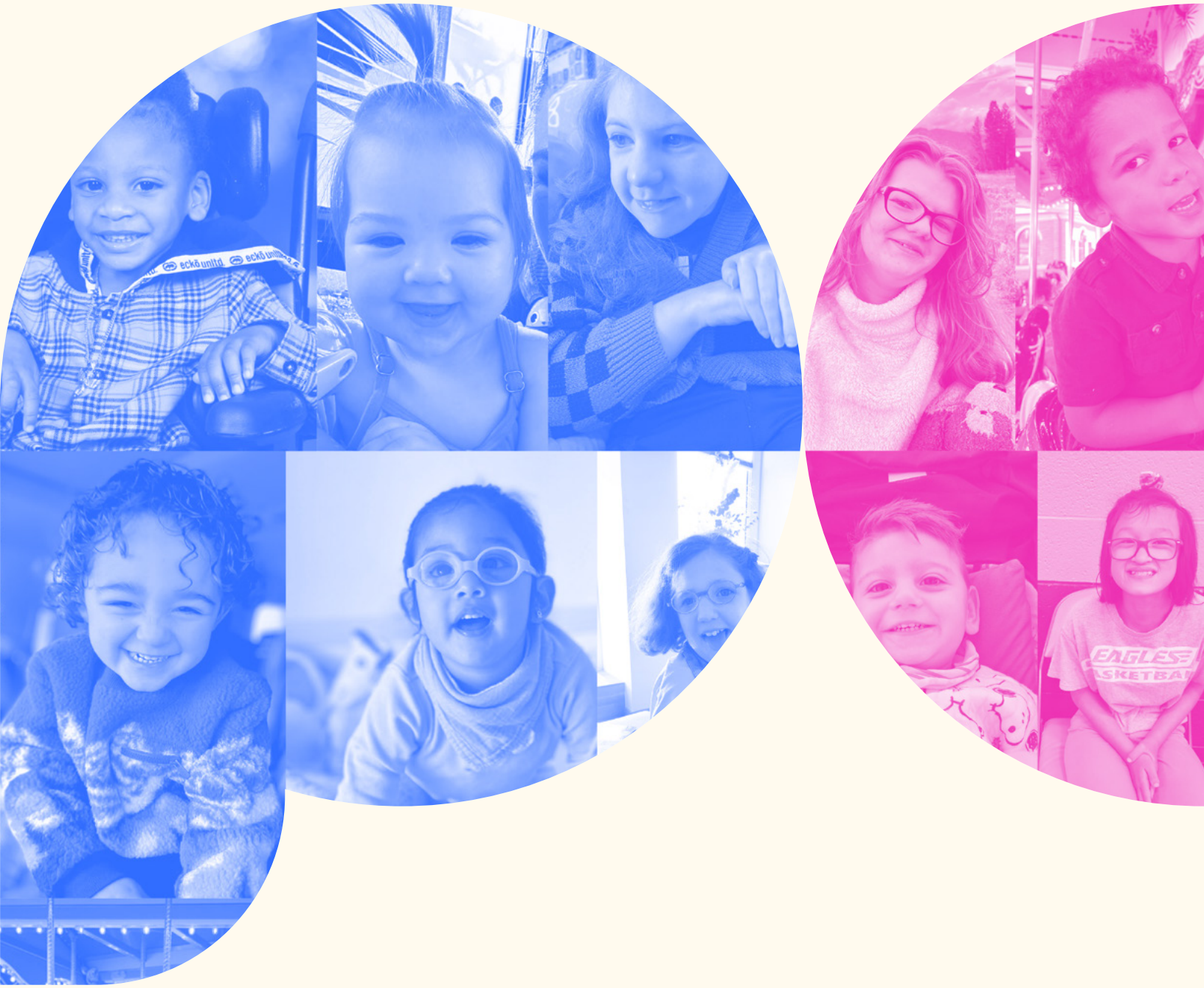
project™ cask

2025 Annual Impact Report



Introduction

2025: Moving the entire research roadmap forward

In the early days of Project CASK, much of our work happened quietly. Behind screens and kitchen tables, between school drop-offs and late-night or early-morning emails, a group of parents and scientists began asking questions about what was known, what was unknown, and what could be done. By 2024, we were building the scaffolding, inviting researchers into a new way of working, shaping scientific collaboration, and gathering families who were ready to participate as partners in this mission. It was careful, deliberate, necessary work.

In 2025, something shifted. The questions grew sharper. The conversations deepened. Research that once felt abstract began to yield insight – not answers yet, but direction. Collaborations formed across institutions and disciplines. Our natural history efforts expanded, turning individual stories into shared understanding. CASK gene research, long scattered across papers and clinics, began to cohere into a field people could see, engage with, and build upon. None of this happened all at once, and none of it happened by accident.

What makes 2025 remarkable is not only the visible achievements, though those matter, but the accumulation of small, disciplined steps that changed what is now possible. A dataset strengthened. A researcher newly engaged. A family deciding to enroll. A conversation that didn't end with "there's nothing to be done." This is what progress looks like when it is built by parents who refuse to accept the limits handed to them, and by scientists willing to meet that resolve with rigor. The story of 2025 is not one of arrival. It is the moment the path ahead became undeniable.

What follows is a closer look at how 2025 took shape; how ideas moved into action, how scattered efforts became coordinated, and how progress is being built piece by piece. You'll see the structure underneath the work, the choices that guided it, and the early signals that tell us we're moving in the right direction.

We're deeply grateful to everyone who supported this journey—our donors, partners, researchers, and advocates—and especially to the CASK community who showed up, again and again, to make this work possible. We hold close the CASK angels we lost too soon, whose lives continue to guide us toward a better future.

Thank you for being here. This is what 2025 made possible.

16+
research partners actively engaged

6
scientific meetings and webinars convened

11
studies in progress

1
research publication from PC funding

1
workshop on drug development for neurological disorders

550 families and 54
countries united through the Liocorn Roster

Advancing the Roadmap

Developing treatments for ultra-rare diseases requires more than a single breakthrough.
It demands progress across every stage of the drug development pathway. In 2025, we advanced multiple components in parallel, strengthening the foundation needed to move toward clinical trials and making CASK a viable candidate for future investment.

Together, these elements form the foundation required to move CASK therapies from concept to clinic.

1. Natural History & Disease Characterization

What: Comprehensive understanding of how CASK presents clinically, how it progresses, and what the patient population looks like.

Impact: Establishing the evidence base that makes clinical trials possible.

Citizen Health Platform
131 global enrollments collecting longitudinal clinical data for digital Natural History Study.

CASK Data Collection Program with Rare-X
151 global enrollments collecting comprehensive caregiver-reported information on all aspects of health & development.

Epilepsy Study
Dr. Asim Shahid, NY Presbyterian Hospital and Weill Cornell Medical School
Characterizing CASK-related epilepsy and identifying biomarkers.

MRI Study
Dr. Xilma Ortiz-Gonzalez, Children's Hospital of Philadelphia and Dr. Cesar Alves, Boston Children's Hospital
Analyzing structural brain abnormalities in CASK disorders and changes over time.

Determining CASK Disorder Prevalence
Dr. Karen Malone, GeneScape
First systematic prevalence study to establish incidence rates, essential data for attracting pharmaceutical investment.

Genotype-Phenotype Analysis
Dr. Kevin Jiang, Baylor College of Medicine
As part of prevalence study, analysis of one of the largest CASK cohorts to date, providing critical insights into genotype-phenotype relationships.

Liocorn Roster
550 diagnosed individuals mapped worldwide across 54 countries
Most comprehensive count of CASK diagnoses around the world.

2. Disease Mechanisms & Therapeutic Target Identification

What: Understanding what goes wrong at the molecular level and what to target therapeutically.

Impact: Multiple therapeutic targets identified through collaborative science.

Three Global CASK Science Meetings
Infrastructure for collaboration across researchers and institutions to share knowledge and deepen understanding, including with adjacent disorder researchers.

Research into neuronal loss mechanisms
Examining the molecular triggers driving cerebellar granule cell death to test targeted inhibitors.

Uncovering cellular signaling dysregulation & protein interactions
Uncovering impact of CASK loss on cellular developmental pathways and molecular binding sites to identify drug candidates

3. Preclinical Models

What: Tools to deepen understanding and test potential therapies.

Impact: Expanding our understanding of molecular processes affected by CASK loss and enabling targeted testing of drug candidates.

Cerebellar Brain Organoids
CASK patient-derived 3D brain models developed to understand early brain development, particularly in the cerebellum, and enable drug screening.

New CASK Gene Mouse Model
Conditional knock-in model in development at Jackson Laboratory.

Patient Cell Lines
Multiple CASK variant cell lines developed with plan to expand CASK biorepository.

4. Therapeutic Development

What: Developing treatments for CASK-related disorders, with multiple shots on goal.

Impact: A diversified therapeutic pipeline, including a disease-modifying therapy.

Gene Replacement Therapy
Dr. Mingshan Xue, Baylor College of Medicine
Funded $375,000 over 2 years for a disease-modifying treatment for females and males.
2025 Oxford-Harrington Rare Disease Scholar, external validation of research quality.

Small Molecules (multiple drug targets)
Dr. Hans-Jürgen Kreienkamp, University of Hamburg and Dr. ChangHui Pak, University of Massachusetts, Amherst
Funded $250,000 over 2 years to identify critical disease mechanisms and to test multiple small molecules.

Next Generation JNK Inhibitors
Secured state-of-the-art JNK inhibitors with greater brain penetrance for testing by Dr. Katsuhiko Tabuchi, Shinshu University (*Project CASK is not funding Dr. Tabuchi's work).

Partnership with Rare Disease Translational Center, Jackson Laboratory
Therapeutic investigation once mouse model development is complete.

5. Biomarkers & Outcome Measures

What: Ways to measure if a therapy is working and what changes are happening.

Impact: Building the tools required to run meaningful and feasible clinical trials in CASK disorders.

Epilepsy Study
Dr. Asim Shahid, NY Presbyterian Hospital and Weill Cornell Medical School
Characterizing CASK-related epilepsy and identifying biomarkers.

COMBINEDBrain Biomarker Study for Neurodevelopmental Disorders
Identifying relevant biomarkers across neurogenetic conditions.

Outcome Measure Consortium
Establishing a research team to identify effective outcome measures and endpoints for CASK disorder clinical trials.

Kim Pulliam

My journey – and why Project CASK

My daughter Shea was a joyful young woman who loved music, swimming, bowling, and being outdoors in nature. She had an infectious laugh and a love for silly things, like the beat of electronic dance music, the antics of SpongeBob Squarepants, and the crazy sounds and faces her Daddy made to always entertain his Shea-bug. I was told many times by family, friends, school-mates and strangers who crossed our path that they felt calm and at peace when they were around Shea.

When she was eight years old, she was diagnosed with a CASK gene mutation — a rare disorder that gave us a name but little guidance. She lived with severe health challenges, including epilepsy, gastrointestinal issues, and being non-verbal and non-ambulatory. As she grew older, her illnesses became more frequent, and doctors struggled to treat her because there was so little research or understanding of the disease. They could only manage her symptoms, and when treatments didn't work, we were often sent home after long hospital stays without answers, feeling alone and scared.

Her journey was painful and ultimately took her life. Shea was unique, and a blessing to me. Through it all, I was proud to be her mom, advocate, caregiver, educator, friend and voice — keeping my promise that she would never face this alone.

Now, I am determined to extend Shea's legacy, sharing my professional and personal skills and my learnings from Shea's life journey by directly supporting Project CASK's mission. I feel called to partner with other families to push for better understanding, treatments, and improved quality of life for those affected. My mission is to reduce suffering and ensure that no family facing CASK has to walk this road alone.

KIM PULLIAM, MOTHER TO SHEA PULLIAM, 2002–2023

Research Breakthroughs & Ecosystem

"By identifying promising science and deploying parent-driven capital at a critical moment, we accelerated preclinical work by a leading researcher who caught the attention of one of the world's most prestigious rare disease programs."

Parent-Led Drug Development: Gene Therapy for CASK

We identify promising science, deploy capital at critical moments, and create momentum to attract larger institutional investment.

Dr. Mingshan Xue at Baylor College of Medicine had been investigating CASK, but required resources to move preclinical work forward at the speed families needed.

In 2024, Project CASK invested $375,000 in Dr. Xue's program. Not grant money requiring years of applications. Parent-driven capital, deployed to accelerate the science.

The investment paid off. Dr. Xue's strengthened preclinical data caught the attention of the Oxford-Harrington Rare Disease program, one of the most selective therapeutic development initiatives in the world. In 2025, he was named an Oxford-Harrington Scholar, validating both his science and the strategic impact of family-led funding.

This is how we compress timelines — because our children don't have time to wait.

Building the CASK Ecosystem: From Silos to Collaboration

For rare diseases, scientific collaboration is essential.

When Project CASK launched, CASK researchers were scattered across continents, working largely independently. Knowledge stayed in individual labs and therapeutic development was limited.

One of our first initiatives in December 2023 was to convene the inaugural scientific meeting on CASK, bringing together ~30 researchers and clinicians to discuss CASK, what we know and what questions we need answered. We have continued to convene the scientific community dedicated to CASK disorders, as well as to invite collaboration with adjacent disease areas where the cross-fertilization of knowledge and therapeutic approaches can advance our efforts.

Strategic collaboration accelerates discovery. The Kreienkamp-Pak partnership—which Project CASK facilitated—has led to a full spectrum research pipeline from biochemical analysis to cell lines and organoids, fast-tracking the identification and testing of potential therapeutic targets.

"By connecting researchers who had never spoken before, facilitating partnerships, and convening the scientific community, Project CASK is transforming isolated efforts into a coordinated ecosystem capable of fast-tracking discoveries for CASK disorders."

Activating the Community: Families as Partners in Discovery

For ultra-rare diseases, progress depends on participation. Without families willing and able to contribute data, insights, and lived experience, even the most promising science stalls. From the beginning, Project CASK partnered with platforms that make family participation possible as a core part of the research infrastructure. These include the Citizen Health Platform, Rare-X, and the CASK Biorepository with COMBINEDBrain, which together allow families to contribute longitudinal clinical and caregiver-reported data as well as biosamples.

Alongside these partnerships, Project CASK built the Liocorn Roster, the most comprehensive count to date of CASK diagnoses globally. By mapping over 550 individuals across 54 countries, we created a foundation that turns individual stories into collective knowledge and a global network.

When families are engaged as partners, studies can enroll more quickly, data is richer and more representative, and research priorities stay grounded in real-world needs. What emerges is not just a stronger dataset, but a more resilient ecosystem, one where discovery is accelerated because the people most affected are helping to build it.

"What emerges is not just a stronger dataset, but a more resilient ecosystem, one where discovery is accelerated because the people most affected are helping to build it."

Alexandrea Hardesty
Research that sees him

Being a mom to Sunny, my 3 year old with CASK, has been one of the most challenging and rewarding journeys of my life. When Sunny was diagnosed, doctors gave us a long list of things he would never do, but time and time again, Sunny has proven them wrong. He is walking now, something we were told would never happen, and that's just one of many milestones he has accomplished. Everyday he grows into a strong and incredible little boy that we cherish.

Through Project CASK, I have found not only knowledge but confidence. I've learned how to advocate for Sunny, making sure he receives the support and medical care he needs to thrive. I no longer feel like I'm navigating this path alone.

This community surrounds us, no matter how far apart we are. It's a group of people who show up for one another with open hearts and unwavering support. Without them, I would have been lost and instead I have hope.

ALEXANDREA HARDESTY, MOTHER TO SUNNY, AGE 3

Community Engagement & Impact

Building the Foundation for the Road Ahead

Therapeutic development takes years. While we advance science, Project CASK ensures families are supported, informed, and connected every step of the way. In 2025, our work focused on creating meaningful opportunities for engagement, sharing knowledge, and building a resilient global network of families and advocates.

Engaging and Educating Families

Families connected directly with researchers through virtual events, including the CASK Virtual Family Forum with Dr. Kreienkamp and Dr. Pak, and a gene therapy update webinar with Dr. Xue. Educational resources — including info sheets on sleep and gastrointestinal issues, and a genetics 101 primer created by Emily Janeiro through the Orphan Disease Center, Genetic Counseling Student Exchange program — helped families navigate day-to-day challenges and make informed decisions about care and research participation.

Raising Awareness and Strengthening Community

Initiatives like Roar for Rare on Rare Disease Day and CASK Gene Awareness Day foster visibility for CASK gene disorders, connect families to advocacy networks, and create opportunities for collaboration with the broader rare disease community. By sharing stories, knowledge, and resources, Project CASK strengthens both local and global connections, helping families feel part of a larger movement.

Community-Driven Engagement

Families are at the heart of Project CASK. In 2025, they organized and participated in creative campaigns to raise awareness and support, including the Ultra Rare Collection art show, "A Walk with James," Faith in Action in honor of Shea Pulliam, Make a Splash for CASK, Cayucos Sip and Support, and the Bishop's Reindeer Rumble. These efforts foster connection, build solidarity, and generate the resources that sustain our work.

Through engagement, education, and advocacy, Project CASK nurtures a global community that is informed, connected, and ready to act. Families are not just recipients of support, they are central to building the ecosystem that will carry research from discovery to treatment.

Sophia Marcengill
What we found when we needed it most

Piper was diagnosed with CASK just two weeks before her first birthday. We felt overwhelming fear — fear of what this meant for her future and for our family. While we were relieved to finally have an answer, we also felt lost knowing how little research exists. Our doctor connected us to the CASK community on Facebook, and finding them meant everything to us. For the first time, we didn't feel alone. Other families offered support in our hardest moments, shared in our victories, and gave us invaluable advice, resources, and hope. They also empowered us to become advocates — not only for Piper, but for all children living with CASK.

Ongoing research means there is a possibility for more answers, better treatments, and a brighter future for children like Piper. It reassures us that our community is seen and that dedicated doctors and researchers are working tirelessly to help our children thrive. Because of this hope, we have found our voices — raising awareness, sharing Piper's story, and advocating for continued research and support so that no family has to face this diagnosis alone.

Despite the challenges she faces each day, Piper is the happiest little girl. She loves Ms. Rachel, her brothers, and light-up toys, and her giggle can brighten any room. She works incredibly hard on gaining independence — sitting, weight bearing, interactive play, and exploring new textures. Piper's strength inspires us to keep fighting for her future and for the futures of all children with CASK. Through advocacy, community, and research, we hold onto hope every single day.

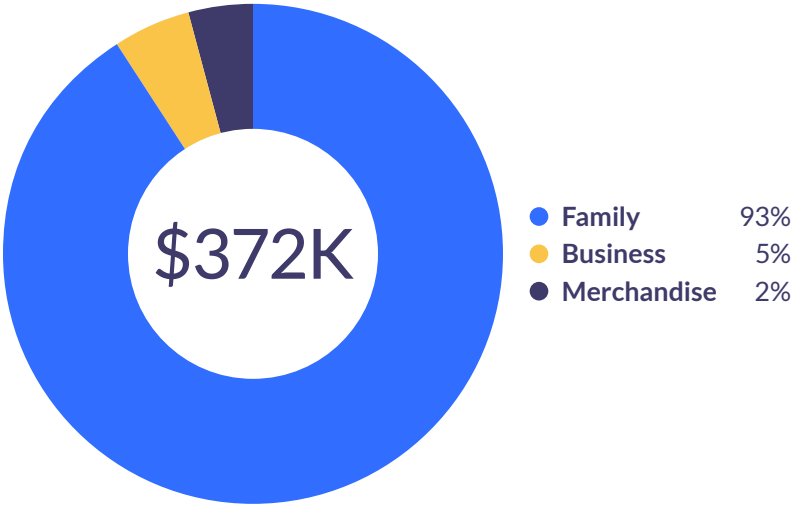
SOPHIA MARCENGILL, MOTHER TO PIPER, DIAGNOSED IN 2025

Finances

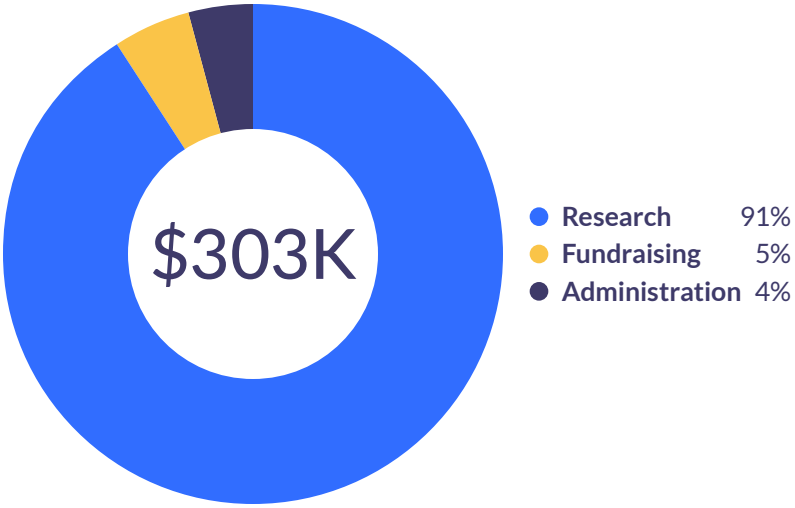
Your Investment, Our Execution

Every dollar invested unlocks institutional research value.

2025 Fundraising Contributions



2025 Expenditures



Looking Ahead

Turning Foundation into Progress

In 2026, Project CASK will advance every element of our roadmap:

- A therapeutic landscape assessment based on CASK biology to ensure our Global CASK Therapeutic Roadmap is appropriately sequenced and costed
- Natural history data revealing new patterns and insights to guide therapeutic priorities
- Our first in-person CASK Global Scientific & Family Conference, bringing researchers and families together in Houston, Texas
- New therapeutic approaches moving into testing, expanding the pipeline of potential treatments

We are not waiting for treatments to arrive, we are building them. Every advance depends on the continued engagement of families, partners, and funders. With your support, 2026 will be another year where possibility becomes tangible progress.

With gratitude

Behind every dataset, experiment and conversation that moved the science forward, there were families sharing stories, volunteering time, and making space for the work to happen. Across continents, researchers collaborated in ways that once seemed impossible. Volunteers, board members, and advisors lent their expertise, judgment and energy, turning ideas into action.

This was not just a year of milestones. It was a year of momentum built quietly, deliberately, together. It is proof of what happens when a community refuses to accept limits, and when curiosity, care, and persistence shape the path ahead.

We are deeply grateful to every person who has helped move our journey forward. We also want to give a special thanks to Sophie's Smile Fund and its generous supporters who have made extraordinary contributions to advancing therapeutics for CASK gene disorders.

Thank you from the bottom of our hearts.

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