November 22, 2026

Dear Friends,

Autumn has arrived in St. Louis. The trees around our medical campus have turned deep red and gold, the mornings are crisp and cool, and fallen leaves are gathering along the paths. This is one of my favorite times of the year. Autumn is a season of harvest, when the work of many months finally becomes visible, and with Thanksgiving only a few days away, it is also a natural time to pause and give thanks. As I write to you this month, I find myself feeling both of those things. Thank you, as always, for being part of the Wolfram syndrome community. Your trust, patience, and partnership mean a great deal to my team and to me. Everything we do in the clinic, the clinical trial unit, and the laboratory is guided by one shared goal: **CURE4WOLFRAM**.

Since my August update, our research has taken another meaningful step forward, especially in gene editing, and I am grateful to be able to share it with you. In this letter I will also tell you about our drug discovery work, our planning for future clinical trials, the international clinical guidelines, and our growing clinic. As always, I will try to be clear about what we have learned in the laboratory and what is ready for patients, because those are not the same thing.

Gene Editing and Delivery: Where We Stand

I would like to begin with one of the most encouraging updates I have been able to share with our community. Gene editing is an approach that aims to correct the genetic change that causes a disease, rather than treating its symptoms one by one. In a mouse model of Wolfram syndrome, meaning mice that carry changes in the WFS1 gene and develop features of the disease, our gene-editing experiments have produced substantial improvements across several important features of the condition. We had previously observed improvements in balance, movement, strength, and diabetes-related function. We have now found that vision and hearing also improved markedly in the treated mice.

I know how much this particular finding will mean to many of you. Vision loss and hearing loss are among the hardest parts of living with Wolfram syndrome, for patients and for the people who love them. In patient-derived nerve cells and insulin-producing cells grown in the laboratory, gene editing had already improved several measures of cellular health and function. The mouse studies take us a step further, because they show that correcting the underlying genetic problem can improve several organ systems at once in a living animal.

At the same time, I want to be careful and clear-eyed about what this means. These are preclinical findings in mice. They **are not** evidence that vision or hearing can yet be restored in people. We **still** need to confirm these results, learn how long the benefits last, evaluate safety thoroughly, and develop delivery methods that are suitable for patients. Delivering gene-editing tools safely to the brain, the retina, the inner ear, and the other tissues affected by Wolfram syndrome remains the central challenge. We are continuing to study viral delivery systems, as well as engineered virus-like particles, which are particles designed to carry gene-editing tools into cells the way a virus would, but without the virus's own genetic material, along with other

approaches. These results do not change our commitment to moving carefully. They do give us a strong reason to keep moving forward.

Compound Screening: Drugs and Supplements

Alongside gene editing, we continue to test existing drugs, supplements, and new compounds using nerve cells generated from patients with Wolfram syndrome. We are looking for compounds that reduce cellular stress, improve energy production, and protect the cells that are most vulnerable in this disease. At the moment we are placing particular emphasis on sigma-1 receptor agonists. The sigma-1 receptor is a protein inside cells that helps manage stress, and compounds that activate it may help support the health and function of nerve cells. We are also continuing our work on antioxidants, NAD-related approaches, idebenone, GLP-1 receptor agonists, and the other candidates I described in my previous update.

MANF (mesencephalic astrocyte-derived neurotrophic factor) remains an important part of this effort. MANF is a protective protein that our bodies make naturally, and we are studying it as a possible regenerative and neuroprotective therapy, meaning one that might help preserve, or even restore, the function of vulnerable nerve cells. These studies are ongoing. **I want to be clear that none of these screening results should be taken as a treatment recommendation.** Please do not start or change any medication or supplement based on this letter without talking with your own physician.

PB&TURSO (AMX0035): Next Steps

Many of you have asked what comes next now that our Phase 2 HELIOS study has been published in The Journal of Clinical Investigation. We continue to work closely with our colleagues at Amylyx Pharmaceuticals to prepare the next phase of clinical development, including the design of the trial, the outcome measures that will tell us whether the treatment is helping, and the regulatory requirements that must be met.

I know that families are eager for a clear start date, and I understand why. The plans are still being developed, and I do not want to give you a timeline before it is confirmed. I will share reliable information as soon as I can. Please know that we are working on this with the same sense of urgency that you feel.

A New Platform Trial Initiative

We are also working hard to establish a new kind of clinical trial for Wolfram syndrome, called a platform trial. In a conventional clinical trial, each treatment is usually tested in its own separate study, which must be designed, approved, and staffed from the beginning. A platform trial instead creates one shared structure in which different potential treatments can be evaluated over time, with new options added as they become ready.

This approach could be especially valuable for a rare condition like Wolfram syndrome. Our patients live in many different places, and enrolling enough participants for many separate trials

is very difficult. Our hope is to make future clinical research more coordinated, more efficient, and easier for families to join, while keeping rigorous standards for safety and scientific evaluation. I want to be clear that this initiative is still being developed. It is not an open trial, and there is no enrollment announcement at this time. When there is, you will hear it from us.

International Consensus Clinical Guidelines: Further Refinement Underway

In August, I shared that our first international consensus clinical guidelines for Wolfram syndrome had been made publicly available. Since then, we have received feedback from independent expert reviewers, and we are using their comments to refine and strengthen the recommendations.

The purpose remains the same: to help physicians around the world provide more consistent, coordinated care for people with Wolfram syndrome, so that families do not have to explain the disease to each new doctor they meet. We will share the updated version when the review and revision process is complete.

Wolfram Syndrome and Related Disorders Clinic

Our multidisciplinary clinic at Washington University in St. Louis has seen a substantial increase in requests for appointments, from many states across the United States and from families living abroad. To meet these growing needs, we have assembled a team of approximately 20 physicians across multiple specialties. Our goal is to make comprehensive, coordinated care available to every family who seeks our help.

Our specialist team includes Fumihiko Urano (Director of the Clinic, medical genetics and endocrinology genetics); Huda Al-Bahadili, Paulina Cruz Bravo, Maamoun Salam, Bess Marshall, and Stephen Stone (endocrinology); Judith Lieu (ear, nose, and throat); Richa Bhardwaj (gastroenterology); Jessica Williams and Angela Reiersen (psychiatry); Robert Bucelli, Manouela Valtcheva, Samuel Ahmadi, and Amy R. Viehoever (neurology); Yunshuo “Caroline” Tang and Gregory Van Stavern (neuro-ophthalmology); James Hoekel (pediatric ophthalmology); and Douglas Coplen and Hubert S. Swana (pediatric urology). Other services, including audiology, speech and swallowing evaluation, and physical therapy, can be coordinated when appropriate. Availability varies by specialty. I am deeply grateful to each of these colleagues for the time and care they give to our patients.

Because of the growing number of inquiries, our responses may sometimes take longer than we would like. If you have contacted us and have not heard back, please reach out again. We do not want your request to be missed. Our nurse navigator, Ashley Raterman, coordinates visits and will work with you to arrange appointments based on your needs and provider availability. Families traveling from outside Missouri or from other countries are very welcome to contact us to discuss their options. More information is available at https://wolframsyndrome.wustl.edu/ . For appointments and coordination, please contact WolframSyndrome@wustl.edu.

With Gratitude and Hope

When I look at the autumn trees this time of year, I am reminded that what we see in autumn is the result of a long season of quiet growth. Our work is like that. The improvement in vision and hearing that we are now seeing in our treated mice did not appear suddenly. It grew out of years of work by many people: the patients who donated cells and joined our studies, the families who advocated when few were listening, the researchers and clinicians in our laboratory and clinic, our partners in industry and the patient organizations and donors who have kept this work alive through the years when progress was slow.

These results are not yet a cure, and there is still much work ahead. I want to emphasize that I have never been more hopeful than I am today. No single laboratory, clinic, or country can solve Wolfram syndrome alone. What brings us closer is that we are doing this together: scientists sharing what they learn, physicians coordinating care across specialties and borders, and families trusting us with their experiences and their hopes. That partnership is the foundation on which everything else is built.

As we enter this season of thanksgiving, I want to thank each of you, sincerely, for walking this road with us. I wish you and your loved ones a peaceful and warm holiday season. Together, step by careful step, we are moving closer to **CURE4WOLFRAM**.

With gratitude and hope,

Fumi

Fumihiko “Fumi” URANO, MD, PhD, FACMG
Samuel E. Schechter Professor of Medicine
Director, Wolfram Syndrome Clinic and Research Program, Center of Excellence
Chair, International Gene Therapy Consortium for Wolfram Syndrome
Co-Chair, Gene Therapy and Advanced Therapeutics Committee, BJC HealthCare
Washington University School of Medicine