August 23, 2026

Dear Friends,

As summer begins to turn toward early fall here in St. Louis, I am writing to share what has happened since my last update in May. 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.

This summer has been an unusually full one for our field. We held the 11th International Wolfram Syndrome Symposium in England, we made our first international consensus clinical guidelines publicly available, several new studies have appeared, and I have taken on two new responsibilities in gene therapy that I would like to explain to you directly, because they are connected to where I believe our field is heading.

New Roles in Gene Therapy

I would like to begin by sharing two new appointments I have taken on this year. I am mentioning them not as personal news, but because both exist to move gene-based therapy for Wolfram syndrome forward, and I want our community to understand what they are for.

First, I have been appointed Chair of the International Gene Therapy Consortium for Wolfram Syndrome. Gene-based therapy for Wolfram syndrome is now being pursued by several groups in several countries, using different strategies: gene replacement, base editing, and different delivery technologies. Wolfram syndrome is rare, and our community is small. If each group works in isolation, we will repeat the same experiments, use different outcome measures, and reach the clinic more slowly than we should. The purpose of this consortium is to bring those groups together, to share models, protocols, and safety data, to agree on how we will measure benefit and risk in a consistent way, and to prepare the groundwork so that when the first gene therapy trial for Wolfram syndrome opens, it is designed as well as it can possibly be. I take this responsibility seriously, and I am grateful to the colleagues and patient organizations who have agreed to work together in this way.

Second, I have been appointed Co-Chair of the Gene Therapy and Advanced Therapeutics Committee at BJC HealthCare. This committee oversees how gene therapies, cell therapies, and other advanced treatments are evaluated, prepared, delivered, and monitored across our health system. This may sound like an administrative role, and in part it is. But I want to be clear about why it matters for our families. A gene therapy is not only a molecule. It requires a hospital that can manufacture or receive it safely, administer it correctly, monitor patients closely for years afterward, and respond quickly if something unexpected happens. Building that capability takes time, and it must be built before the therapy is ready, not after. Serving on this committee allows

me to help make sure that when a therapy for Wolfram syndrome is ready, the institution that treats our patients is ready as well.

These two roles sit alongside my continuing work as Chair of the International Wolfram Syndrome Clinical Guidelines Consortium. Taken together, they reflect a simple conviction: the science, the standards of care, and the delivery infrastructure all have to advance at the same time.

First International Consensus Clinical Guidelines: Now Publicly Available

I am very happy to share that our international consensus clinical guidelines for Wolfram syndrome have now been completed and posted publicly as a preprint on medRxiv. A preprint is a manuscript shared openly before peer review is complete, so that clinicians and families can read it and comment while formal review continues. The final published version may change in response to that review, and I want to be transparent about that. I am sharing it now because families and physicians have been waiting for this guidance for a long time, and because I believe it should be freely available to anyone who needs it.

These recommendations are the result of several years of work. Our team reviewed more than 350 scientific publications and drafted recommendations spanning genetics, endocrinology, ophthalmology, neurology, urology, gastroenterology, psychiatry, and the transition from pediatric to adult care. Nearly 50 experts from around the world then refined those recommendations through three rounds of a structured Delphi consensus process, in which feedback is collected, incorporated, and reassessed until broad agreement is reached. The Snow Foundation and Wolfram Syndrome UK served as core committee members throughout, which means that patient and family perspectives shaped the guidelines from the beginning rather than being added at the end.

For families, the practical value is this: you should not have to teach each new physician what Wolfram syndrome is and what needs to be monitored. These guidelines are written so that a clinician anywhere in the world can open them and know what surveillance is recommended, at what intervals, and by which specialists.

Preprint: Consensus Recommendations for the Clinical Management of Wolfram Syndrome Using a Delphi Method. medRxiv 2026.07.02.26357130.

The 11th International Wolfram Syndrome Symposium

In June, I had the privilege of organizing and attending the 11th International Wolfram Syndrome Symposium in Windsor, England, organized by Stephanie Snow Gebel of the Snow Foundation and Tracy Lynch of Wolfram Syndrome UK. I gave two lectures, one on our three-step strategy from drug discovery to base editing, and one on real-world experience with GLP-1 receptor

agonists from our international registry, and I led the discussion on the consensus clinical guidelines described above. I have written a full report of the meeting, which is available on our blog.

What struck me most was how the conversation has changed. At the first symposium in 2009, we were largely discussing what this disease is. This year we were discussing genome editing, gene delivery technologies, regenerative medicine, clinical trials, and international standards of care. The 12th symposium will be held in France in 2027, and I look forward to seeing many of you there.

Learning Who Is at Risk, and When

One of the questions families ask me most often is what a particular WFS1 variant means for their child's future. We cannot answer that question precisely today, but we are working to answer it better.

We have posted a preprint describing a genotype-based severity scoring system for Wolfram syndrome, examining how different types of WFS1 variants relate to the age at which cardinal symptoms appear. The goal is to move toward a more individualized picture of the disease, so that surveillance and, eventually, treatment decisions can be tailored rather than uniform. This work is still under peer review, and it is a first step rather than a finished tool.

We have also published two studies on WFS1-related disease outside of classic Wolfram syndrome. The first is a natural history study of 15 patients with autosomal dominant WFS1 variants associated with sensorineural hearing loss and optic atrophy, published in the Orphanet Journal of Rare Diseases. The second is a retrospective analysis of visual outcomes and biomarker correlates in optic atrophy in Wolfram syndrome type 1, published in the Journal of Neuro-Ophthalmology. Families affected by WFS1-related disorders have often felt that their condition sits outside the main conversation, and I want them to know that it does not. Understanding the full spectrum of WFS1-related disease helps every patient carrying a variant in this gene.

Preprint: Genotype-Based Severity Scoring System in Wolfram Syndrome. medRxiv 2026.03.24.26349216.
Publication: Natural history of 15 patients with autosomal dominant WFS1 pathogenic variants associated with sensorineural hearing loss and optic atrophy. Orphanet J Rare Dis. 2026;21(1):210.
Publication: Optic Atrophy in Wolfram Syndrome Type 1: A Retrospective Analysis of Visual Outcomes and Biomarker Correlates. J Neuroophthalmol. 2026.

Gene Editing and Delivery: Where We Stand

Because Wolfram syndrome is caused by pathogenic changes in the WFS1 gene, correcting those changes has the potential to address multiple aspects of the disease at their source. Using patient-derived induced pluripotent stem cells, we have corrected WFS1 pathogenic changes in laboratory-generated brain cells, and those corrected cells show improved survival, healthier energy production, reduced oxidative stress, and more stable calcium balance. We are seeing similar improvements in insulin-producing beta cells derived from patient cells.

The harder problem, and the one absorbing most of our effort now, is delivery. Correcting a gene in a dish is not the same as correcting it in a living brain or eye. We are continuing to develop delivery systems based on nanoparticles and engineered virus-like particles, rather than relying only on conventional approaches such as AAV, because we believe these offer a safer and more flexible path. Our aim is to build the strongest possible package of data in patient-derived cells and humanized mouse models before we approach regulators. I would rather move carefully and arrive with a therapy we can stand behind than move quickly and put patients at avoidable risk. The consortium I described above exists in large part to help the whole field do exactly that.

Regenerative Therapy and Neuroprotection

Our work on MANF, a naturally occurring neurotrophic factor that helps cells survive endoplasmic reticulum stress, continues to gain momentum. This program is now being guided by our finding, published this spring, that the earliest detectable change in the visual system is a quiet weakening of synaptic connections rather than the death of retinal ganglion cells themselves. If the cells are still present when the connections begin to fail, then there is a real window in which protection and restoration are possible. We are designing our regenerative and neuroprotective work around that window, and we plan to present new data at the next symposium.

Compound Screening: Drugs and Supplements

Our screening platform continues to run in parallel with the gene-based and regenerative programs. Using brain cells generated from patient-derived induced pluripotent stem cells, we test existing drugs, supplements, and new compounds for their ability to improve cell survival, reduce stress responses, support mitochondrial function, and restore healthier cellular balance. Our priorities remain antioxidants, sigma-1 receptor agonists, NAD activators, idebenone, GLP-1 receptor agonists, and other compounds targeting endoplasmic reticulum stress and mitochondrial dysfunction. Our preprint on GLP-1 receptor agonists in Wolfram syndrome remains publicly available and is progressing through peer review.

PB&TURSO (AMX0035): Next Steps

Many of you have written to ask what happens now that our Phase 2 HELIOS trial has been published in The Journal of Clinical Investigation. I want to answer honestly. We are working

closely with Amylyx Pharmaceuticals on the design of the next phase, including outcome measures and regulatory strategy. This work is active, and it is detailed, and it is not something I can compress into a timeline that I would be confident sharing today. What I can promise is that I will tell you as soon as there is something concrete to tell, and that I will not describe a plan as settled before it is. Please know that the urgency you feel is the urgency we feel.

Wolfram Syndrome and Related Disorders Clinic

Our multidisciplinary clinic at Washington University in St. Louis continues to provide comprehensive, coordinated care for individuals with Wolfram syndrome and WFS1-related disorders. We prioritize same-day or two-day visits whenever possible for families traveling long distances, including out-of-state and international families. Our nurse navigator, Ashley Raterman, coordinates these visits and remains a key point of contact for families.

More information is available at https://wolframsyndrome.wustl.edu/. For appointments and coordination, please contact WolframSyndrome@wustl.edu.

With Gratitude and Determination

When I accepted the chairmanship of the international gene therapy consortium this year, I thought about how differently that sentence would have read even five years ago. There was a time when there was no gene therapy effort in Wolfram syndrome to coordinate. That there is now enough activity in this field to require coordination is, in itself, a measure of how far we have come, and it is a direct result of the courage of patients who joined our studies, the persistence of families who advocated when no one was listening, and the support of the patient organizations and donors who kept this work alive through years when progress was slow.

We are not finished. A published Phase 2 trial, a set of consensus guidelines, and a coordinated international gene therapy effort are not a cure. But each of them is a piece of the structure that a cure will require, and this year we built several of those pieces at once. My team and I remain fully committed to this work, every day, with the same urgency I know our families feel.

Thank you for walking this journey with us. Together, step by careful step, we are moving closer to CURE4WOLFRAM.

With gratitude and hope,

Fumi

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