HOPE in FOCUS
Seeing a cure for blindness
Supporting the LCA and rare retinal disease community

# SEEING HOPE | Newsletter

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## Through the Eyes of Love: Just James!

***By Katherine L. Kraines, MS***

*James with his toys*

Caitlin and Greg Smith eagerly looked forward to the birth of their fourth child, who would complete their busy family of two girls and a boy. Caitlin's pregnancy was unremarkable, and the family excitedly welcomed baby James in June 2023. But when he was about two months old, the couple noticed that James wasn't visually tracking as they had expected. "His eyes were closed much more than our other children, and I remember thinking that was odd," Caitlin said. "He also wouldn't lock eyes with us or look directly at objects or our faces." Worried, the Smiths took James to their pediatrician, who wasn't overly concerned given his age but who suggested seeing a pediatric ophthalmologist.

**A Diagnosis**

Unfortunately, the ophthalmology exam revealed that something was wrong. "The doctor noticed pigmentation in his macula and mentioned it could be a number of things but recommended that James be seen by a retinal specialist at Boston Children's Hospital," said Caitlin. "The doctor did a clinical exam and, based on seeing degeneration in the retina, diagnosed James with Leber congenital amaurosis (LCA). It was a terrible shock. We knew nothing about inherited retinal diseases or LCA."

The next step was genetic testing, which revealed James had LCA9, caused by a mutation in the *NMNAT1* gene. Greg and Caitlin were also tested, and their results verified that James' LCA was inherited and not the result of a random mutation. "Just knowing what we were dealing with was a big milestone," Greg said. "But we needed to know where to go from here."

***Continued on page 2***

## From the Founder:

*Laura Manfre*

Hope in Focus will attend the Foundation for Fighting Blindness VISIONS Conference in Chicago from June 21–22, 2024. We look forward to seeing old and new friends there and would love to introduce you to some of our new team members. Stop by our booth and say hello!

In April, our team participated in the Denise D'Ascenzo Foundation's Walk to Fight Rare Diseases. It is challenging for small rare disease organizations like ours to host events of this scale, and we're grateful to the walk organizers for providing a platform for rare diseases in Connecticut. To everyone who supported us—thank you!

By the time you receive this newsletter, we will be underway with developing a strategic plan for Hope in Focus. The goal of this initiative is to ensure we can continue advancing treatments for blindness and supporting the needs of our LCA community. A special thank you to Mary and John LaMattina for contributing to this critical initiative.

With gratitude and joy,

Laura

# Through the Eyes of Love: Just James!

***Continued from page 1***

After learning that many children with LCA9 are born with no light perception or severe vision impairment, they were encouraged that James appears to be on the better end of the spectrum. "We know he has light perception, can see colors, and has some functional vision. Sometimes, he appears to track people or large objects, but it's hard to know if it's because he's hearing or seeing something," Caitlin said.

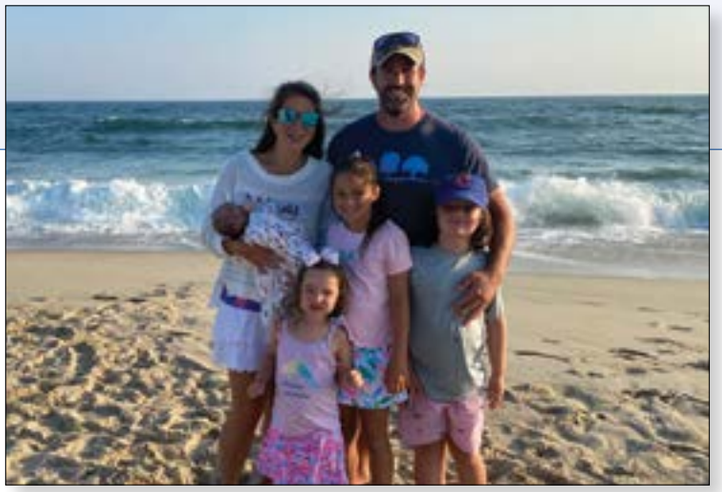
**Finding Support, Getting Educated**

Immediately after the diagnosis, the Smiths dedicated themselves to researching and understanding all they could about LCA and visual impairments. "As a parent, you always want what is best for your child, and to think about and create what would be best for him, we needed to educate ourselves," said Caitlin. As they searched LCA online, Hope in Focus popped up. "The day we got the clinical diagnosis, or maybe a day later, we found Hope in Focus," Greg said.

Several days later, Greg spoke with Courtney Coates, Hope in Focus Director of Outreach and Development, who provided him with family and research connections and a high-level review of the current treatments and technologies relevant to LCA9. "It's hard to put into words how impactful it was to get this diagnosis and to be able to go online and get connected to a community of people that could hear our story and help," he said. "Having Hope in Focus was incredible for us as we began this journey. It makes such a difference knowing you're not alone. We are forever grateful to Laura, Courtney, and the rest of the Hope in Focus team."

Courtney also connected the Smiths with another Hope in Focus family whose son had LCA9, which Caitlin said provided an "awesome jumping-off point for connecting to other families with the same mutation." They've also found other LCA9 families in the US and abroad through social media.

Through recommendations from Hope in Focus and via their research, the Smiths began reaching out and networking with people researching and developing potential treatments. "Getting more involved with the research community has been very helpful, and as a family, we are very focused on helping to advance a treatment for James and others with LCA9," Greg explained.



*The Smith family*

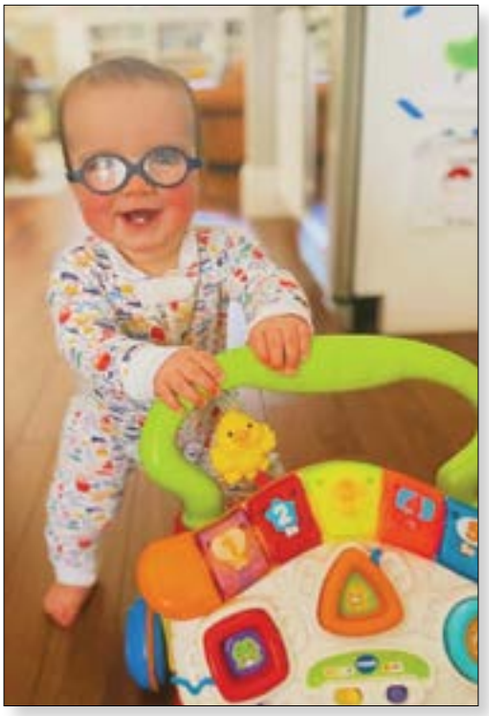
In James' case, early-stage preclinical work has been conducted on a potential gene therapy treatment for the *NMNAT1* mutation, with promising results in mouse models. "With these rare diseases, taking a traditional path to treatment development is very challenging given the economics involved," said Greg.

**Living Life**

His parents describe James as outgoing, adventurous, fearless, and a ball of fun who is always smiling and laughing. "His siblings are totally in love with him," said Caitlin. Now, James is just another sibling rather than a sibling with a vision impairment."

Greg said that he and Caitlin dealt with James' diagnosis in different ways. It was more challenging for him to accept the vision impairment, and his mind went to all of the things that his son might not be able to do that his siblings could do. "I think Caitlin did a much better job internalizing all of that," he said.

Caitlin said that she turned her grief into action by focusing on the next steps, such as identifying and arranging for therapies. "It felt like a blessing that our life is so busy. There wasn't time to sit around and be



*James walking*

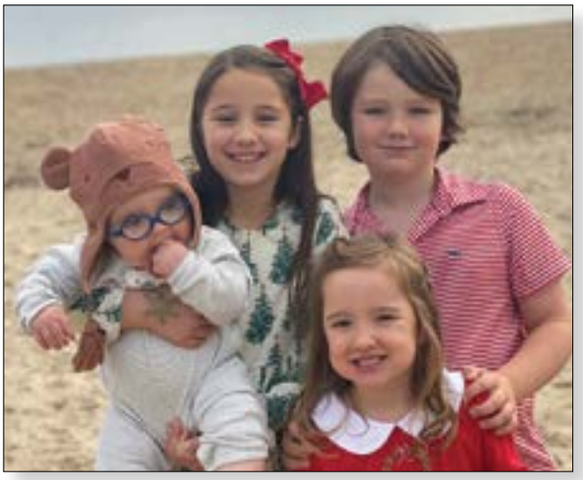
depressed or in shock—instead, I focused on James' immediate needs and how we could best support him and give him an amazing life, just like our other children. I didn't want him to be treated any differently from other kids. We will not allow his vision to define him, but we will make sure he has every opportunity every other child has," she said.

Daily life at the Smiths is essentially divide and conquer. Greg works at an investment firm and has taken the lead in researching the disease and potential therapies in his spare time. Caitlin is a stay-at-home mom who is incredibly busy with the three older children's sports schedules and James' physical, occupational, vision, and speech therapies. They have gotten involved with the NAPA Center in Boston, which offers specialized coaching and therapies for children with disabilities, and they attend a weekly baby group at the Perkins School for the Blind. They feel lucky and thankful for access to excellent resources and support nearby. "It's been incredible to see how much James has grown and all the milestones he has accomplished. In certain areas, he is more advanced at this age than our other three were," Caitlin said.

James currently sees three different doctors, including a local eye specialist who used to work at Boston Children's Hospital. He also goes to Boston Children's Hospital once a quarter, and there is a yearly trip to the Children's Hospital of Philadelphia.

Regarding advice for other LCA families, Greg and Caitlin said it may seem overwhelming initially, but everything will be okay. "I struggled with the diagnosis for a while. But now we're at a place where we feel like James is not our child with LCA. He is just James!"

*James with his stuffed bunny*



*The Smith siblings*

HOPE in FOCUS

LET'S CHAT ABOUT...

# LET'S CHAT ABOUT...Bespoke Gene Therapy Consortium: *A Summary*

**Moderator: Ben Shaberman, Vice President, Science Communications, Foundation Fighting Blindness**

**Topic: Webinar Introduction**

The Bespoke Gene Therapy Consortium's (BGTC) mission is to improve and accelerate gene therapy development for a wide variety of rare diseases, including rare inherited retinal diseases (IRDs).

Inherited retinal diseases (IRDs) are an excellent target for gene therapies for two reasons: the retina is small, easily accessible, and doesn't require much gene therapy to treat it, and almost all IRDs, including Leber congenital amaurosis (LCA), are the result of just one mutated gene, i.e., monogenic. If the mutated gene can be augmented or replaced, then there is the possibility of saving and restoring vision.

With the success of LUXTURNA® in treating *RPE65*, many other IRD gene therapy trials are occurring that hold promise with further gene therapy development. However, because any of 300 gene mutations can cause an IRD, of which about two dozen cause LCA, this process is complicated and means that many therapies must be developed. These factors present a technological and economic challenge, and this is where the BGTC is involved as it seeks ways to accelerate gene therapy development.

**Presenter: Brad Garrison, MBA, PMP, Sr. Project Manager, Translational Science at BGTC, also with the Foundation for the National Institutes of Health (FNIH)**

**Topic: Overview of the Accelerating Medicines Partnerships® (AMP®) and Bespoke Gene Therapy Consortium (BGTC)**

The BGTC is one of seven programs within the FNIH that is an Accelerating Medicines Partnership®. This unique public-private partnership model brings together top scientists from the NIH and industry with participants from nonprofits and patient engagement groups such as Hope in Focus.

More than 10,000 rare diseases collectively affect over 30 million people in the US. Eighty percent of rare diseases are caused by a single gene, meaning some form of gene therapy might address them. The BGTC is focused on adeno-associated virus (AAV) therapy, which uses viruses engineered to deliver the missing gene to target cells

The BGTC has two tracks. One track focuses on research to optimize the delivery vehicle, the AAV, for therapy. The second track is clinical and will manufacture the AAV necessary to begin preclinical testing and for clinical trials for selected diseases. The BGTC aims to develop best practices for the clinical development of gene therapies and the regulatory process for the regulatory playbook.

For a condition to be effective for the BGTC model, it must—be addressable, result from a single gene defect of no commercial interest, have a short follow-up time for results, and have an assembled patient group. Additional information needed includes—patient demographics, clinical presentations, and clinical and preclinical research history. The disease selection process aims to choose five or six diseases with a high likelihood of success in proceeding to clinical trials.

Of the 62 disease applications received, 14 disease candidates rose to the top, and eight were selected to move forward. The diseases were then paired with a manufacturer to produce the vector for the trial. Of the retinal diseases, *NPHP5* and *CNGB1* were high on the list.

**Presenter: Snehal Naik, PhD, Head of Regulatory Policy; Strategy Leader (Senior Director) at Spark Therapeutics, Inc.**

**Topic: Some Brief Thoughts about the BGTC**

The BGTC's unique structure will help move clinical development forward because different committees and their members have very diverse experiences, backgrounds, and expertise. Gathering members' input at the beginning of the process will streamline development at every phase, collectively moving the needle faster than any single investigator possibly could.

Because the Food and Drug Administration (FDA) will be present during committee discussions, FDA members can contribute their current thinking. The FDA's presence will not replace the regulatory process but will help develop the BGTC's regulatory playbook.

**Presenter: Artur V. Cideciyan, PhD, Center for Hereditary Retinal Degenerations, Scheie Eye Institute, University of Pennsylvania**

**Topic: Inherited Retinal Disease Associated with NPHP5/IQCB1 Mutations and Its Treatment**

The key cells being looked at are the photoreceptors on the retina. These are very long cells with one tip, called the outer segment that captures the light and starts the signaling process of vision. The functioning of the outer segment requires all of its proteins to come from the inner segment, where the proteins are made, and the energy is generated for the photoreceptor. There is a tiny isthmus between the inner and outer segments, called the ciliary transition zone, where many proteins are located that appear to do very important things, much of which is not understood.

Among the ciliary proteins are CEP290 (NPHP6) and IQCB1 (NPHP5); these form a multiprotein complex in the transition zone and, when individually mutated, cause severe vision problems. The mutations result in a mound of dysfunctional central cone photoreceptors that stay alive for decades, offering an opportunity for treatment. It was hypothesized that gene therapy could undo the defect and that vision would recover.

This theory was tested in human trials for *CEP290*. Two trials have been conducted: a gene-editing multicenter trial and a trial using an intravitreal antisense oligonucleotide, sepofarsen.

The gene editing trial results will be released soon. However, the sepofarsen trial results have been published, and there is dramatic and clear evidence of vision improvement in a short time in a subset of patients. This trial superficially supports the idea that undoing the genetic defect will restore vision.

**Presenter: Aykut Demirkol, MD, Columbia University Ophthalmology Department, Postdoc Research Scientist**

**Topic: CNGB1 Project**

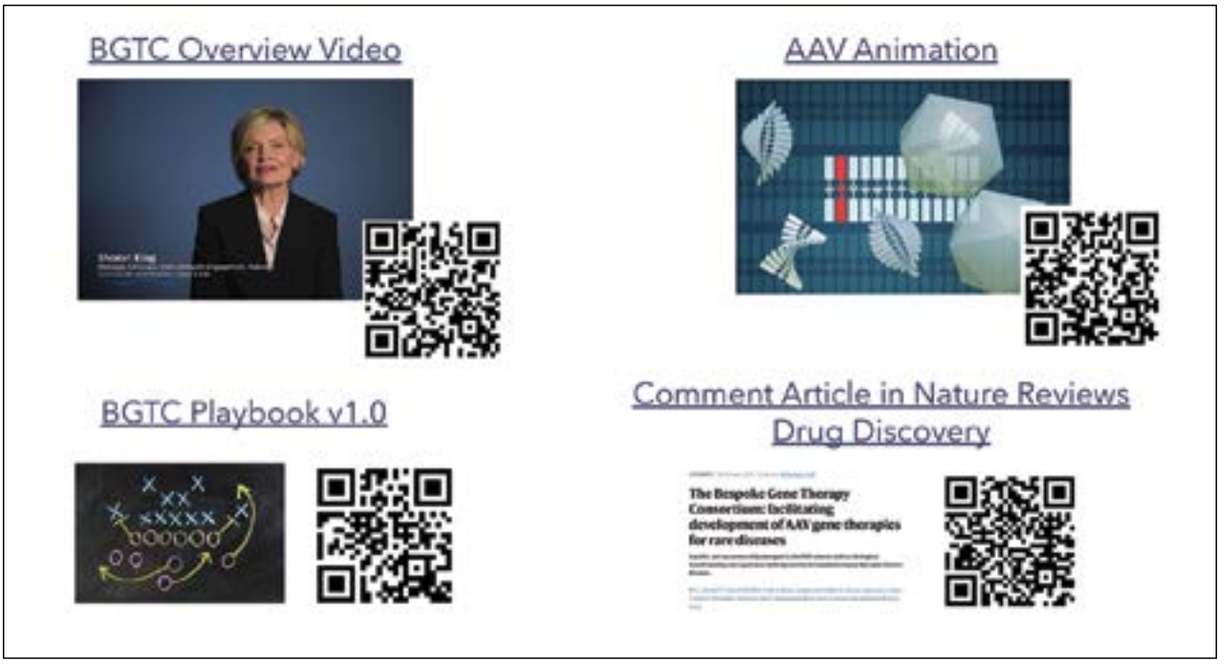
Mutations in the *CNGB1* gene impact the photoreceptor cells in the retina, leading to retinitis pigmentosa (RP), a condition marked by progressive vision loss. Current therapeutic strategies focus on symptom management and slowing disease progression. Gene therapy offers a groundbreaking advance for genetic retinal diseases, like RP gene therapy, which has shown the potential to repair and preserve the structural function of the retina.

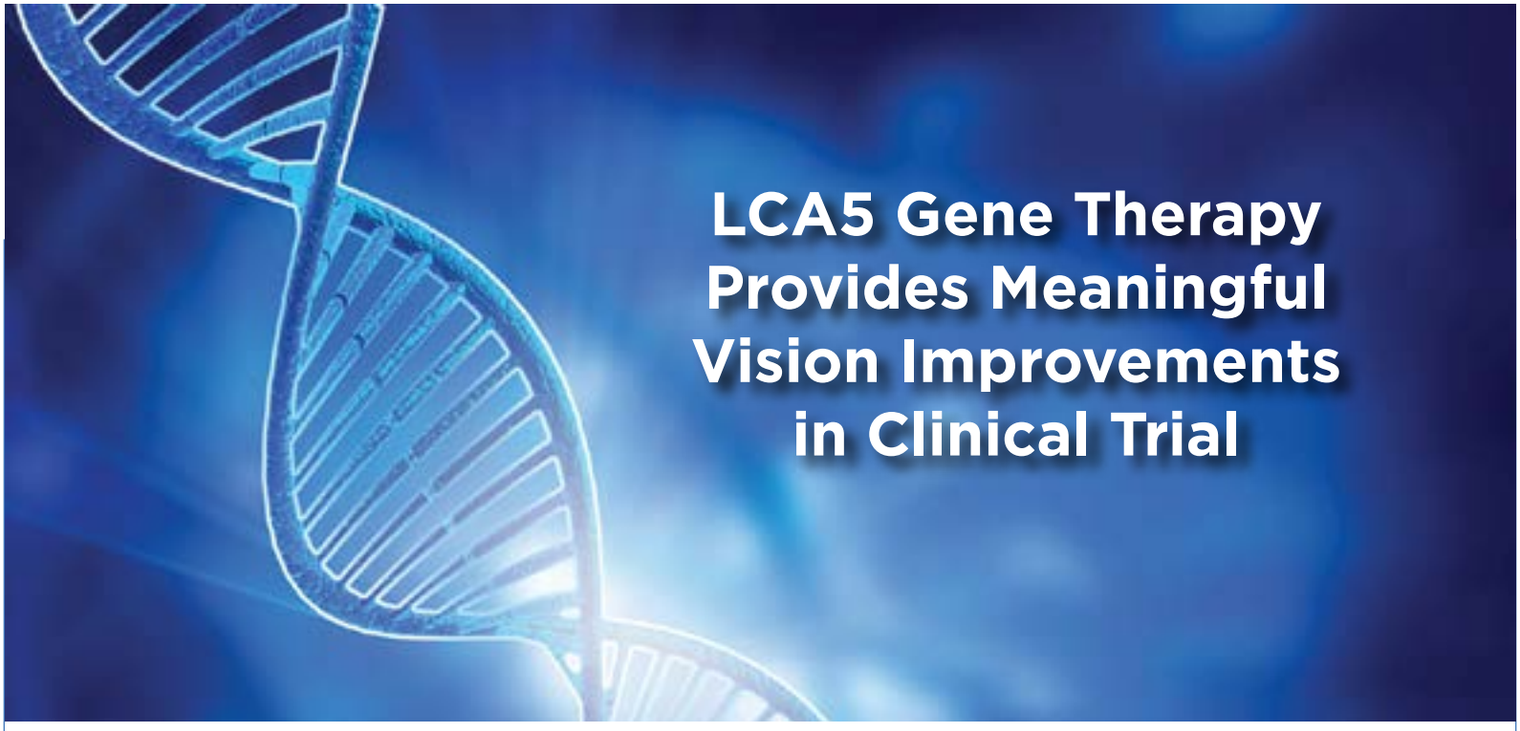
In the clinical study, adults with RP due to a specific mutation in the *CNGB1* gene were given a dose of AAV5-CNGB1 via a subretinal injection. The central hypothesis is that this will pose no major safety issues and preserve the photoreceptor ellipsoid zone (EZ).

The rods in the eye may be unhealthy before treatment, and the injection introduces the correct gene to express the right protein to restore the rods and outer segments to a healthy condition, potentially preserving or improving vision.

Study participants are divided into three groups and monitored for 36 months—one group gets a lower dose, the second gets a higher dose, and the third is the control group, which receives no injection. This study will help determine the safe and effective dose for future treatments. It is being done at Columbia University and two sites in Germany, Munich and Tübingen.

The study focuses on evaluating the precision and effectiveness of the AAV5 gene therapy and checking for safety and how well participants can tolerate the treatment. The secondary goal is to see if the treatment is effective.





# LCA5 Gene Therapy Provides Meaningful Vision Improvements in Clinical Trial

***Ben Shaberman***
***Vice President,***
***Science Communications***
***Foundation Fighting Blindness***

Nothing is more hopeful or gratifying for the retinal disease community than an emerging or FDA-approved therapy that provides vision to people with advanced retinal disease. Such is the case with Opus Genetics' gene therapy for Leber congenital amaurosis 5 (LCA5) in an early-stage clinical trial.

In March 2024, the company announced vision improvements for the first three adult patients in its Phase 1/2 LCA5 gene therapy clinical trial. Some patients, who had been almost totally blind since birth, can now see and identify objects for the first time. The company has also reported positive safety data for the trial thus far.

Though LCA5 patients have severe vision loss at birth, they have some surviving retinal structure that researchers believe can be harnessed for improved vision using gene therapy.

Known as OPGx-001, the gene therapy uses a human-engineered adeno-associated virus (AAV) to deliver healthy copies of the LCA5 gene to patients' retinas, augmenting the mutated copies that cause vision loss. The therapy is administered through a one-time injection underneath the retina. Researchers believe gene therapies will be effective for many years, perhaps for the patient's lifetime.

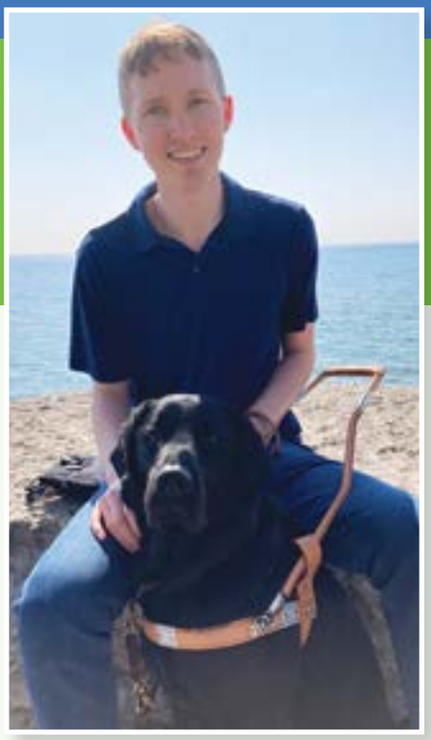
Opus plans to administer the next highest dose of its LCA5 gene therapy to the next cohort of adult patients in mid-2024. The company also has plans to dose patients as young as 13 years old sometime in the future.

The Phase 1/2 clinical trial is led by Tomas S. Aleman, M.D., at the Center for Advanced Retinal and Ocular Therapeutics (CAROT), Scheie Eye Institute, Department of Ophthalmology of the Perelman School of Medicine, University of Pennsylvania.

Courtney Coates, Hope in Focus Director of Outreach and Development, stated, "We are thrilled that patients in this trial are having early success with the low dose treatment. We look forward to hearing more as the next cohort is enrolled for the mid dose."

The LCA5 gene therapy clinical trial is the first launched by Opus, a company founded in 2021 by the RD Fund, the venture arm of the Foundation Fighting Blindness, which is investing in companies near or in early-stage clinical trials for their retinal degenerative disease treatments.

# Seeing Home Differently: Purchasing a Home for Life with a Visual Impairment



*Jack and his guide dog, Baloo*

As someone with a visual impairment, I've learned the importance of choosing accessible environments. I recently purchased my first home and wanted to share some lessons I learned about accessibility and the home-buying process.

One of the most important decisions anyone makes when selecting a home is picking a real estate agent who understands your needs and desires. Of course, you want someone who knows your local market and won't pressure you to make a decision you aren't ready for. But as someone living with with a visual impairment, I also wanted an agent who had experience helping people with disabilities find a home. I started by speaking with a few agents who mentioned having this expertise on their websites, but I did not find anyone I felt comfortable working with.

## The Right Agent

Thankfully, I asked a friend who is also visually impaired and who had recently moved. He had an excellent referral for an agent whom I contacted and chose to work with. Because of my real estate agent's knowledge and experience, he was able to help me narrow my search by eliminating areas with poor public transit or limited businesses within a walkable distance. He also helped me identify features that would make my life easier as a visually impaired person, such as green space for my guide dog, nearby access to trails making it easier for me to run with a guide, easy-to-use appliances, and lots of lighting.

I looked at a lot of properties, and it was overwhelming! As I searched, I also discovered several things that would make my life better. I eliminated properties that required renovations. I'm not handy and have no interest in supervising a construction project. I also excluded properties on busy roads because it's much easier for me to navigate quieter spaces, and I like to avoid noise as much as possible.

## Adding Accessibility

I ended up purchasing a first-floor condo, which provides for trouble-free maintenance. It has a large patio, making it easy to take my guide dog outdoors, and it allows me to be outside as much as possible.

Once I moved in, there were a few things I needed to do to make my new home more accessible for me. Some rooms were not as bright as I wanted, so I purchased the brightest LED lightbulbs I could find. I was also tired of having thermostats that I could not control independently. Thankfully, there is a wide selection of thermostats that you can control with an app on your phone. I got an EcoBee thermostat and found the app fully accessible. Finally, I put braille labels on all my appliances so I can use them independently. The Braille Superstore is a great place to get a Braille label maker and other stickers/labels to make your home more accessible.

I'm thrilled to have my own home and to live in an accessible and comfortable place. I hope my experience gives you some ideas regarding purchasing a home and how to make it more accessible for you or a loved one.

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*Jack McCormick graduated in 2018 from Canada's Wilfrid Laurier University in Waterloo, Ontario. He was diagnosed in high school with LCA2 (RPE65). Jack is a Hope in Focus ambassador, helping people living with LCA and IRDs. You can read his blog at* ***jackdamccormick.wordpress.com***

# Events

**DO YOU HAVE AN EVENT YOU WANT TO SHARE? LET US KNOW!**
**Email info@hopeinfocus.org with the information and a link.**

## Global Genes • RARE Advocacy Summit

**September 26–27, 2024 • Kansas City, Missouri**
globalgenes.org/rare-advocacy-summit
Each year, Global Genes convenes one of the world's largest gatherings of rare disease patients, caregivers, advocates, healthcare professionals, researchers, partners, and allies at the RARE Advocacy Summit.

## NORD Orphan Drug & Breakthrough Summit: Washington DC Rare Disease Conference

**October 20–22, 2024 • Washington, DC**
nordsummit.org
The summit offers an unparalleled opportunity to discuss complex, multi-faceted topics with all rare disease stakeholders—medical and academic experts, regulators and policymakers, innovators, patients, caregivers, and industry leaders.

## Hope in Focus • Dinner in the Dark

**NEW DATE • November 2, 2024 • Foxwoods Resort Casino**
hopeinfocus.org/get-involved/dinner-in-the-dark
Dinner in the Dark, our primary fundraiser for the year, helps fund research to cure blindness caused by LCA, provides support for genetic testing, and drives awareness, education, and connections for LCA and IRD families. Get ready for an incredible evening that is a lively sensory adventure with a stellar menu, fine wines, and more!


HOPE in FOCUS
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**The *Seeing Hope* Newsletter** is published quarterly by Hope in Focus, a 501(c)3 patient advocacy organization dedicated to generating awareness, raising funds for research, and providing education and outreach to the LCA and rare inherited retinal disease community.

**To learn more about Hope in Focus, visit www.hopeinfocus.org.**

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