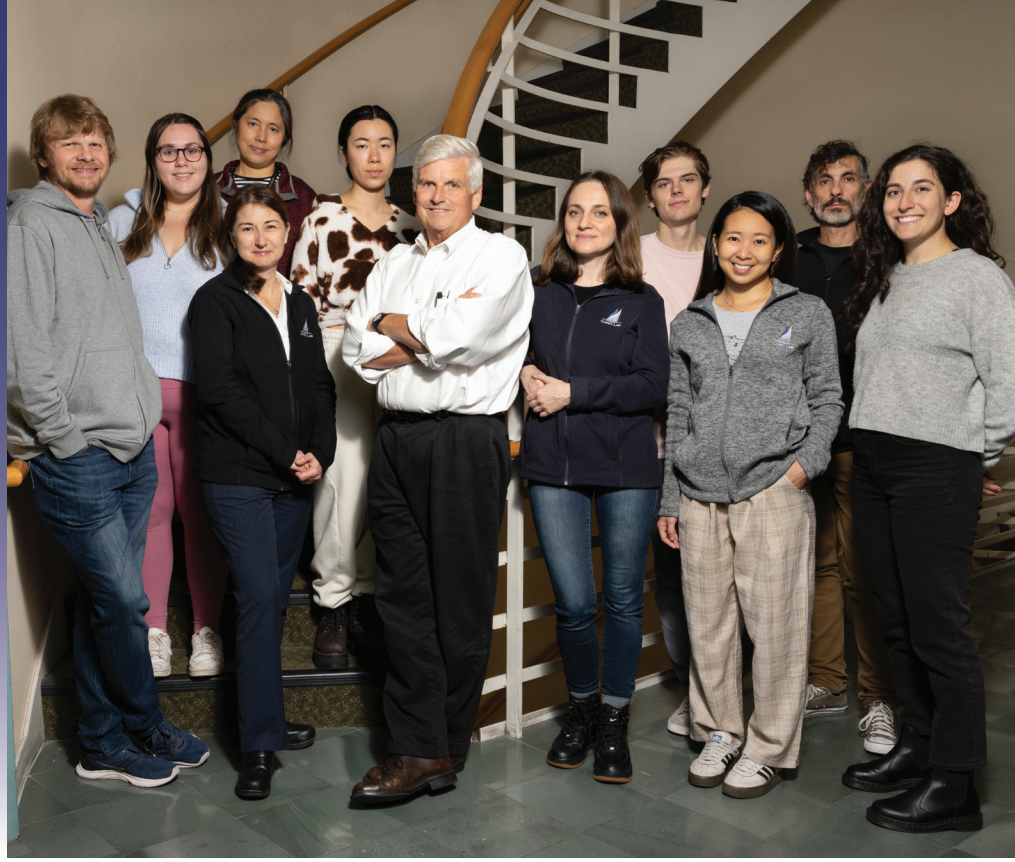
USHER 1F COLLABORATIVE

10th ANNIVERSARY

NEWSLETTER

Spring 2023



Corey Laboratory, Center David Corey and Maryna Ivanchenko

We Have Exciting Research Progress to Share!

In the April 26, 2023, issue of *Nature Communications*, our Harvard research team published an article, "Mini-PCDH15 gene therapy rescues hearing in a mouse model of Usher syndrome type 1F."

What does this mean?

Catherine Caruso, Harvard Medical School covered the story in their online *News & Research*, Toward a Therapy for a Rare Genetic Disease, stating
At a glance:

- *Researchers have designed a "mini gene" that could eventually be developed into a gene therapy for Usher syndrome type 1F.*
- *In mice, the mini gene increased production of an essential protein whose absence contributes to deafness and progressive vision loss in Usher 1F.*
- *The work sets the stage for therapies that prevent Usher 1F blindness, for which there are currently no treatments.*

Usher 1F Collaborative first met David Corey, PhD, Harvard Medical School Department of Neurobiology, in May of 2017 at our Usher 1F researchers conference in Boston. Board Vice Chair Elliot Chaikof, MD, PhD, is a member of the Harvard Stem Cell Institute and reached out to the Institute to publicize our conference, opening it to all interested scientists. Dr. Corey recounts the story of what led him to tackle Usher 1F:

> *We had worked for many, many years on the protein that is involved in Usher 1F, protocadherin 15, and so the Usher 1F Collaborative has workshops to bring together the experts in the field. I thought that seemed pretty interesting—We should probably go to that. The science was good, but the thing that just blew me away was meeting Rachel and Jessica Chaikof [daughters of Usher 1F Collaborative cofounders Melissa and Elliot Chaikof] because I know what the protein does. I know the sensory challenges they were both trying to meet, and they were doing such a good job and doing it so bravely that I really felt we know as much as anyone about this protein, and we really are obligated to try to do something with that knowledge to try to help people with this disease.*

Armed with their knowledge, Dr. Corey, Maryna Ivanchenko, MD, PhD, also of the Department of Neurobiology at Harvard Medical School, and

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Delta 717 Simulator: Ryan, David, Capt. Bennett, Chief Pilot Patrick Burns

Ryan Vlazny – A Vision for Flying

Ryan Vlazny, who has Usher 1F, has long been a fan of airplanes, especially DC-9s. Knowing this, in December 2022 his father David approached Delta Air Lines pilot Capt. Mike Bennett at the Chicago-O'Hare airport to introduce Ryan, whose dream is to fly on as many DC-9 aircraft as possible before they are retired. The DC-9 is also Capt. Bennett's favorite airplane.

While Ryan has lost his vision, he can hear on his right side thanks to a cochlear implant he received as a child. On DC-9s, he always chooses to sit in seat 24F because it allows him to best hear the plane's engine.

Ryan with his father David and Capt. Bennett

Upon meeting Ryan and hearing his story, Capt. Bennett invited him into the cockpit, and thus began their friendship. They began emailing each other, and David shared with Capt. Bennett Ryan's essays about flying.

"Although we are both huge fans of flying, we experience it in a very different way. As a pilot, much, if not most, of what we experience is through sight and voice. Ryan shows through his story that neither of those are requirements to love aviation as much as we do." – Capt. Mike Bennett

Capt. Bennett was further drawn to Ryan because he also has a son with special needs.

"I know what that life looks like. For every parent of a kid with special needs, that life is different," Bennett said "I don't think it's something I do consciously. But I know I may approach it in a different light."

After meeting Ryan, Capt. Bennett contacted Delta Flight Operations leadership to develop a plan for Ryan. In March, he first took Ryan and David to the Delta Flight Museum, allowing Ryan to touch every part of

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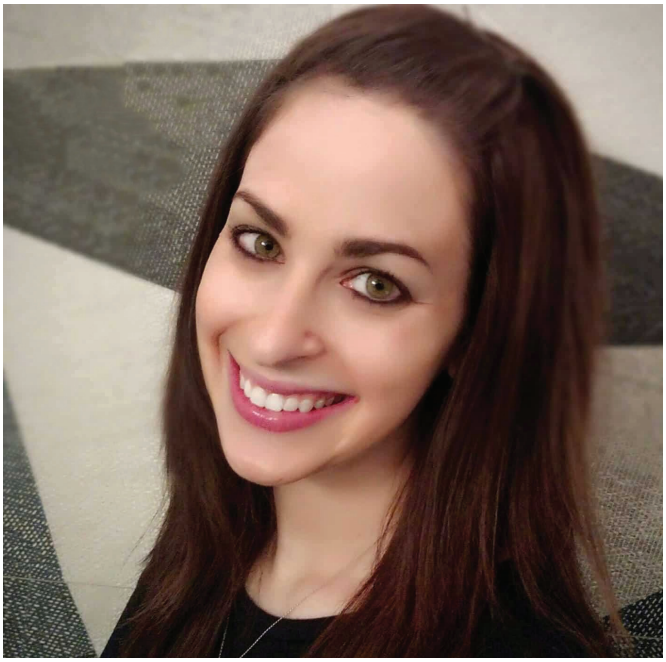
Getting to Know Your Genes

Usher syndrome type 1F is one of many recessive genetic diseases, that is those that hide through generations until two parents both carrying the mutation have an affected child. With the tremendous advances in genetic testing over the past decade, couples can now get prescreened prior to having children.

Estie Rose is a genetic counselor at JScreen. Usher 1F is one of over 200 recessive genetic diseases for which JScreen tests. In March, Usher 1F Collaborative was fortunate to host a virtual event with Estie Rose. Estie provided a refresher on Genetics 101, explaining how recessive genetic diseases, such as Usher 1F, can be carried through generations with no affected children until two carriers have a child together. While 80% of babies born with a heritable genetic disease are born to parents who have no known family history of that disease, about 75% of people who JScreen tests are carriers of at least one disease. Carriers are generally healthy people.

Many were surprised to learn how simple it is today to test to find carriers of so many recessive genetic diseases. Estie outlined the options young couples have if they learn they are both carriers of the same mutation.



Estie Rose

We also learned that several ethnic groups carry genetic diseases that are more common in their populations. For example, sickle cell disease is more

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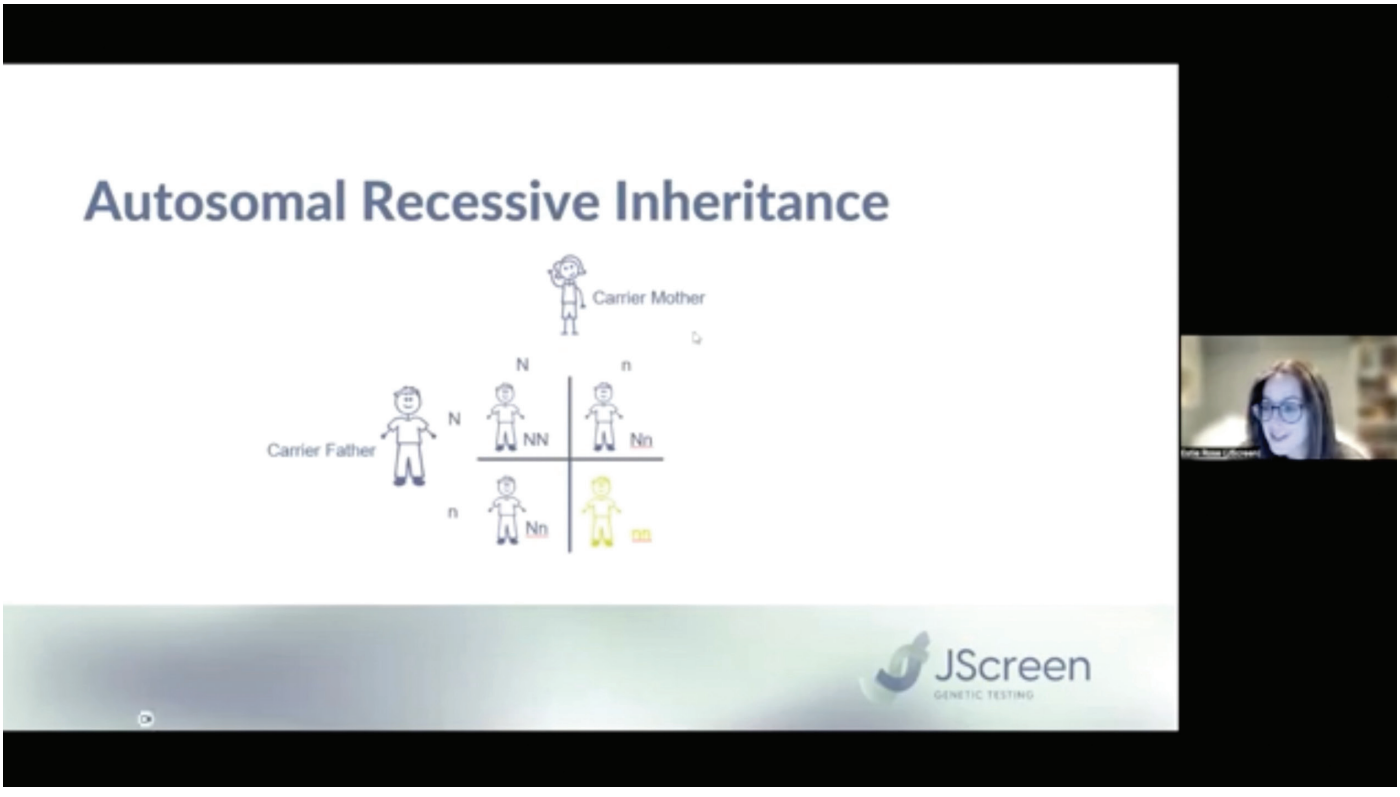

Esti Rose conducts a virtual genetics lesson to explain how genetic diseases are passed from parent to child and can go undetected for generations.

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Maryna Ivanchenko presents her Usher 1F research at the international ARVO conference

their team hit the ground running. In addition to Drs. Corey and Ivanchenko, this team includes Marcos Sotomayor, Department of Chemistry and Biochemistry, The Ohio State University, and Artur Indzhykulian, Department of Otolaryngology – Head and Neck Surgery, Harvard Medical School and Massachusetts Eye and Ear. Six years later, we now have an Usher 1F mini gene that results in increased production of the protocadherin 15 (PCDH15) protein in the inner ear of a mouse with Usher 1F, restoring hearing.

While the team stated in their article that the absence of PCDH15 in the eye results in the vision loss of Usher 1F, giving them hope that this same mini gene will also rescue vision in those with Usher 1F, **we now have even more exciting news to report**. At the Association for Research in Vision and Ophthalmology (ARVO) conference in April, Dr. Ivanchenko's talk was entitled Mini PCHDH15b gene therapy rescues visual deficits in a zebrafish retinopathy model of Usher syndrome type 1F.

This effort demonstrates the benefits of our collaborative research network with the partnership between our Harvard team and our University of Oregon Institute of Neuroscience researchers, Monte Westerfield, PhD, and Jennifer Phillips, PhD. Drs. Ivanchenko, Corey and their collaborators have now tested the mini-PCDH15 in our Usher 1F zebrafish model that Drs. Westerfield and Phillips developed. The photoreceptor cells (those that deteriorate in the eyes of those with Usher 1F) in zebrafish eyes are more similar to those in humans than are mouse photoreceptors. While mice lacking PCDH15 have a modest reduction in photoreceptor function, the zebrafish model shows photoreceptor degeneration and reduction of visual response within just the first seven days of life. It is thus a good model for testing prevention of blindness by our mini gene. As Dr. Ivanchenko described at the recent ARVO meeting, "Usher 1F model fish which made the mini-PCDH15 in their photoreceptors showed proper location of the protein along calyceal process, prevention of photoreceptor degeneration, and rescue of vision to wild type [normal] levels, as assessed with electrical and behavioral tests." That is, **the Usher 1F mini gene rescued vision in our Usher 1F zebrafish model**.

Make no mistake, without your support, this project would not have happened. Your contributions to Usher 1F Collaborative are bringing about a transformation, and we are proud to share the results. Together, we are making a difference in the lives of those with Usher 1F. ◆

Usher 1F Collaborative Celebrates Ten Years

Recognizing that there was no organization focused on a cure for Usher syndrome type 1F, in 2013, our founders Melissa Chaikof and her husband Dr. Elliot Chaikof took things into their own hands and set out on a mission for change. They formed Usher 1F Collaborative to stimulate cutting-edge medical research to find an effective treatment to save or restore the vision of those who live with Usher 1F, including their two daughters.

This year marks the Ten-Year Anniversary of the founding of Usher 1F Collaborative, and together with our families, friends and strategic partners, we have accomplished so much. Since 2013, $9 million has been invested in medical research, resulting in:

- Nine research labs focused on a cure (in 2013 there were 0)
- Development of zebrafish and mouse models on which therapies are tested
- Launch of a worldwide natural history study in partnership with Foundation Fighting Blindness
- Interest from biotech in moving our work to the next critical stages of new treatments

We are truly at a turning point, with gene and drug therapies now in sight. Usher 1F Collaborative is positioning itself to be at the forefront of changes that will have implications not only for those with Usher 1F but also for other inherited retinal diseases and other diseases caused by mutations in a single gene. This would not have been possible without the support of our most dedicated contributors. We remain deeply grateful for your support of and faith in our work.

While we celebrate our accomplishments, we cannot rest because the next few years are critical for the development of a viable therapy. We stay steadfast in our mission for a cure, and we hope you will remain a part of this life-changing work. Together, we will ensure that no child will face an ever-darkening world from Usher 1F, and no adult will live in darkness and silence. ◆

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the planes. Delta hired an ASL interpreter to enrich the experience for Ryan so that he wouldn't miss anything.

"He showed me that there is joy in airplanes that I have been missing. I've seen a lot of airplanes in my life, but I've never taken the time to enjoy one rivet by rivet, from the nose of the airplane to the tail. Just by touch he was able to show me parts of the aircraft that had been modified through the lifespan of the airplane. As a pilot, I'm naturally a visual person. Looking only takes a second, but I have been missing details all these years. Ryan has taught me you can often get more out of your experience if you take the time and try to look at things from different perspectives."

Ryan's experience next included a seat in the flight simulator, sitting beside Capt. Bennett as his first officer. This was the highlight of his day at Delta. Delta even presented him with a sim certificate printed in Braille. ◆

Photos and quotes from Capt. Mike Bennett – Credit: Delta Air Lines

Announcing Usher 1F Collaborative Canada

We are excited to announce that Usher 1F Collaborative Canada is now an official tax exempt charitable foundation in Canada.

We have had a presence in Canada from the start. Usher 1F families in Toronto, Ottawa, and Newfoundland have worked alongside us, and one of our researchers, Vincent Tropepe, is at the University of Toronto.

Without the ability to issue Canadian tax receipts, though, our fundraising in Canada was limited. With Usher 1F Collaborative Canada, we have changed this. We can now accept donations in Canadian dollars and issue Canadian tax receipts!

As we grow and increase our efforts in Canada, we invite you to join us. We love our volunteers, and no gift is too small.

Please email us at usher1fcanada@usher1f.org for more information or to volunteer.

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common in African Americans, and cystic fibrosis is more common in Caucasians. Those of Ashkenazi Jewish descent, that is Jews whose ancestry is descended from eastern Europe, comprise another ethnic group with many recessive genetic diseases. Included in the list of diseases for which JScreen tests are over 100 diseases, including Usher 1F, that have mutations more prevalent in those of Ashkenazi Jewish descent. Approximately 60% of those with Usher 1F share the same genetic mutation.

If you are interested to learn more about reproductive genetic testing, please see Resources and Partnerships under About Us on our website, where you can watch Estie Rose's presentation. In addition, please visit JScreen's website, jscreen.org, to learn more about their work, including their cancer gene testing. ◆

> **WITH THE TREMENDOUS ADVANCES IN GENETIC TESTING OVER THE PAST DECADE, COUPLES CAN NOW GET PRESCREENED PRIOR TO HAVING CHILDREN.**