Senses Lost: The impossible dilemma of Usher Syndrome, and its possible solutions

by

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ABSTRACT

Usher Syndrome is an inherited disease that leads to the progressive loss of hearing and vision (retinitis pigmentosa). Increasingly, genetic testing, either through panels or whole exome sequencing, lets people know which of the twelve genes identified to date is responsible for the loss of their senses. Researchers are using these genetic ascertainment data to identify patients for clinical trials: There is no approved treatment for retinitis pigmentosa. A philanthropically-funded translational research program led by Dr. Edwin Stone at the University of Iowa seeks to provide an at-cost personalized gene therapy for everybody with Ushers, regardless how rare. His efforts focus transfecting patient-derived induced pluripotent stem cells with a viral gene vector to replace the broken Ushers gene. Meanwhile, a phase I/II clinical trial led by Dr. Eric Pierce and ReNeuron takes a different approach—injecting participants' subretinal space with healthy donor stem cells. Critically, both of these methods risk remaining vision.

This is the story of two people with Ushers—an infant with *MYO7A* –associated Ushers who was genetically diagnosed in her first year of life, and a retired man who likely suffers from *USH2A*-associated Ushers, whose life experience exemplifies the condition, but whose specific genetic mutation has never been identified. Both have opted for cochlear implants to improve their hearing, and both work to adapt each day to their changing senses.

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As Beth Lacourse took her first child, Reagan, home from the hospital in 2009, she knew she had been put on earth to be a mother. She lives with her husband, Jake, a hardware engineer, in a suburb between Boston and Cape Cod. She describes those first heady days of motherhood as "falling in love again." Several years later Beth found out that, after a miscarriage and with the help of medications and a number of doctors' appointments, she was pregnant again. Reagan would have a baby sister.

Rebecca Lacourse was born last January. Reagan came to meet the newborn at the hospital, and the family soon brought Rebecca home. She left the natal care unit without one standard test, the newborn hearing screening, because of a simple snafu: the ear muffs for the test machine were missing. When Beth took her back to the hospital the next week, Rebecca didn't pass the test, and the nurse explained that this was probably because she had residual amniotic fluid in her ears—they saw this in lots of babies, and there was nothing to worry about. But the following week, Rebecca failed again. At home, the Lacourses conducted hearing tests of their own—banging on pots, yelling, and clapping—but Rebecca didn't respond. An auditory brainstem response test at the Durfree Center in Fall River confirmed what Beth already suspected. Rebecca's ears weren't full of fluid. They just couldn't hear.

Beth and Jake participated in deaf community events around their neighborhood, and started learning ASL. The family joined a Shared Reading program at Northeastern University, and even seven-year-old Reagan began learning to sign. They signed stories. They gave Rebecca a signed name, combining the signs for "R" and "beautiful." When Rebecca whimpered in her car seat on the drives back and forth to Boston , they would twist around from the front and sign comfort, reassuring her that they were there even if she couldn't hear their voices soothing her.

It's not that bad, Beth and Jake thought. We're learning so much. Rebecca grew, her brown hair now long enough to be pulled back with a hair bow. But when Rebecca reached four months, Beth noticed that she was still holding her as she would a new baby, supporting her back and neck with her arm. Rebecca couldn't hold up her own head. She also resisted being handled. When Beth picked her up, she pushed against Beth's arm, howling until Beth laid her flat. "She just wanted to be laid on the floor. And that would calm her down right away," Beth told me.

Beth posted on a deaf-community Facebook group, asking other parents if this sort of "head lag" was typical. "I expected people to write back and say it's because she's deaf and she wants to see everything around her, and that's not at all what people wrote," she says. Responses flooded in: had she heard of Usher Syndrome?

Beth began Googling descriptions of a rare genetic disorder. People with Usher Syndrome have a hearing loss at birth, she learned—sometimes they are born profoundly deaf. And depending on the genes involved, they display further symptoms as children, teenagers, or adults. The blindness comes as tunnel vision, caused by a condition known as retinitis pigmentosa, the gradual death of light receptor cells around the edges of the retina. A person with Ushers might have 20/20 vision, but have such a limited field of vision that they can't see below their nose, can't see to shake a stranger's hand, or notice a car turning in front of them when they are driving. And because it is the light receptors that break down, people with Ushers are usually night blind—unable to see in the dark—even in early childhood. The most severe types also come with vestibular ataxia, balance problems.

The more she read, the more Beth recognized Rebecca in the list of early symptoms. Jake and Beth took their daughter to Boston Children's Hospital for genetic testing, and during the two months they waited for results, Beth tried to talk herself out of her internet-research scenarios—surely she was jumping to the worst possible conclusion. Rebecca had profound hearing loss, and that was it. As they waited for conclusive results, Rebecca went for a vestibular function test. The vestibular system is responsible for balance and spatial orientation, and closely tied to hearing. The labyrinth of the inner ear where the system lies is connected to the spiraling cochlea bone, and is often disrupted in the severest types of Ushers. Beth was strapped into a chair and held Rebecca on her lap. The lights went out and the chair spun them around the room. Next, the technician pumped ice cold water into Rebecca's ears. The tests left Beth dizzy, but Rebecca remained stoic, and Beth assumed that this meant that Rebecca aced the test. In the days after the test, Rebecca was sitting on her own, holding her head up; her balance looked normal. Beth convinced herself that she had made up this Usher-Syndrome business. The genetic test would confirm no irregularities and the family planned to celebrate with a dinner out.

Then one afternoon Beth received an automated email from the patient portal. A result for the genetic test had been updated. Beth clicked the link. The results from Rebecca's Usher gene panel were back. Positive for two pathogenic mutations in her *MYO7A* genes. Rebecca had a molecular diagnosis—genetic proof—for Usher type 1b.

Rebecca is one of the estimated 150 babies born globally with Usher Syndrome last year. Ushers was named for the Scottish ophthalmologist and surgeon who described the condition as "an association of retinitis pigmentosa with congenital deafness" in 1914. It is now recognized as the leading cause of deaf-blindness, and thought to affect half a million people around the world. Usher can be regional; Usher 1c emerged from a small intermarried group of American settlers in 1604 and is limited to 300 French Acadians in southwestern Louisiana. Usher 1f occurs only in descendants of Ashkenazi Jews. Only Finnish people are thought to experience the late onset and vestibular havoc of Usher type 3. Usher 2a is the most common. Children with Usher 2a are born with a moderate hearing loss. As adults, they get their prescription checked, only to find that new glasses won't restore the expanding doughnut of ruined retinal cells.

Some doctors and researchers doubt the efficacy of grading the various stages in which people lose their hearing, and then their sight. The types exist more as a historical remnant, a diagnostic short-hand that is becoming outdated in an era of whole genome sequencing. Dr. Eric Pierce, an ophthalmologist and the director of the Ocular Genomics Institute at the Massachusetts Eye and Ear Infirmary, believes a more accurate language would focus on the culprit gene, twelve of which are now known: *USH2A*-associated Usher Syndrome, or *MYO7A*-associated Usher Syndrome. Not only would this distinguish patients who could one day receive a similar gene therapy, but the natural history and disease progression for each type overlaps in ways that are yet to be unsnarled.

Ushers is the result of two defective copies of one of the Usher genes in the same person. For a child to develop Ushers, each parent has to contribute a gene whose letters spell a mistake. It doesn't have to be the same mistake. A mother might pass along a copy of *MYO7A* instructions

for making a protein that only gets made half way before being abandoned, and the father's maybe a third of the way. When healthy, the product of *MYO7A,* a protein called Myosin VIIA, joins a band of other proteins to translate mechanical stimulation on the ear drum into an electrical signal that the brain processes as sound. Because the child doesn't have even one set of correct instructions, their cells have no way of producing Myosin VIIA.

Much of the population born before the newborn hearing screening requirement lived for years without any inkling that they needed hearing aids because of their genetics. The older generation also grew up closer to the deaf community—often learning sign language first, and then finger signing and braille when they could no longer see a conversation partner's hands. Parents and doctors found ways to attribute the hearing loss to a strong course of antibiotics, or a childhood ear infection. Ophthalmologists didn't consider that hearing and sight might both be lost as a result of a single letter swapped out somewhere in the genetic code.

Tom Van Arman remembers his senior prom in the spring of 1970 as the night he lost his vision. He picked up his date earlier that evening, and just as they sat down to dinner, he felt a headache coming on. He popped several aspirin, but the searing headache persisted. Van Arman had suffered from headaches throughout high school. Long headaches, sometimes lasting for thirty-six hours or more.

The after party was at a friend's barn, along a dark road in rural Pennsylvania some fifteen miles from Van Arman's house. By midnight, Van Arman couldn't take it anymore. He asked around to get his date a ride, and then got back into his '69 Chevy Nova to drive himself home. "The white line on the side of the road was much dimmer than I could remember. The spacing of the lines in the middle of the road was equally dimmed. The car headlight didn't show me enough roadway to make me comfortable," he recalls. Decades later, from the reading he's done, he thinks this was because of the optic neuritis common in people with Ushers. The nerve behind his eyeball was inflamed, causing, along with a fierce headache, the cells in his retina to die off. Usually this leads to vision loss several days after the initial headache and inflammation. Van

Arman feels that he lost almost half his peripheral vision that night alone, not days later—but he will never be sure.

Several months later, and two days before his first day of college, Van Arman was diagnosed with retinitis pigmentosa. Nevertheless, he kept driving until he was in his thirties, when he had only twenty degrees of vision left. By then, he was using street lights along the road as "beacons" to orient himself, because he couldn't see what the lights were actually illuminating. Driving at night is one of the first things adults diagnosed with Ushers are told to stop; many, like Van Arman, realize that they had been driving for some time with fewer degrees of vision than is legal in their state. While it may seem like common sense to not drive if you can't see, many people with Ushers never realize they aren't seeing what everyone else is seeing. Nobody knows exactly what other people see, or what is a "normal" amount to see at night. When trying to diagnose night blindness in a child, pediatricians ask parents leading questions about their child's behavior. Does he refuse to go from a lit hallway into his dark bedroom? When you go into your toddler's room after her nap, does she notice you before you say her name? Does he try to hold your hand in parking lots at night?

Usher diagnoses as early as Rebecca's remain relatively rare. They used to be rarer. Before the routine hearing screening, it often took much longer for anyone to notice symptoms. Surprisingly for a child who grew up in the 50's, Van Arman was fitted with a hearing aid so early that he can't remember if he still wore diapers or not. Though his natural history fits that of *USH2A*-associated Usher syndrome almost exactly, forty years after he had been diagnosed with retinitis pigmentosa Van Arman has still not received a genetic diagnosis for Ushers. In 2010, his doctor sent some of his blood away for genetic testing to the Carver Lab at the University of Iowa, a place that was quickly becoming a center for inherited eye disease research. The clinic wrote back: one copy of Van Arman's *USH2A* carried a mutation typical of Usher syndrome, but no definite molecular diagnosis. They couldn't locate the misprint in the other copy.

At promptly 5:30 on a January evening, Dr. Edwin Stone stepped into a conference room at the University of Iowa Hospital in Iowa City. He had something to share, something that

the bioinformaticians, the clinical administrators, and the molecular biologists all needed to see. Stone is balding, and his suit seemed to hang slightly from his tired frame. He swallowed half of a Jimmy John sandwich and downed a cup of Diet Coke that was mostly ice. He waited another minute, glancing at the time, for the arrival of a resident. Everybody needed to see this video.

Stone had shot the video on his iPhone earlier that day during his weekly eye clinic. A projector sat warmed up on the conference table, at the ready to show visual field tests and retinal scans, the yellow discolorations that decorated the pink retinal orb between purple arteries like tie-dye. Stone connected his phone. He made sure the volume was up.

On the screen, a nine-year-old not of Western descent glances at her parents, and then back at the phone camera. She hops from one foot to the other, her faulty vestibular system barely an impediment to the mass of childhood energy. She tells the person holding the camera that she wants him to fix her eyes. She needs them fixed *soon*. Earlier that day, she had been diagnosed with Usher 1b.

The need to fix vision for Usher suffers, and soon, presses on a handful of labs around the country. Eric Pierce, the ophthalmologist at Mass Eye and Ear, works on Ushers and several, even more rare, inherited eye diseases. Van Arman's doctor at the University of Pennsylvania, Samuel Johnson, was involved with some of the earliest gene therapy trials for eyes, and scattered other researchers look at various aspects of individual types, or create models from zebrafish or mice. Others experiment with retinal prosthetics, or ocular implants that will secrete a protein that might prevent further retinal degeneration. William Kimberling, perhaps the most renowned Usher researcher in the United States, gave his collection of blood and tissue samples from Usher families to the University of Iowa when he retired. A combination of Stone's tireless efforts and a philanthropic gift made the hospital, genetic testing facility, and research at Iowa somewhat of a hub for Ushers, in large part because of Stone's efforts. He is one of only a few researchers whose approach focuses on developing treatment for actual patients—understanding the basic mechanisms, but working equally to create a therapy that could go into people. Almost every patient I've talked with mentioned Stone or Kimberling, and a blood sample they sent long

ago. It's been years, and some of them haven't received news of a diagnosis, and still, they are somehow patient with science.

In many ways, the young patient in the video is an everyday sight for those working with Stone. From the hospital's perspective, there is really nothing exceptional about her—except, perhaps, that she lives during a time where the personalized gene therapy that could save her sight always remains just around the corner.

As he finished his ophthalmology residency in 1989, Stone thought he would treat patients with gene therapy. The revolutionary, "forever fix" therapy was just beginning to get attention, and he thought that one day soon other doctors would write to him, asking if he wanted to participate in their clinical trial, and he would enroll a couple of his patients. "And then I would be a gene therapy person, and I would do a little treatment, that is how it would work. But there were no treatments," Stone says.

An early-onset type of retinitis pigmentosa, Leber congenital amaurosis, was the first inherited eye disease to see a gene therapy. Tested in dogs in 2000, the therapy injected a virus with an intact copy of the dysfunctional gene. Despite the initial success of the method in humans, first administered in 2007—expertly navigated mazes and claims to see colors brighter—follow up studies are divided on the procedure, safety, and efficacy. In 2011, another handful of people began a *MYO7A* gene therapy trial at the Casey Eye Institute in Oregon, but conclusive results await publication. When Stone was contacted about including his work on administering the amaurosis gene therapy to a cohort of patients in Iowa in a forthcoming documentary, he asked: as an example of success, or failure? "I am not trying to be cute," he says. "It's 2017, and I still can't write a prescription."

Watching the glacial progress toward a remedy—and suspecting that even when a commercial therapy was approved, it wouldn't be affordable for the people it was supposed to benefit, who because of their disabilities are more likely to be unemployed—Stone decided that if he was going to be a "gene therapy guy," he needed to start working on creating accessible gene therapies himself.

Stone grew up on a car lot, watching his dad sell cars. If he is a talented surgeon, he is a better salesman. Stone realized that to offer an affordable treatment, he first needed a three million dollar manufacturing facility to make a cell or gene treatment to the standard needed for implanting into people. Using the resources of an academic molecular biology lab and with such a factory in place, the cost to create a personalized gene therapy is five thousand dollars per case, and the cost of the surgery another five. People could realistically raise that kind of money to fund their gene therapy. Stone dreams that philanthropists would also pay for treatments, avoiding involvement with insurance companies, the pharmaceutical industry, or the government. "They give twenty-five grand for that, or fifty grand for this and that, just regular people who give regular old philanthropic gifts. They can now give a gift that could pay for five people to get gene therapy," he says.

As they research and fundraise, Stone and the University of Iowa's Carver Nonprofit Genetic Testing Lab work to molecularly diagnose as many people with Ushers as possible. Where before a general diagnosis of the condition might suffice, doctors will soon need to know the exact mutation on the exact gene responsible for Ushers in children like Rebecca. *MYO7A* and the other most common Usher-related genes are systematically searched for a disease-causing mutation. Scanning each DNA base of the *MYO7A* behemoth is laborious—all of the Usher genes are huge—so the 135 most common mutations are checked first. The process takes only weeks, costs a set price, and pinpoints the faulty section of gene. Though not as comprehensive as searching the whole genome, the chip provides a diagnosis for 75 percent of patients.

But while this approach might work for Rebecca, like many things in medicine, the tools and data available to geneticists skew heavily towards the experience of descendants of white Europeans. Chip designers need to be judicious about which common genes and mutations to include to maximize the chance of finding a patient's mutation with the first pass. But that first past—or even several passes—might be unable to find the disruptive gene in children like the girl in the video.

This narrow, targeted, screen-just-the-suspected-gene approach is critical for the nonprofit lab, which seeks to let people know the genetic cause of their disorder as quickly, accurately, and as cheaply as possible. Stone is in the process of designing a question system that will help researchers identify exactly which gene should be screened, based on the age, ancestry, and severity of symptoms. Yet such a direct approach excludes the chance to glimpse what else is happening in the genome, and Pierce wonders what is being left out. And albeit few, there are still patients with inherited eye disease for whom the problematic gene remains unknown.

Even as the understanding of Usher DNA unfolds, the natural history of the disease remains muddy. Historically, physicians divide Usher genes into three types of disease roughly by the stages of life at which senses are lost, yet the gold standard of a molecular diagnosis still leaves patients without the information they need the most: how to prepare for communication, perception, and mobility in the future. Learning braille seems like a waste of time for someone who anticipates always being sighted.

While studies are underway to gather information to create a comprehensive natural history of Ushers—a sort of map that patients can follow to predict when their sense might begin to fade—even siblings with the same mutation in the same gene experience Ushers very differently. By the time Hank Gorbsky realized he was losing his vision as a young adult, his older brother had not experienced any significant changes in sight, though his hearing was much worse than Hank's. Thanks to the variation in the brothers' sensory loss, at the time the Gorbsky's didn't realize they had the same condition. Talking with families in the Usher community revealed that this wasn't at all uncommon.

Aside from, or maybe in addition to, the genetic vagaries that dictate the narrowing of the visual field, Usher eyes are plagued by seemingly random cataracts and swelling edemas. Cataracts form over the retina and cloud the central vision, blocking light from the one place it can be received. Fluid-filled cysts of macular edema swell in the layer inside the retina. The way the cysts wax and wane is almost fortunate—at least at times they wane. They are impervious to

medication. Treatment becomes monitoring, with the expectation that the cysts will shrink with time, improving central vision as arbitrarily as peripheral vision disappears.

The time of year and the surrounding light influence visual perception, and how someone perceives vision. I met a college student with Usher 1f, who had spent last summer studying in Denmark. She loved it not for the architecture, but because of the seventeen hours of sunlight each day. A mother in Alaska says that each year, her son begins struggling to navigate outside in the fall; the early dusk makes his night blindness more pronounced. Two weeks later, and often accompanied by the first snow fall, day light savings time extends the day by an hour. The bright white reflects light back to him, and overnight the child reports seeing better than ever. Another woman's sight became suddenly worse after the ophthalmologist diagnosed her with retinitis pigmentosa. Knowing that she would one day be blind brought depression, and "depression clouds your vision in a literal and metaphorical sense," she told me.

Each sufferer develops his or her own particular tactics and compensations to deal with declining senses in a hearing, seeing world. With encroaching loss, people with Ushers balance stability and familiarity with their evolving needs.

After college, Van Arman landed a job as a quality control manager in a medical rubber laboratory in Blue Bell, Pennsylvania. He remembers the conditions as ideal. He worked with a small group of other people experimenting to make vaccine stoppers, needle covers, and syringe plungers. Everyone knew about his vision loss and knew not to startle him. They took care never to leave drawers pulled out or cabinets open. Except for the occasional run in with a mop handle or mechanical lift, Van Arman worked in the laboratory for years without ever having an accident.

The fact that Van Arman adapted so well to an especially dangerous workplace—fumes, machinery, chemicals—does not mean that more common places are not equally or even more challenging for people who are losing their senses. Kathy Thompson, a program management contractor at NASA, lost most of her peripheral vision in the three years following her diagnosis

for Ushers. She describes what is left as looking out of a bathroom window: shorter, smaller, narrower. If she maps the vision of each eye onto a world map, she says "I can see straight ahead, and I have a small bridge, and then I have Australia on the periphery," meaning that she can see directly in front of her, and through a narrow sited path to another little island of sight at the edge of each eye's vision field. And that's it. Every day she sits down in her cube, facing her computer. Her hearing aids pick up the sound of three hundred people typing, so as she works she listens to her iPod.

"People come up, and stand there, and I'll keep looking, but I won't see them," she says, "that has been rectified, now I have a motion detector, and it has a little pager that vibrates. People wonder why I am ignoring them." As her eyes change, Thompson uses different types of lighting. The lights above her desk were too bright, so she had them turned off and relies heavily on task lighting from lamps. The glare of the lights in some conference rooms gives her headaches, so for meetings she angles to be in rooms with a dimmer switch. On days that her mother or husband or co-worker isn't able to give her a ride, she works from home. In order to continue working, Thompson needs to be upfront with her family and colleagues.

Sometimes, strangers misconstrue symptoms, often forcing someone and their diagnosis deeper into the closet. A physician in Australia learned never to tell anyone. Six months from finishing her medical degree, she told her mentor about her Usher diagnosis. He told her she couldn't graduate, and threatened to report her as "unfit to practice" to the dean of medical faculty at the university. Years later when she was picking her child up from school, several other mothers confronted her in the parking lot. They had mistaken her stumbling and bumping into things for a substance abuse problem, and said they didn't want her near their kids anymore. When she told them about Ushers, their tone immediately changed.

Van Arman worked in the laboratory for twenty-five years. Then the company was acquired, and he lost his job. "At that point, to my surprise, I could not even board a bus, get on a train, or walk by myself. It's one of those situations where I led a cloistered life. Things I couldn't do, my wife helped me out," he says. "When I had to go looking for a job on my own, it was like, 'where do I

start? I can't even cross the street.'" He knew where everything was in his lab and in his house, down to the inch. Before the layoff, he didn't need to know the position of anything else.

Without his daily work in the lab, the years of hearing and seeing loss caught up with Van Arman quickly. Even with his hearing aid, his conversation became limited to, "'Tom, somebody is at the door,' or 'close the door.' But if you changed the subject while talking, I was lost."

The imminent loss of vision makes dealing with hearing loss critical. Eventually, it becomes impossible to amplify sound sufficiently with hearing aids, and sign language is a visual language. Enter the cochlear implant, or the bionic ear. A single surgery implants a small electrode array into the base of each cochlea, the spiraling auditory portion of the inner ear. A processor and microphone attach to the outside of the head, filtering and translating sounds and converting them into electrical impulses that directly stimulate the auditory nerves. Beth and Jake wondered about implants as soon as they learned of Rebecca's hearing loss, but this communication alley is not without controversy. Some members of the deaf community vocally oppose decisions of hearing parents to force their children into a hearing world. But with Rebecca's fate genetically confirmed, her parents' resolve was set. Jake added a countdown timer on the side bar of their blog, Memories for Becca, to count the days before the seven-hour implantation surgery.

Ten days before Christmas the family bundled up and left the house in the dark, driving the hour to Boston Children's Hospital before the sun was even close to rising. Beth sat in the back seat, smiling at Rebecca in her navy blue sleeper covered in pink hearts, and rubbing Rebecca's cheek. At the hospital, doctors coordinated to use the time that Rebecca was anesthetized to do a vision check before she was sent to the operating room, laying electrodes on her eyes to measure the rod and cone responses with an electroretinogram. With the test done and Rebecca under the care of the anesthesiologist, the waiting began.

The parents staked out a couch in the still-empty waiting room. Minutes inched by. They ordered omelets in the hospital café. Just as they finished their food, they got a call. The

electroretinogram results were back. The results were not good. The rods and cones responded to a strobe flash with 11 microvolts of electricity coursing through Rebecca's eyeball. Other toddlers respond with at least 100 microvolts. Jake asked how the 11 compared to other Ushers toddlers. The ophthalmologist couldn't say, but she did note another way that Rebecca's eyes differed from the usual patient's. The electroretinogram looks like a globe sliced with latitude and longitude lines, overlaid with a squiggle that represents the electrical response in each region. Instead of a stronger center with a weaker periphery, Rebecca's one tenth of a squiggle peaked at the edges. The rods and cones at the center of her eyes couldn't distinguish the flash. The reason, the doctor explained, was that her retinas were covered with cysts.

Beth and Jake spent the night after Rebecca's surgery at the hospital, in a private room with Rebecca's crib in arms' reach. She seemed a little fussier than usual, waking up to nurse in the middle of the night. By the morning, Rebecca was back to herself, mostly annoyed with the equipment attached to her, and the wrestling headgear-type bandage that cocooned both her ears and the snaking incisions behind them. Her doctor warned that the implants might further disrupt her balance, but two days after the procedure and one month shy of her first birthday, Rebecca began to crawl. Still, the news about her eyes was daunting. In the months following the surgery, they would try to give her the eye drops three times a day, but Rebecca hated it. She is still too young to undergo the testing needed to find out if the drops are shrinking the cysts, and without evidence that the drops help Beth hesitates to torture Rebecca needlessly. Meanwhile, with Christmas a week away, Beth and Jake had a few weeks to recoup from the surgery before returning to the hospital to have the implants activated.

Cochlear implants are not a one hundred percent satisfactory solution. The cochlear implants of the early 2000's helped Van Arman's hearing, yet he couldn't distinguish people's voices. The voices coming through the processor intermittently sounded like whistling birds or the garbled mumbling of the adults from the Peanut specials. He realized that the implant selectively filtered sounds, and that he never heard *both* the whoosh and the click of someone hitting a golf ball. Other times the implant would manufacture sounds not in the environment—tapping his wedding band on the table made the expected knock, but was followed by a hiss.

Quiet rooms became intolerable. "I discovered very quickly, that if the room is too quiet it starts making its own sound. My god, that could drive people nuts, literally, so I found I have to use low level background music to keep it at bay," he told me. Still, he could hear. He had eight or nine degrees of vision left. He went to speech therapy, and trained himself to listen for patterns. Different people used "how are you?" or "how's it going?" to ask about his day.

Cochlear implants continue to improve, and in 2013, years before Rebecca Lacourse was born, Van Arman upgraded his implants to the latest model. For the first time in his life, he recognized music. He heard a song on the radio, and within minutes of searching YouTube he was able to identify Carly Simon's "Anticipation." He hangs on to the ancient Google Plus for his browser, because the red-blue text of Firefox is hard for him to distinguish, and Chrome has a large white banner at the top, making it difficult for him to read the page. Van Arman's vision is cloudy on a good day, but not because of cataracts that could be burned off with a laser. This time, it's because his retina is fragmenting. In places where the outer retina is missing, light shines through and reflects back. He struggles with glare, and loses clarity in bright sunlight. Perfect days are the overcast and gloomy ones. What remains of his eight degrees of vision is color weak. But with his improved cochlear implants, he's since discovered Stevie Nicks and Creedence Clearwater Revival. He wonders about installing an ad blocker, so he can get past the pesky YouTube ads faster. Often he hides a window playing Pandora while typing an email, challenging himself to guess the artists.

The devices and the surgery have become so successful that the first symptom of Usher Syndrome is no longer the primary concern for most. The community waits for the move from successful hearing to sight remedies, daring themselves to hope that cell and gene therapies will arrive in time to stop the world from going dark for Rebecca's generation.

In the Dezii Translational Vision Research Facility in Iowa City, passersby squint through a narrow pane in the door and the glare of a shockingly white production room. A stainless steel counter enclosed in glass stretches across the windowless space, protecting an assembly line

that will never be exposed to air. Sets of rubber sleeves break the glass, letting sterile hands reach the bench to orchestrate the birth of a retina.

New retinas begin with a bite of flesh taken from a discrete place on the patient's forearm or hip. Gloved and gowned, a laboratory worker nurtures the tissue into a cell line, growing endless generations of skin cells in cell culture dishes. Once established, the skin cells are treated with viruses bearing genes that signal the cells to erase memories of skin and reincarnate themselves as stem cells.

Stem cells exist at a brink of potential—a skilled practitioner can direct these patient-specific cells to become liver cells, or neurons, or the self-contracting cells of the heart. Retinal cells are some of the most complex in the body. They are the neurons that are first to interface with the outside world. To make a retina, stem cells are cued with molecules that drive forebrain development. Within a couple of weeks, cells associate into a structure known as the eye cup, the developmental predecessor of the eye. The cells need to be fed daily—and in isolation from the environment or other cells—for them to develop properly and to meet the standards for human transplantation. The facility plans to use a robot to manage some of the feeding, keeping the cells farther away from human error.

Technicians sticks their arms through another set of sleeves, reaching down the pristine production line, to slice off the eye cup and put it into a fresh culture. The culture is then seeded onto a 3D-printed scaffold, a mesh that separates each cell while surrounding it with channels for communicating with its neighbors.

More than nine months after the skin sample collection, a tiny sliver of retina will exit the production line. A courier will put a vial on ice in a Styrofoam box, and walk the quick ten minutes to Elevator L in the hospital complex. The cell-loaded scaffold will be rolled up inside a hollow needle and injected into the deteriorating retina of a waiting patient with a slight mark on their arm.

Below the ground, a portrait of Dezii hangs at the mouth of the blinding white hallway that leads to the rooms that will make medicine for six people a year. The Dezii facility is part of the Stephen A. Wynn Institute for Vision Research. The Wynn Institute nestles among other modern steel and plate glass buildings tastefully adjoined to the older brick of the medical school campus. Inside the main staircase bends and angles so many times that the receptionist asks guests if they would prefer walking up the fire escape to avoid nausea.

For now, the building feels sort of empty, echoing like a cathedral between masses. As director of the Wynn Institute, Stone works to create a place where even people with the rarest form of Ushers or other inherited eye diseases will be able to receive gene or cell therapy. He runs through each thing he does: get the money, take care of the patients in the clinic, diagnose the patients, teach the next generation of people how to run the nonprofit testing facility, recruit people to run the lab, get the money, on a never-ending loop.

Making a retina out of a patient's induced stem cells includes one other critical step: fixing the gene that is broken in those cells in the first place. Without first fixing the gene, the new retina will suffer the same degradation as the one that it is replacing. The excitement of CRISPR gene editing system carries over to the retinal cell growers. The CRISPR-Cas9 could be applied to cells outside of a patient's body, and the cells could be carefully checked for correct editing before transplantation. This is part of Stone's vision of providing patient-derived treatments. Using cells specific to the individual lowers the risk of rejection or inflammation, or the potential need for a lifetime of immunosuppressing drugs.

The other approach is to use cells from healthy donors, cells that don't have a broken gene. Pierce, from Mass Eye and Ear, is leading a trial in collaboration with ReNeuron, a UK stem cell research company, that takes advantage of the eye's sub-retinal space. The tiny folded pocket between the light sensitive cells and the retinal pigment epithelium is believed to be immune-privileged. Foreign or non-self cells implanted here seem to be exempt from the body's general xenophobia, making the eye an appealing target for cell therapy. Cells on their way to becoming retinas are harvested from aborted fetuses and injected into the sub-retinal space of participants.

Instead of first finding which gene was responsible, the study aims to relieve the symptoms of retinitis pigmentosa by adding healthy cells. The cohort is small—just fifteen patients—and doesn't necessarily include Ushers sufferers.

What the participants do have in common, though, is at least a fragment of a normal retina. For the therapy to have any hope of success, those enrolled need to have some healthy retinal cells that can integrate with the new cells. One drawback of a study design that combines the usual first two phases is that efficacy is being tested alongside safety. Despite promising experiments in animal models, patients are risking their remaining sight while hoping that this treatment will preserve it. "Either just by the trauma of the injection, or the stem cells themselves, or by an immune response. It could make things worse instead of better, and they have to decide themselves if they want to take that risk. It's an enormous contribution. It blows me away. It makes me emotional." Pierce paused.

"They are like astronauts going to the moon. They are taking a step that hasn't been taken before."

As the holidays cleared, Reagan began counting down the days until Activation Day. With the surgery nearly a month in the past, it was time to switch on Rebecca's cochlear implants for the first time. Regan wanted her voice to be the first Rebecca heard. The family packed back into the car and drove to Boston Children's.

Beth had been waiting for this day for almost a year—and the time felt like it had started almost before Rebecca was born. In many ways, she feels robbed of enjoying her second baby. She looks back at pictures to remind herself of the good things that the year brought. She writes that every passing year is one year closer to what now seems the inevitable moment when Rebecca will be blind. She tries not to be sad, because each moment spent in sadness is a moment lost she could be enjoying Rebecca.

Rebecca sat in Beth's lap, intently playing with a Thomas the Tank Engine. Despite her hearing loss, she had always been vocal, mumbling and making little growls and grunts, typical for

babies trying to feel vibrations instead of hear sounds. Her teacher of the visually impaired says that if her waning depth perception interferes with play—if she weren't able to find the floor of her Fisher Price barn to set up the animals—Jake and Beth could mark the edges with colored tape, but Rebecca hadn't seemed to need that yet. Reagan sat beside in a low chair, playing with plastic food and waiting for the moment. Jake sat across the table, filming on his iPhone.

The audiologist checked to make sure everybody was ready. The room hushed. The audiologist held up three fingers, ticking off to zero.

"Hi, baby! Baby!"

Rebecca blinked. Her eyes saw Reagan offering her a toy cookie. She glanced towards Jake saying her name. She looked at the audiologist, blinking with every clap, and then made a swipe at a plastic fish tank full of plastic fish.

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