

Inherited Retinal Disease

REDEFINING PATIENT CARE

The first gene therapy approved for a small subset of IRD patients puts the profession on the cusp of a new era in genetics. Peek inside an IRD clinic to learn whether, when, and how to do genetic testing.

By Annie Stuart, Contributing Writer

AT THE END OF 2017, THE U.S. FOOD and Drug Administration (FDA) approved Luxturna (voretigene neparvovec-rzyl), the first gene therapy for an inherited retinal disease (IRD). “Patients with Leber congenital amaurosis due to mutations in the *RPE65* gene now have hope that their progressive blindness can be arrested,” said Alan E. Kimura, MD, MPH, at Colorado Retina Associates in Denver.

This step is remarkable, he said, not only for establishing the scientific principles of successful gene therapy, but also for attracting greater financial capital to develop subsequent marketable gene therapies for IRDs. But that’s not all. It reveals what can be accomplished when previously fragmented silos of human activity integrate to achieve an aspirational goal, said Dr. Kimura. “And it likely heralds the dawn of a new role for ophthalmologists, working collaboratively to deliver care to people with inherited retinal diseases in our communities.”

Common patient experience. To date, however, the experience of a patient with a rare disease such as an IRD has often been punishing, said Dr. Kimura. “They may end up seeing multiple doctors, receiving several misdiagnoses, and spending a lot of their own money for testing.” But worse, he said, is getting to an ophthalmologist who lacks knowledge about IRDs and doesn’t know where to

refer the patient for a proper diagnostic evaluation. “Too many patients report, ‘The doctor said I am going to go blind and walked out the exam room door.’”

Benign neglect? Misdiagnosis or mismanagement of these patients isn’t intentional; instead, it’s largely due to a lack of awareness in the ophthalmic community, said Christine N. Kay, MD, at Vitreoretinal Associates in Gainesville, Florida. “The field has grown so much in the last 10 years that doctors might not have the most up-to-date information to share with their patients.”

Find the specialists. For MDs who don’t know what to do for these patients, it’s important to reach out to specialists who can pick the right tests, interpret the results, and answer patient questions, said Josie Kagey, a certified genetic counselor who worked with Dr. Kimura’s practice until recently. “Patients need to be guided to physicians and genetic counselors experienced in treating IRDs.”

First Step: Specialized IRD Testing

“I was born with nanophthalmos,” said 20-year-old Seth Bynum, who was referred to Dr. Kimura’s practice, Colorado Retina Associates, in the spring of 2017. “I’ve lived my whole life going to eye clinics, and I grew up accepting that,” he said. “The best I’ve ever seen was close to 20/20 with

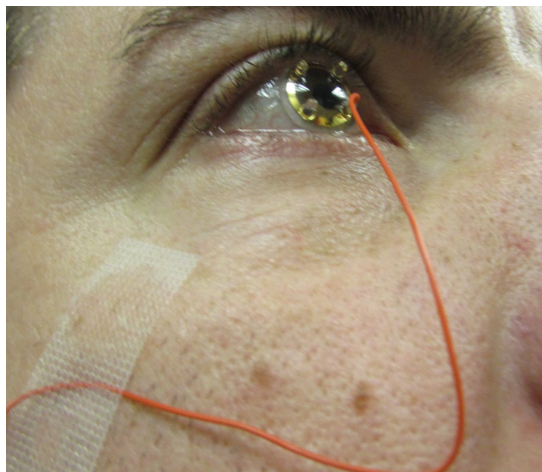
really strong corrective lenses. But recently, I was diagnosed with retinitis pigmentosa (RP) and am now at about 20/80.”

First contact. Patients like Mr. Bynum first make contact with Colorado Retina Associates’ ocular genetics coordinator, Andy Humes, who runs the eye lab, conducts specialized IRD testing, and helps facilitate genetic testing by sending out test kits and receiving results.

Because of the variety and rarity of IRDs, there’s nothing “typical” about these patients. Diagnosis can be elusive. Some have subtle conditions previously masquerading as cobblestone degeneration or early macular degeneration, for example, so a diagnosis of IRD can come as quite a surprise, said Mr. Humes. “Before patients come in, I may spend 30 minutes to 3 hours talking with them on the phone, explaining some of the implications of testing.” For example, test results will not legally affect employment.

Specialized IRD testing. Dr. Kimura emphasizes the importance of first confirming a phenotype to home in on the type of genetic testing needed. “Although it is expensive and used infrequently in most practices, specialized diagnostic equipment, including electroretinograms (ERGs) and full-field perimetry, is integral to establishing a good clinical diagnosis,” he said. “For this reason, patients are often referred into regional testing centers across the country.”

The Foundation Fighting Blindness (FFB) just designated Colorado Retina Associates as one of more than a dozen IRD testing sites across the country. FFB, as well as other offices or members of the community, refer about 50 new IRD patients annually to Colorado Retina Associates, which has seen IRD patients from 7 different states, said Mr. Humes.



ERG. Electroretinography is one of the many specialized tests conducted at Colorado Retina Associates for patients with inherited retinal diseases.

Patients are scheduled for time-consuming specialized tests a couple of weeks in advance of seeing Dr. Kimura for an exam. “Visual fields are important because retinal dystrophies present so differently,” said Mr. Humes. “Monitoring whole retina function, ERGs provide a signal of the eye much like an EKG provides a signal of the heart.” As it involves dilation, electrodes, gold-plated contact lenses, and bright lights, an ERG is no picnic for the patients, he added.

Other testing. “You can also use imaging and other tests, such as OCT (optical coherence tomography) and visual acuity, to give you clues that the cones are more involved,” said John W. Kitchens, MD, at Retina Associates of Kentucky in Lexington. “As far as a rod-mediated process, autofluorescence and peripheral visual fields will help.” Imaging is also incredibly helpful for patients and their families who may never have previously seen what their inherited retinal process looks like, he said.

Scheduling New Patients

The pace and rhythm of an IRD clinic is much different from that of a high-throughput clinic of established macular degeneration and diabetic patients.

The new IRD patients who are typically referred to Dr. Kitchens’ practice often have a preexisting diagnosis of a hereditary cone or rod disorder. “That gives us the opportunity to schedule them at a time when I’ll have more time to talk with them upfront. Last patient in the morning or last patient in the afternoon are good places for these patients, who may take 3 to 4 times as long as a patient with diabetic retinopathy or a macular hole, for example.”

It can be challenging to break unexpected news to patients, who need different information and levels of support at different ages, said Mr. Humes. To allow undivided time for discussions like these, Dr. Kimura schedules his IRD patients into half-day clinics devoted exclusively to the needs of IRD patients.

Medical and family history. Dr. Kimura takes a medical history and performs a standard clinical eye exam. Then, said Ms. Kagey, “I would have my conversation with the patients. I start with a targeted family history, asking about siblings, children, and other family members.” This information, she said, lets you “get a picture of where this patient is on his or her journey.”

Building rapport along the way, Ms. Kagey begins to assess which patients need more education or support to grapple with a serious diagnosis. “There are so many places where these patients can fall out of the system—where they can get lost

or misdirected—and so I think a key piece of a genetic counselor’s work is being that safety net,” she said.

Taking a thorough family history also helps better direct genetic testing and develop your differential, said Ms. Kagey. She cited the example of a patient who years earlier had pursued about \$800 in testing for X-linked RP. “We drew his family tree and found male-to-male transmission of RP, which made it impossible for his RP to be X-linked. Helping him choose the right testing could have saved him a lot of money.”

Genetic Testing—More Important Than Before

“In the past, we couldn’t do much for patients with IRDs, so knowing a patient’s genetic defect was more academic,” said Dr. Kitchens. “Now we’re entering an era where, although it’s still limited, we’re starting to have options that will undoubtedly grow in the future.”

When Dr. Kimura first saw Mr. Bynum, he suspected that he had a rare form of RP due to his nanophthalmos, so he recommended genetic testing to confirm. “Within 4 months, Mr. Bynum had

What Gene Therapy May Mean for the Future

The FDA approval of Luxturna gives hope to patients with IRDs, said Dr. Kitchens. “If this is successful for a devastating condition such as *RPE65*-mediated blindness, then less severe conditions may respond even better.”

The data on Luxturna. Colleagues who participated in the Luxturna trials call this a game changer, said Dr. Kitchens. “Patients have a 200% to 300% improvement in their field of vision. This isn’t just a marginal benefit—it’s functionally relevant and life changing for patients.”

Dr. Kay is personally calling all her patients with *RPE65* Leber congenital amaurosis (LCA) who don’t have significant vision loss and advising them to get treated—and not wait for other trials. “Having delved into the 3-year follow-up data on Luxturna, I am convinced of both its safety and efficacy,” she said.

Excitement mixed with realism. At the same time, Dr. Kay clarifies with other patients that only one FDA-approved gene therapy is currently available and that their likelihood of having this form of LCA is very low. The prevalence of *RPE65* mutation-asso-

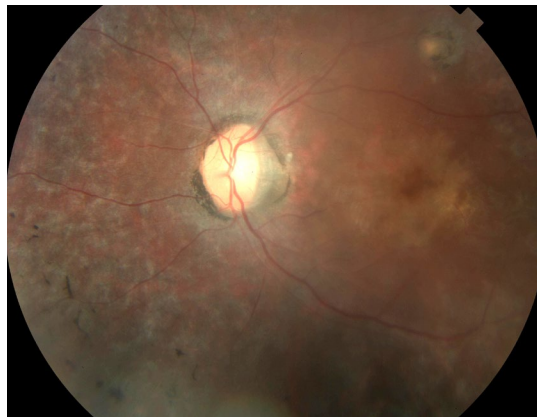
ciated retinal dystrophy is thought to be approximately 1/200,000.

Finding trials. When there’s a

strong suspicion of a genetic disease or a confirmed genetic diagnosis, Dr. Kitchens typically checks Clinicaltrials.gov to see whether any appropriate drug or gene therapy trials are available and then refers the patient for an evaluation. It’s important to help patients discern which trials are not legitimate, added Ms. Kagey, especially those that require fees to participate. Dr. Kimura and staff have also found the FFB website and events to be a great source of information about trials.

Not a one-stop shop.

Gene therapy is not an easy fix for all IRD problems, said Dr. Kay. “For example, with a prevalence of 1 in 4,000, RP is the most common type of inherited retinal dystrophy, but it is caused by hundreds of genes, so developing replacement-based gene therapies for all genetic forms of RP would be challenging. There’s less we can offer these patients



LCA. Luxturna, the new gene therapy for IRD patients with mutations in both copies of the *RPE65* gene, holds hope for future IRD treatments.

right now from a gene therapy standpoint.”

Other areas of research.

However, optogenetics is an example of a therapeutic field that may someday be able to address multiple retinal conditions, even where significant visual loss has already occurred, said Dr. Kay. This form of treatment uses light and gene therapy but is not dependent upon a specific genotype, as it doesn’t replace a missing or mutant gene. Optogenetics involves reprogramming healthy inner retinal cells to function like photoreceptors.

And, although human clinical trials are still in very early phases, the field of stem cell therapy holds some promise for the future, she said.

a molecular diagnosis and family genetic counseling,” said Mr. Humes, “something that could have taken upward of 5 years and thousands of dollars in the past.”

Who should be tested? After the initial testing and exam, it’s important to equip patients with enough information to decide whether to do genetic testing. To prepare for prospective clinical trials and treatment, and to inform patients and subsequent generations about their risk of passing on the disease, Dr. Kimura strongly recommends genetic testing for most—if not all—of his IRD patients.

Dr. Kay does not think testing is mandatory for every patient with an IRD but recommends it for most patients. “I would say it absolutely is necessary for pediatric patients with a diagnosis of an IRD and anybody with an X-linked or autosomal dominant disease because of the importance of genetic counseling within families. It is also

absolutely mandatory to perform genetic testing if the diagnosis is Leber congenital amaurosis or early onset retinitis pigmentosa, given the recent FDA approval of Luxturna for RPE65-associated retinal degeneration.”

In addition, Dr. Kay recommends testing for anyone who may be a candidate for a current gene or drug clinical trial, such as patients suspected of having choroideremia, Stargardt disease, X-linked RP, X-linked retinoschisis, Usher syndrome, or achromatopsia.

The kids are all right? When a parent is diagnosed with an IRD, often their first question is, “Are my kids affected?” What follows is a discussion about whether to test seemingly unaffected minors, said Ms. Kagey. “Are they at a point in their lives where they have the capacity to process this information? Or should we wait until later? The general guideline is not to test unaffected minors.” However, she said, a 16-year-old might

IRD Resources for Doctors and Patients

For doctors and patients who want to learn more, a wealth of information exists.

Education for clinicians.

For each of the past several years, Dr. Kay has taught a course with several international and domestic faculty at the annual meetings of the Academy and the American Society of Retina Specialists. The instruction course provides information about IRDs, genetic testing, and gene therapy updates. In addition, Dr. Kay wrote a comprehensive overview titled “Logistics of Genetic Testing: An Overview for Retina Specialists” discussing the how-tos of genetic testing in a clinical setting.¹

Genetic testing services.

Commercial labs that offer comprehensive retina dystrophy panels, said Dr. Kay, include Baylor Genetics, Blueprint Genetics, GeneDx, Molecular Vision Lab, and PreventionGenetics. In addition, some universities and nonprofit labs, such as the Carver Nonprofit Genetic

Testing Laboratory at the University of Iowa, offer testing.

Genetic counseling services.

The website of the National Society of Genetic Counselors has a tool for finding genetic counselors in your area, said Ms. Kagey. “And online resources that provide telephone genetic counseling, such as InformedDNA, are good options for those who don’t have local access to genetic counselors.”

Registries. In addition to My Retina Tracker, the National Institute of Health’s Genetic Testing Registry is a central location for providers to voluntarily submit information about genetic tests.

Other websites. A variety of websites, including the following, provide more insights about IRDs:

- NEI’s **eyeGene** (The National Ophthalmic Disease Genotyping and Phenotyping Network) facilitates research into the causes and mechanisms of rare IRDs and works

to accelerate development of treatments.

- **Foundation Fighting Blindness** was founded by families of loved ones with IRDs; today, it is the leading private funder of retinal disease research. To date, its support has helped researchers identify more than 250 genes linked to retinal disease and has helped launch 20 clinical trials.

- The **National Organization for Rare Disorders** is a patient advocacy organization dedicated to individuals with rare diseases and the organizations that serve them.

- **Online Mendelian Inheritance in Man** is an online catalog of human genes and genetic disorders, including IRDs with syndromic conditions.

- **Low vision resources.** The Academy offers resources for physicians working with low vision patients at aao.org/low-vision-and-vision-rehab.

¹ Kay C. *Retinal Physician*. 2017; 14:55-58.

benefit from testing, for example, because it might help direct career choices.

Advise and consent. As part of the consent process, it's important to infuse realism into the discussion and inform patients that not every test finds every mutation, said Ms. Kagey. "There are 20,000 genes in the human body, and we are only testing some of them. We don't always find an answer."

On the other hand, testing can spring surprises on everyone involved. "Years ago, we tested one gene at a time," said Ms. Kagey. "Now, with the advent of next-generation sequencing, we can sequence multiple genes on a chip and may uncover a gene we hadn't suspected—possibly one associated with a genetic syndrome." This means that, out of the blue, a patient could not only be grappling with an IRD diagnosis, but also be asked to undergo a scan to check for kidney involvement, she explained.

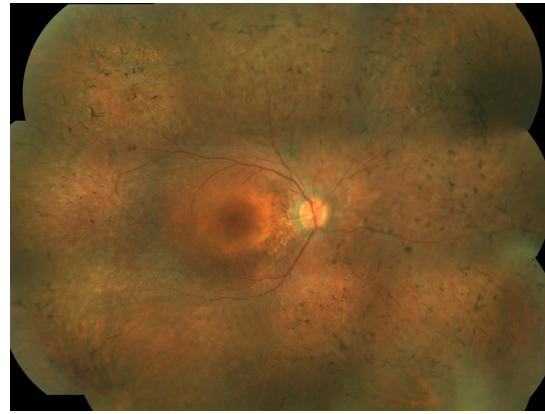
A tale of 2 sisters. Sometimes, however, the ability to do genetic testing can have strikingly positive consequences. Dr. Kitchens recounts meeting a 40-year-old patient with RP, who also had severe hearing loss but thought it was due to a viral infection she'd acquired as a child. While taking a family history, Dr. Kitchens learned that another sister was also blind and deaf. Genetic testing subsequently confirmed that both sisters had Usher syndrome. "Even though we couldn't do anything for the RP part of the syndrome," he said, "the sisters could get cochlear implants and hear again."

How to pay for genetic testing. First, you can help patients investigate whether there's a way to get genetic testing for free. The FFB is supporting genetic testing and counseling for ophthalmic practices that are members of the My Retina Tracker registry. "I am now able to offer these patients free, very accurate, grant-funded genetic testing typically with a 6-week turnaround," said Dr. Kay.

Today, a genetic panel of 180 to 250 genes costs somewhere between \$1,500 and \$2,500, said Ms. Kagey, but insurance coverage is "all over the map." Sometimes that cost is eaten up by huge deductibles, for example, or there's a 20% copay. "That's why finding a lab that works with the patient's insurance is so important," she said. "If necessary, you can follow up with a second lab that conducts testing utilizing a different methodology."

Who Counsels Patients?

"At Retina Associates of Kentucky, we do some of the rudimentary pretest counseling, draw the blood or collect saliva samples, and send samples



CAUSATION. A classic case of retinitis pigmentosa caused by a mutation in the *PRPF31* gene.

out for testing," said Dr. Kitchens.

In-house certified genetic counselor. With more than 250 genes implicated in inherited retinal dystrophies, the genetic landscape is vast, said Ms. Kagey. "When you run that many genes, you are going to get background noise. A certified genetic counselor helps patients sort through the ambiguity of genetic testing—explaining which genetic changes mean something and which may be disease-causing but are something we've never seen before."

Posttest counseling also helps patients navigate the emotional landscape of a molecular diagnosis, said Ms. Kagey. For example, parent studies can confirm the cause of the IRD, but results are often accompanied by guilt. "We help parents process these emotions," she said. "Having a space for families to voice these emotions is critical for adapting to a new diagnosis."

Physician input. Dr. Kay spends many evenings calling patients from home to counsel them about their genetic results. She describes the genetic components, the demographics of the disease, the prognosis, and whether a relevant clinical trial is available—offering to help patients navigate their options. "I tell my patients that they will also get ocular genetic testing through InformedDNA, which is an ocular genetic testing telecounseling service."

Local resources. Dr. Kitchens prefers having someone local do the genetic counseling. "We typically use the University of Kentucky, where they have a geneticist and genetic counselors on staff," he said.

In Denver, however, getting appointments with local genetic counselors is not as expeditious or easy for patients to access as online resources, said Mr. Humes. Now that Ms. Kagey is no longer working with Colorado Retina Associates, Dr. Kimura prefers making use of the services provided by InformedDNA.

Patient Care in the Absence of Tx

Genetic testing isn't the end of the road. But without a treatment to offer, doctors tend to pull away from patients, said Dr. Kimura. Yet, there is much that physicians can do to help, he said.

Low vision resources. Of course, low vision resources are an important part of the continuum of care. Mr. Bynum's vision has changed for the worse recently, said Mr. Humes, so he's at a point in his life where these services can be of great use. (The Academy offers low vision resources at aao.org/low-vision-and-vision-rehab.)

Social services. Dr. Kimura has also integrated social services into the traditional clinical model of care, and he said that patients seem to find it very valuable, although not currently reimbursable. "These services can help patients manage a range of challenges, from school to driving, employment, family, and concerns about risks to the next generation."

Local services. Helping patients find local resources where they can connect with others like them is also invaluable, said Mr. Humes. "These patients often form a close-knit community, taking advantage of social events and peer-to-peer counseling." Mr. Humes recently referred a long-time IRD patient to a newly diagnosed patient, who found the connection quite helpful. Likewise, Mr. Bynum was inspired after he met another person born with RP who was able to navigate working in an office.

One of Dr. Kimura's patients is exploring an entrepreneurial idea to create a rideshare service similar to Lyft and Uber but specifically tailored for the blind. Mr. Bynum expressed excitement about the prospects of a service like this because he voluntarily stopped driving due to the risks. But it's taken a toll. "Transportation and freedom are big things to learn to let go of," he said, adding that he also lost his job (which involved climbing telephone poles) due to hazards related to his vision loss.

Data registries. Registries are another helpful aspect of care. Hosted by the FFB, My Retina Tracker empowers patients who have their genetic information, said Ms. Kagey.

Online data registries like My Retina Tracker are a platform for patients to voluntarily and securely share their genetic information, making it easier for qualified researchers to find patients with a given IRD and known molecular diagnosis, said Dr. Kimura. "From this enriched pool of patients with an accurate diagnosis of a specific molecular defect, scientists and clinicians can work together to drive toward the next gene therapy," said Dr. Kimura.

Mr. Bynum said that being on My Retina Tracker has taken a weight off his shoulders. "You'll always have the feeling that if a clinical trial starts up, you'll be considered for participation because you're right where all the doctors are looking."

MEET THE EXPERTS

SETH BYNUM Patient at Colorado Retina Associates in Denver. *Relevant financial disclosures: None.*

ANDY HUMES Ocular genetics coordinator at Colorado Retina Associates in Denver. *Relevant financial disclosures: None.*

JOSIE KAGEY Certified genetic counselor formerly with Colorado Retina Associates in Denver. *Relevant financial disclosures: None.*

CHRISTINE N. KAY, MD Vitreoretinal specialist at Vitreoretinal Associates in Gainesville, Fla. *Relevant financial disclosures: Spark*

Therapeutics: C; AGTC: S; Foundation Fighting Blindness: S.

JOHN W. KITCHENS, MD Vitreoretinal specialist at Retina Associates of Kentucky in Lexington. *Relevant financial disclosures: None.*

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See financial disclosure key, page 8. For full disclosures, view this article at aao.org/eyenet.