
Cleveland Clinic
OPHTHALMOLOGY UPDATE
COLE EYE INSTITUTE WINTER 2022

MESSAGE FROM THE **CHAIR**

As we enter our third year of the pandemic, Cleveland Clinic Cole Eye Institute continues to improve how we care for patients while doing our part to limit the spread of SARS-CoV-2. Although the virus continues to lurk in our communities, we are excited to resume work on many plans that were postponed due to COVID-19. These plans include the design and construction of a new 26-lane eye clinic on Cleveland's West Side as well as the addition of more satellite locations around Northeast Ohio.

However, most important for us in the coming year will be the construction of a 150,000-square-foot addition to the Cole Eye Institute building on Cleveland Clinic's main campus. We are excited to break ground in the spring of 2022. The project includes a renovation of our existing 130,000-square-foot building constructed in 1999.

While designing this new, integrated, leading-edge 280,000-square-foot facility, we have reimagined how we will care for patients going forward. Our construction and renovation plans are centered on reducing wait times, increasing our capabilities and enhancing patient experience.

The addition of these new spaces has been fueled by our institute's exponential growth over the past 13 years. With that growth has come the opportunity to expand our residency program. In July 2022, we will welcome the first group of trainees into our integrated four-year program. The new first-year internship has been specially designed to provide a solid foundation for future ophthalmologists. In addition, we will expand the number of trainees from four to five per year. By 2025, our residency program will have increased from 12 to 20 residents.

In other news, I am pleased to share that Bela Anand-Apte, MBBS, PhD, MBA, has been appointed our new Chair for Ophthalmology Research. She has brought a new energy to our research efforts — efforts that will grow considerably with our expanding facilities. Also growing is our Vision First community outreach program (featuring our Vision First van), which recently received a $1 million donation from TransDigm Group.

During the past two years of the pandemic, we all have faced adverse conditions. But out of adversity comes opportunity and growth. I look forward to healthier times ahead and to the increase in size and strength of the Cole Eye Institute.

Daniel F. Martin, MD | THE BARBARA AND A. MALACHI MIXON III INSTITUTE CHAIR IN OPHTHALMOLOGY
CHAIR, COLE EYE INSTITUTE

IN THIS **ISSUE**

One of the things I value most about working at the Cole Eye Institute is being at the forefront of ophthalmic care, not just for common eye conditions but for some of the rarest. In this issue of *Ophthalmology Update*, we highlight our latest work on:

- Uveal melanoma, reporting that ocular treatment is not curative for the highest-risk forms of the disease and that adjuvant therapy should be considered for patients with certain genetic mutations (Page 3)
- Geographic atrophy (dry macular degeneration), discussing that intravitreal injections of pegcetacoplan may slow this disease, which was once thought untreatable (Page 6)
- Thyroid eye disease, featuring a case requiring multidisciplinary treatment including orbital decompression by an oculofacial plastic surgeon (Page 12)

Innovative clinical care like this is often due to the bold work of ophthalmic researchers, which we also feature in this issue. Daniel F. Martin, MD, Chair of the Cole Eye Institute and Chair of the DRCR Retina Network, gives us an inside look at what he calls the "national treasure" in retinal disease research (Page 8). In addition, Bela Anand-Apte, MBBS, PhD, MBA, Cleveland Clinic's new Chair for Ophthalmology Research, discusses basic science's impact on the future of eye care (Page 14).

We also are excited to share with you some important updates to our ophthalmology residency program (Page 18) and our Vision First community outreach program (Page 20).

I hope this publication offers news, insights and inspiration that will benefit you and your practice. Thank you for your interest in the Cole Eye Institute.

Rishi P. Singh, MD | STAFF SURGEON, COLE EYE INSTITUTE
PROFESSOR OF OPHTHALMOLOGY,
CLEVELAND CLINIC LERNER COLLEGE OF MEDICINE
MEDICAL EDITOR, *OPHTHALMOLOGY UPDATE*

COLE EYE INSTITUTE | **BY THE NUMBERS**

330,000+ Outpatient visits annually

18,000+ Surgeries annually

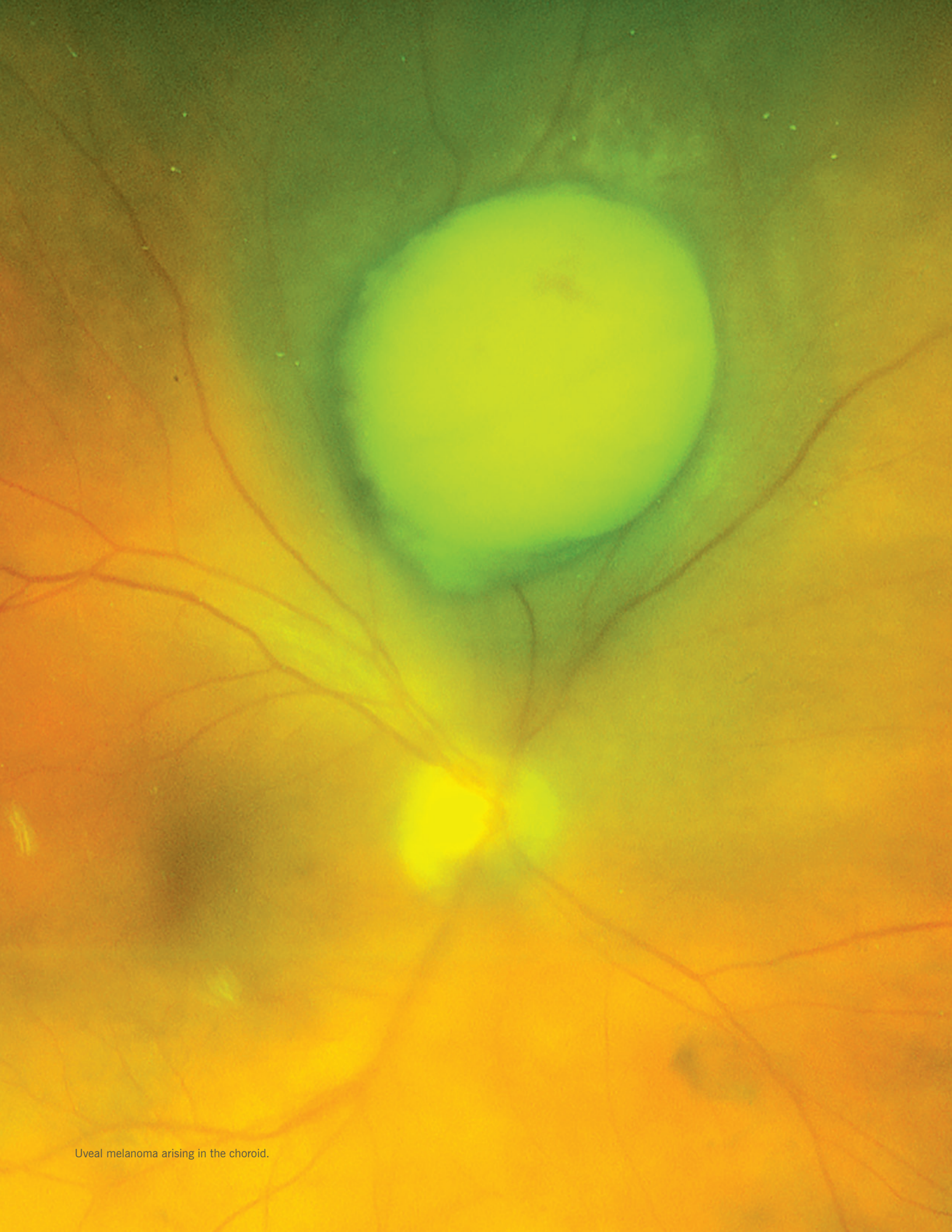
1,500+ Refractive surgeries annually

115 Ophthalmologists, optometrists and researchers

25 Locations

23 Residents and fellows

51 Clinical trials



Uveal melanoma arising in the choroid.

BIOPSY AND ADJUVANT THERAPY MAY HELP IMPROVE MORTALITY RATE IN UVEAL MELANOMA

PATIENTS WITH GENETIC MUTATION NEED MORE THAN OCULAR TREATMENT

Arun D. Singh, MD

Tomas Radivoyevitch, PhD

Emily C. Zabor, DrPH

The impact of ocular treatment on the overall survival of people with uveal melanoma has been largely unknown. While some believe that earlier treatment leads to a higher rate of survival, others believe treatment to be equally effective no matter when it is performed.

A recent study in *JAMA Ophthalmology* has shed new light on cure rates in uveal melanoma, presenting a clearer — although not necessarily brighter — view of the lifesaving potential of ocular treatment.[1]

"The overall survival of patients with uveal melanoma has not improved in the last 40-plus years," says Arun D. Singh, MD, Director of Ophthalmic Oncology at the Cole Eye Institute.[2] "Now we know why we haven't seen improvement like we've seen in breast, lung, prostate and other cancers: Ocular treatment is not curative for the highest-risk forms of uveal melanoma."

"OCULAR TREATMENT IS NOT CURATIVE FOR THE HIGHEST-RISK FORMS OF UVEAL MELANOMA."

– ARUN D. SINGH, MD

MOST DEATHS AT 3 AND 15 YEARS CAUSED BY MUTATION

Dr. Singh, lead author of the study, and two cancer biostatisticians, Emily C. Zabor, DrPH, and Tomas Radivoyevitch, PhD, calculated the excess absolute risk of mortality in uveal melanoma using Surveillance, Epidemiology, and End Results (SEER) data of more than 10,000 patients diagnosed from 1975 to 2016. They identified three groups of patients, those that:

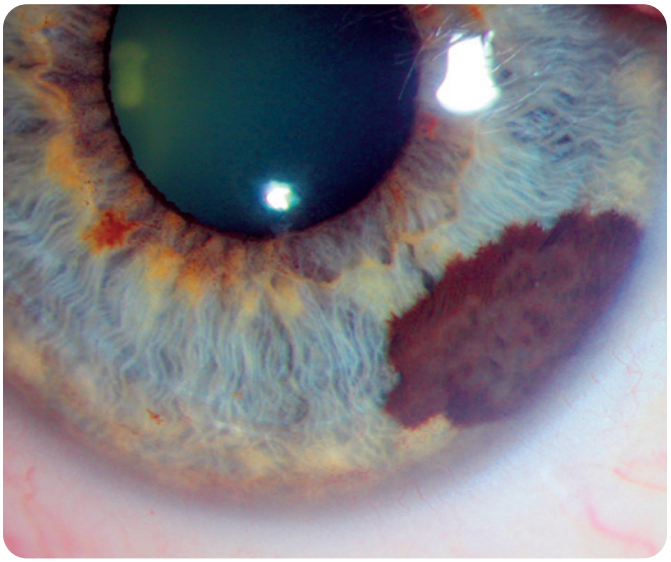
1. Died approximately three years after diagnosis with uveal melanoma ("early death")
2. Died approximately 15 years after diagnosis ("later death")
3. Had a life span similar to people without uveal melanoma ("no death" from uveal melanoma)

"There was a spike in deaths at three years and then again at 15 years, and then deaths from uveal melanoma leveled off," says Dr. Singh.

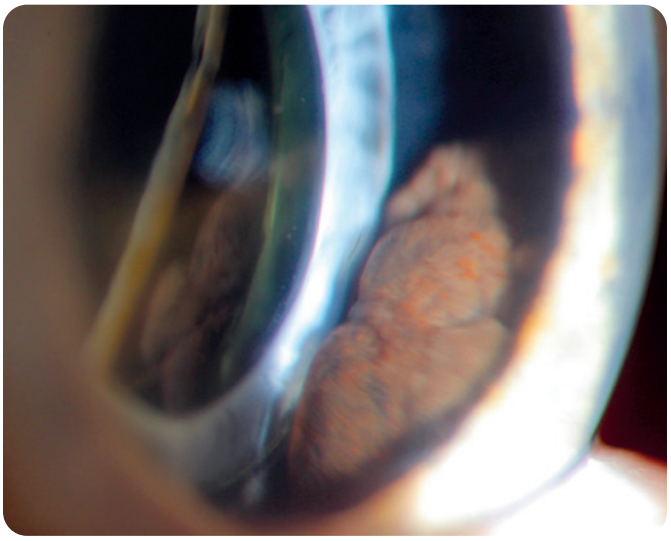
Curative fraction (the statistical cure rate) was approximately 60% at 25 years.

The team also studied records from nearly 800 patients treated at European medical centers that conducted mutation testing on uveal tumors. They found a correlation between early deaths and *BAP1* mutation, and later deaths and *SF3B1* mutation. The third group of patients, who did not die from uveal melanoma, did not have these genetic mutations.

"All of these patients had received standard-of-care ocular treatment for uveal melanoma," says Dr. Singh. "But despite treatment, those who had a mutation died at some point, early or later, and those without a mutation didn't die of uveal melanoma at all. This may indicate that those who died may have been undertreated and could have benefited from adjuvant therapy."



Uveal melanoma arising in the iris.



Uveal melanoma arising in the ciliary body.

TIME FOR NEW CLINICAL APPROACHES

These findings raise questions about the survival benefits of current ocular therapy for uveal melanoma and the need for new clinical approaches.

"It's mutation — more than size, location or any other tumor characteristic — that determines risk of mortality from uveal melanoma," says Dr. Singh. "We should be looking for mutations at the outset."

Safe techniques for tumor biopsy should be developed, he adds, to help ophthalmologists identify mutational status, thus determining which patients must be treated and how.

"For patients with genetic mutations, eye treatment by itself is insufficient," says Dr. Singh. "We need to treat the eye because the tumor can cause blindness, detachment and pain. But for the patient's survival, we need to do more, such as using adjuvant therapy."

Today adjuvant therapy for uveal melanoma is uncommon, although multiple clinical studies are in progress.

"For patients with small tumors and no genetic mutations, observation may be the best approach, especially for those who are asymptomatic or more likely to experience adverse effects of treatment," he says. "No patients in this group died of metastatic uveal melanoma. We could even consider discontinuing surveillance after 15 years in patients with good prognoses."

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PEGCETACOPLAN OFFERS NEW HOPE FOR TREATING DRY MACULAR DEGENERATION

STUDY SHOWS THAT INTRAVITREAL INJECTIONS MAY SIGNIFICANTLY SLOW THE DISEASE, ONCE THOUGHT UNTREATABLE

Rishi P. Singh, MD

There is currently no treatment for geographic atrophy — the "dry" form of macular degeneration, a leading cause of blindness in the U.S. and worldwide. Now a new study has shown that the drug pegcetacoplan can significantly slow the disease.

Two phase 3 clinical trials showed that injecting pegcetacoplan monthly and every other month resulted in a significant reduction in lesion growth. The study also found that pegcetacoplan was generally safe and well tolerated, although a small number of patients converted to "wet" macular degeneration, which is treatable.

"This is a first step in treating this debilitating disease," says ophthalmologist and retina specialist Rishi P. Singh, MD, of the Cole Eye Institute. "It represents a breakthrough therapy for patients with this condition and potentially could reduce legal blindness around the world."

Dr. Singh presented the top-line findings from the phase 3 study at the American Academy of Ophthalmology 2021 meeting.

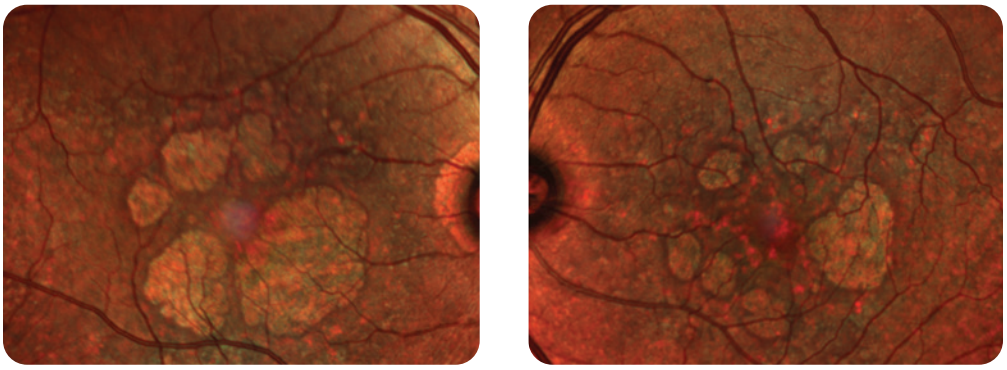
REDUCTION IN GEOGRAPHIC ATROPHY LESIONS

The study built on previous research that showed that dry macular degeneration is linked to the complement system and a hyperactive immune response that damages the eyes.[1,2] Pegcetacoplan is a complement system inhibitor that has previously been used to treat paroxysmal nocturnal hemoglobinuria, a rare autoimmune disorder linked to a systemic complement cascade.

The study involved two multicenter, phase 3 clinical trials (DERBY and OAKS) involving a total of more than 1,250 patients with geographic atrophy. Patients were randomized to receive injections of 15 mg of pegcetacoplan monthly or every other month, or a sham injection monthly or every other month.

"IT REPRESENTS A BREAKTHROUGH THERAPY FOR PATIENTS WITH THIS CONDITION AND POTENTIALLY COULD REDUCE LEGAL BLINDNESS AROUND THE WORLD."

– RISHI P. SINGH, MD



Color fundus images of a patient with geographic atrophy.

At the American Academy of Ophthalmology 2021 meeting, the Cole Eye Institute's Rishi P. Singh, MD, presented the results of a study showing that the drug pegcetacoplan can significantly slow the progression of geographic atrophy.

In the combined results of the two trials, patients who received the drug monthly showed a 17% reduction in geographic atrophy lesions after 12 months, compared to those who received sham injections, while those who were injected every other month had a 14% reduction.

Patients with extrafoveal lesions had an even stronger response, with a 26% reduction in lesions with monthly injections and a 23% reduction with every-other-month injections compared to the sham group.

"We expected this drug to work, but it exceeded my expectations," says Dr. Singh.

The drug was generally safe and well tolerated. The most common side effects were conjunctival hemorrhage, eye pain and vitreous floaters.

However, around 7% of patients developed wet macular degeneration as a result of the medication, not as a normal progression of the disease.

"That's definitely a concern," says Dr. Singh. "While this is breakthrough therapy, the conversions to wet macular degeneration are noteworthy for clinicians and patients."

Wet macular degeneration can be treated with currently available anti-VEGF (vascular endothelial growth factor) agents, he notes.

FDA SUBMISSION IS PENDING

Results of the study are planned to be submitted to the U.S. Food and Drug Administration (FDA) for review by the end of 2021, with a decision on FDA approval for clinical use anticipated in early 2022.

Dr. Singh said the findings are a significant step forward in the treatment of macular degeneration, which affects an estimated 1 million people in the U.S.

"For years we've been telling ophthalmologists and patients that there's no treatment for this condition — that it's just a matter of aging, that its progression is inevitable over time and that there's nothing we can do," he says. "Finally, this drug can show a reduced progression of the disease if given monthly or every other month. It's a game changer."

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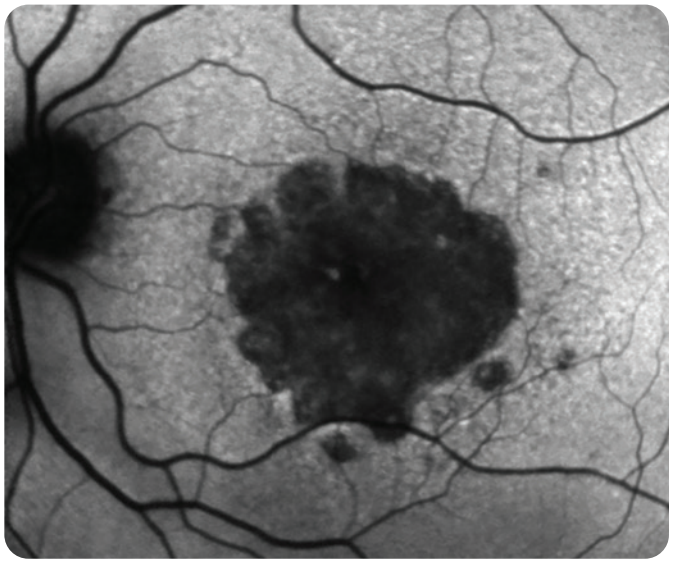


Fundus autofluorescence image of a patient with geographic atrophy.

DRCR RETINA NETWORK: AN INSIDE LOOK AT THE 'NATIONAL TREASURE' IN RETINAL DISEASE RESEARCH

Q&A WITH NETWORK CHAIR DANIEL F. MARTIN, MD

Daniel F. Martin, MD

One of the biggest challenges in clinical research is having the infrastructure to do it.

Historically, to conduct a clinical trial sponsored by the National Institutes of Health (NIH), researchers spent six to 12 months completing a grant application and often another year setting up study logistics once funding was approved. As studies began, study groups were formed. As studies were completed, study groups were dissolved, only to be formed again months or years later for another clinical trial.

In 2002 the National Eye Institute introduced a novel way to streamline this process — a permanent infrastructure for performing clinical studies, the Diabetic Retinopathy Clinical Research Network (DRCR.net). Originally focused on diabetic retinopathy, the organization has since expanded its scope to include the study of all retinal diseases and changed its name to the DRCR Retina Network.

There at the beginning was Daniel F. Martin, MD, Chair of Cleveland Clinic Cole Eye Institute. A member of the original steering and executive committees, Dr. Martin became one of the chairs of the newly expanded Network in 2018.

To date, the organization has completed 30 multicenter studies, involving 160 clinical sites and spawning more than 100 publications.

"The Network is a national treasure," says Dr. Martin. "Our mission is to serve the public's visual health with work that is funded with federal dollars, often in collaboration with the pharmaceutical industry yet independent of it. Our efforts have produced so many meaningful results, not to mention an enormous database of findings and one of the largest repositories of retinal images in the world."

In this Q&A, Dr. Martin shares an inside look at the Network, his role and upcoming clinical trials.

The Cole Eye Institute's Daniel F. Martin, MD, was appointed Chair of the DRCR Retina Network in 2018.

Q: What led to the Network's expansion from focusing only on diabetic retinopathy to including all retinal diseases?

Dr. Martin: Diabetic retinopathy was the original focus because it comprises a large part of most retina practices.

I had been involved with DRCR.net early on and then stepped away in 2005 when I began work as study chair of the Comparison of Age-Related Macular Degeneration [AMD] Treatments Trials (CATT).[1] As the need for more AMD clinical trials became apparent, we began asking the NIH to create an AMD network like DRCR.net. Instead of creating a different network, however, the NIH decided to add AMD research into the very successful, well-established DRCR.net model. That's when I became a Network chair.

Even though the Network now conducts trials for all retinal diseases, we kept the DRCR acronym because of brand recognition. Diabetic retinopathy is still a major priority, but adding other retinal diseases vastly expanded our Network.

Today the DRCR Retina Network is run by two chairs. Jennifer K. Sun, MD, MPH, of Harvard Medical School's Joslin Diabetes Center oversees all diabetes initiatives. I oversee AMD, retinal vascular disease, and surgical and other retinal diseases.

Q: How many research studies are happening currently in the DRCR Retina Network?

Dr. Martin: Outside the Network, doing one trial can be all-encompassing, a significant lifetime contribution. Inside the Network — which includes about 1,800 investigators, coordinators, technicians and coordinating center staff — we currently have six trials ongoing or about to launch. We also have three other major studies in development that should start within the next year.

In 2003 we began with Protocol A and named subsequent trials in alphabetical order. Now we're into double letters, most recently preparing for Protocol AN.

Even with COVID-19, 2020 was a very busy year for us with reporting the results of four major randomized controlled trials, including one (Protocol AB) published in *JAMA* that evaluated the optimal management of vitreous hemorrhage in diabetic retinopathy.[2] In 2021 we published an important two-year study (Protocol W) in *JAMA Ophthalmology* on the use of anti-VEGF therapy in diabetic retinopathy.[3] Quite a few more papers followed.

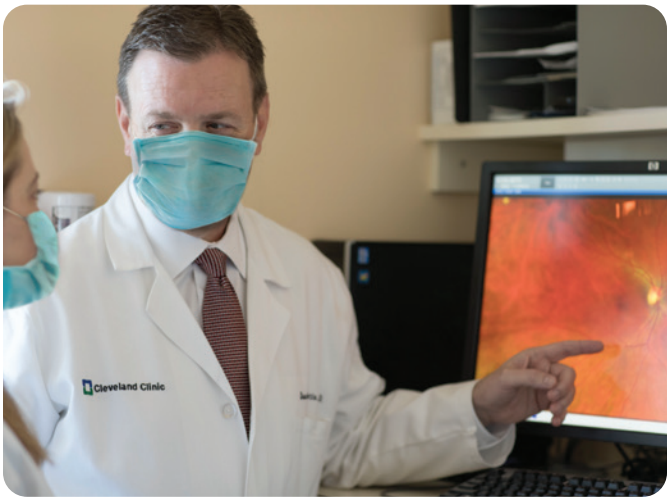
One of my favorite recent papers was published in *JAMA* in 2019. I view it as a landmark study (Protocol V) that showed treatment was not needed for most patients with good vision and center-involved diabetic macular edema (DME).[4] In other words, the presence of mild macular edema in patients who have maintained good vision does not usually lead to long-term visual decline if it is not treated. In many cases, the edema can resolve on its own. It was an important finding for retina specialists and for the whole diabetic community.

Q: How does the Network develop and select trials to pursue?

Dr. Martin: The NIH funds the DRCR Retina Network. We then determine what trials we will conduct and how the money will be spent.

Anyone can put forward a protocol idea, including members of our Network and those outside of it. Many ophthalmologists have questions that arise in their practice, but not every question is answerable in the context of a randomized clinical trial or worth the seven-figure investment often required to answer it.

All ideas are reviewed by the Network's operations group. The most viable ideas are presented to the entire investigator group, which meets twice a year. At each meeting, numerous new ideas are presented to gauge investigator interest. For those that get the most interest, I will write a first draft of the trial protocol. That draft protocol then goes to an executive committee, which votes on whether or not it should move to the next step — a Protocol Design Committee (PDC).



Dr. Martin writes the first draft of trial protocols for research studies being considered by the DRCR Retina Network. An executive committee reviews the draft protocols and selects those for further consideration.

After a full trial has been developed by the PDC, it is then sent for review by an NIH External Protocol Review Committee. If that committee approves it, it goes back to the executive committee for final approval. The person who presented the original idea usually ends up as protocol chair.

It is a detailed, tedious but thoughtful process that helps ensure the Network invests its time and money wisely to answer only the most crisp, focused research questions that will provide the greatest value to our specialty and our patients.

When not crafting protocols, I discuss collaborative opportunities with pharmaceutical companies on behalf of the Network, including arrangements for additional funding or supplying test drugs. While the Network works independently from the pharmaceutical industry, it is important to collaborate since almost no new treatments move forward without a pharmaceutical company partner. My work in CATT underscored the importance of independent clinical trials,[5] but pharmaceutical companies are extremely important partners. The monumental achievements of the DRCR Retina Network have reinforced that.

Q: What are some of the most significant studies done by the Network to date?

Dr. Martin: I recently gave a presentation on the top 5 most important findings from Network studies.[6] In that list I mentioned DRCR Protocol I, which first identified anti-VEGF treatment as most effective for DME. DRCR Protocol T was another landmark study, which showed aflibercept was more effective than bevacizumab and ranibizumab at treating DME in select patients. DRCR Protocol S was the first to show that anti-VEGF therapy was effective for proliferative diabetic retinopathy.

New protocols currently in development could potentially lead to the next breakthroughs in retinal care. Upcoming trials will study the prevention of radiation retinopathy, vitreoretinal surgery for epiretinal membranes and the optimal long-term management of neovascular AMD.

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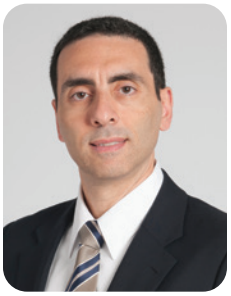
CASE STUDY: DOUBLE VISION AND BILATERAL STRANDING OF ORBITAL FAT

TREATING THYROID EYE DISEASE REQUIRES A MULTIDISCIPLINARY APPROACH

By Christian Nasr, MD, and Catherine Hwang, MD



Christian Nasr, MD

Catherine Hwang, MD

Oculofacial plastic surgeon Catherine Hwang, MD, performs medial-wall orbital decompression on a patient with thyroid eye disease.

A 75-year-old woman presented with a history of hypothyroidism diagnosed four years before coming to Cleveland Clinic's Endocrinology & Metabolism Institute. A primary care physician prescribed levothyroxine, and the patient's thyroid levels returned to the normal range.

However, a month before meeting with a staff physician in the Department of Endocrinology, the patient complained to her primary care physician about double vision. This necessitated neurological workup, including magnetic resonance imaging (MRI). The patient did not show evidence of stroke or neoplasm. However, MRI showed bilateral stranding of orbital fat, suggesting the possibility of thyroid eye disease (TED). MRI of the orbits showed severe enlargement of multiple bilateral extraocular muscles with sparing of the myotendinous junctions. Crowding of the orbital apex threatened the optic nerve.

When the patient presented at the Department of Endocrinology, she was thyrotoxic on 25 mcg of levothyroxine and had elevated TSH-receptor antibodies. She was diagnosed with Graves' disease. The medication was discontinued, but her hyperthyroidism continued after a few weeks with elevation of T4 and T3. She was started on methimazole. Assessment of her TED activity revealed a clinical activity score (CAS) of 5/7. (CAS > 3 indicates active disease.)

At that point, she was referred to an oculofacial plastic surgeon at the Cole Eye Institute. Due to the patient's severe disease, with inflammation and vision loss, the surgeon recommended weekly IV methylprednisolone 0.5 g, with the first dose administered immediately.

Because the patient's vision did not improve, she underwent bilateral medial-wall orbital decompression. She continued to have active TED — manifested by redness, swelling, pain and diplopia — but her vision improved. She was started on immunotherapy teprotumumab, targeting the insulin-like growth factor receptor (IGF-R). Although she had decreased inflammation, she continued to have double vision.

This patient may require future treatment but is currently doing well.

ABOUT THYROID EYE DISEASE (TED)

TED of variable severity occurs in 25%-50% of patients with Graves' disease. TED is more common in women, which is consistent with the epidemiology of Graves' disease, but it tends to be more severe in men. Most patients have hyperthyroidism or Graves' disease, but a small minority of patients, 5%, are euthyroid at presentation. Some patients can be hypothyroid.

In most cases, thyroid dysfunction and TED occur within 18 months of each other. TED usually affects both eyes, but one side can be more affected than the other. Some of the risk factors for the development and progression of TED include cigarette smoking and radioactive iodine therapy.

COMPLEX MANAGEMENT

Management is complex and customized to the patient, as TED is one of the most difficult diseases to predict. Most patients with TED have a mild course, but some can have severe disease with double vision, eyelid retraction, severe dry eye and vision loss. Some treatments used in the active phase, which can last 18 to 24 months, include supportive therapy with artificial tears and maintaining a euthyroid state.

In more severely inflamed patients, intravenous steroids and/or other immune therapies may be indicated. If a patient has compressive optic neuropathy resulting in vision loss, surgery is sometimes needed.

Most patients enter a stable phase of disease approximately 24 months after the onset of symptoms.

COLLABORATION BETWEEN ENDOCRINOLOGY AND OPHTHALMOLOGY

TED is often managed in a multidisciplinary fashion, with collaboration between endocrinology and ophthalmology. Radioactive iodine is often used to treat Graves' disease, but some authorities believe it is associated with new or worsened eye disease. Typically, an endocrinologist monitors thyroid hormone levels closely to ensure the patient does not develop hypothyroidism, which could worsen ocular symptoms. A comprehensive ophthalmologist monitors the patient's vision. When surgery is required, the patient is referred to an oculofacial plastic surgeon.

Dr. Nasr is an endocrinologist at Cleveland Clinic's Endocrinology & Metabolism Institute. Dr. Hwang is an oculofacial plastic surgeon at the Cole Eye Institute.

Dr. Hwang discusses surgical treatment with a patient with thyroid eye disease. Surgery is sometimes required when patients have compressive optic neuropathy resulting in vision loss.

DR. ANAND-APTE NAMED CHAIR FOR OPHTHALMOLOGY RESEARCH

FROM CLINIC TO BENCH TO CLINIC: BASIC SCIENCE'S ROLE IN THE FUTURE OF EYE CARE

Bela Anand-Apte, MBBS, PhD, MBA, now is responsible for shaping the growth of ophthalmic research at Cleveland Clinic, including overseeing more than a dozen principal investigators, each with their own lab.

It was actually her lab research in cancer that inspired her passion for eyes and vision.

Cleveland Clinic's Bela Anand-Apte, MBBS, PhD, MBA, was studying tumor angiogenesis when she became interested in tissue inhibitor of metalloproteinases-3 (TIMP3), a protein whose physiological function is to inhibit pathological growth of new blood vessels. The protein that kept blood vessels in check also was linked to eye disease, specifically Sorsby fundus dystrophy and age-related macular degeneration (AMD), the leading cause of vision loss in people over age 60. A mutation in the *TIMP3* gene causes Sorsby fundus dystrophy, an inherited macular degenerative disease in which patients lose vision because of abnormal growth and leakage of blood vessels in the back of the eye.

That realization was a turning point for Dr. Anand-Apte.

"I started reading more about vision and the eye and was totally engrossed," she says. "The eye is an absolutely beautifully designed organ."

Her reverence for the anatomy is equal to her respect for its function.

"The way vision works is fascinating, and the loss of vision can be devastating," she says. "Vision loss will not end your life, but it can change it drastically. That is why we do research: to make an impact on people's lives. Clinics are full of patients with vision loss. With every scientific finding, we are a step closer to preventing or curing it."

In addition to Dr. Anand-Apte's study of abnormal blood vessel growth and leakage in eye disease, she recently took on a new assignment: the Llura and Gordon Gund Endowed Chair for Ophthalmology Research at Cleveland Clinic. In this Q&A, Dr. Anand-Apte explains more about her department's focus and basic science's impact on the future of eye care.

Q: How will your research responsibilities change now that you are Chair for Ophthalmology Research?

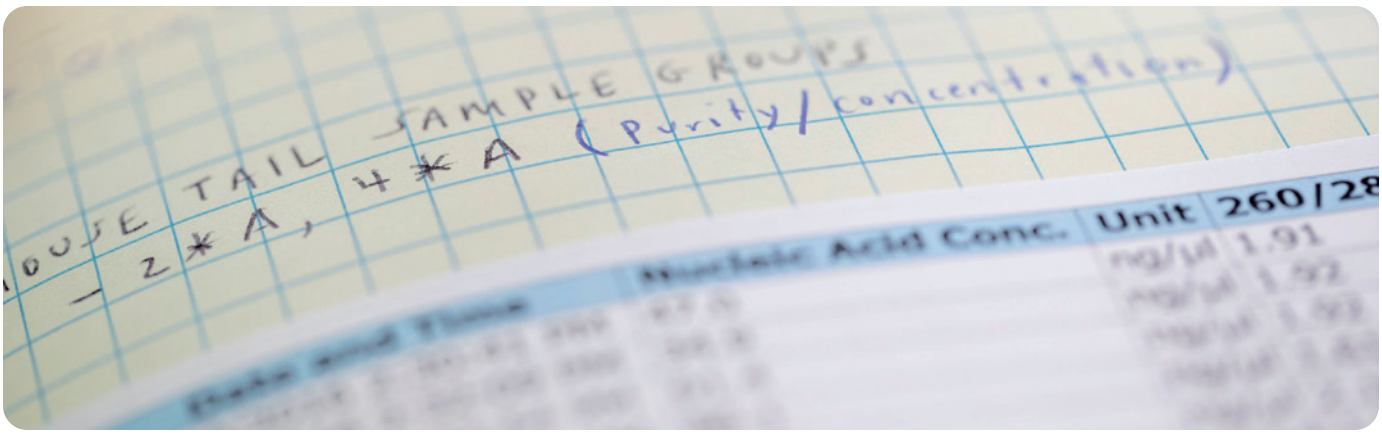
Dr. Anand-Apte: It is a different mindset. Together with Cole Eye Institute Chair Daniel F. Martin, MD, I am responsible for shaping the growth of ophthalmic research at Cleveland Clinic. Our strategic growth initiative will build on our strengths and fill in research areas that will be critical in the near future.

Instead of just running my own lab and focusing on my own research, I am now responsible for all 80-plus people in our department, including more than a dozen principal investigators, each with their own lab. My goal is to make sure they have the tools and infrastructure to make progress and fulfill our mission to do good research, move science forward and train the next generation of scientists. Part of that involves securing and distributing grant money, ensuring investigators have all the resources they need to be successful.

For example, in the past year our department received a $100,000 grant from the Cleveland Eye Bank Foundation, which we will use to begin work on new, innovative ideas before applying for larger grants. Some of these funds are currently being used for a bioinformatics study on amblyopia, helping one of our research teams collect preliminary data on the utility of artificial intelligence. We also have an unrestricted grant from Research to Prevent Blindness as well as P30 funding from the National Eye Institute (NEI) that allows for core services for our investigators. A National Institutes of Health (NIH) T32 training grant funds graduate students, medical students and postdoctoral fellows engaged in eye research. Additionally, we have received significant resources from our philanthropic supporters to move our research forward.

Q: What is your vision for Cleveland Clinic's basic research efforts in ophthalmology?

Dr. Anand-Apte: Our department is committed to improving the understanding of the molecular and cellular basis of vision loss and using that knowledge to develop therapeutics. Currently we have teams investigating macular degeneration (both juvenile and age-related), diabetic retinopathy, retinopathy of prematurity, retinitis pigmentosa, ciliopathies, uveal melanoma and corneal disorders.



The Cole Eye Institute is uniquely designed to house both clinicians and basic science investigators under one roof. This close collaboration provides a huge value, not to mention enabling the involvement of patients in our work.

In order to further our impact, I expect that we will increase the number of lab researchers and physician investigators. Because the Cole Eye Institute is already known for its work in retinal disease, my goal is to build on our strengths and expand research teams investigating macular degeneration, diabetic retinopathy and inherited degenerations (pediatric retinal disease). In addition, we will build our research program in glaucoma and corneal disorders.

I also plan to develop our use of bioinformatics. The Cole Eye Institute has a huge patient population with lots of data that could be invaluable across our retina, glaucoma and cornea research teams. Efforts in gene and cell therapy will be a big push as well.

We also have a very grateful patient population that has generously supported our innovative work through philanthropic gifts. We understand the importance of philanthropy and how it can help move a bold idea into a research protocol that can gain ongoing support from entities such as the NEI/NIH.

Q: What are the current trends in basic ophthalmic research? Where do you see research headed?

Dr. Anand-Apte: Ophthalmology is blazing a trail with gene therapy. It is one of the few areas of medicine where gene therapy has worked so far. Cell therapy is not far behind.

I think the future of ophthalmic research will center on gene therapy. The eye is unique because you can deliver gene therapy straight to the eye, straight into the cells you are targeting. With other diseases, you need to deliver gene therapy systemically, which can cause adverse effects. Systemic effects are usually not a major concern when treating eye disease.

"OPHTHALMOLOGY IS BLAZING A TRAIL WITH GENE THERAPY. IT IS ONE OF THE FEW AREAS OF MEDICINE WHERE GENE THERAPY HAS WORKED SO FAR."

– BELA ANAND-APTE, MBBS, PHD, MBA

Progress toward elimination of vision loss will be made when we invite collaboration between basic scientists, clinicians and patients. It takes those three groups working together. Research isn't just "bench to bedside." It really is clinic to bench and then back to clinic. Without patient involvement — which helps us understand disease and its issues — researchers cannot begin to unravel how to diagnose and treat disease. It is important that patients realize they are part of the research process and that researchers realize the incredible value patients bring.

That collaborative, patients-first model is already in practice at Cleveland Clinic. As the ophthalmology field at large incorporates that model, research can move faster. The COVID-19 pandemic has taught us that when there is an urgent need, we can do things at an incredibly fast pace. COVID-19 vaccines were developed in one year, while previous vaccines took 15 years or longer. If we have that same urgency for vision disorders, who knows what we can achieve?

OPHTHALMOLOGY RESIDENCY PROGRAM EXPANDS TO FOUR YEARS, FIVE RESIDENTS

FORMER INTERNSHIP YEAR NOW INCLUDES SPECIALIZATION IN EYE CARE

Katherine Talcott, MD

Is three years enough time to train future ophthalmologists? Traditionally, residency programs have managed with three years of ophthalmic education following trainees' one year of general internship. But due to changes announced in 2019 by the Accreditation Council for Graduate Medical Education (ACGME), eye programs have begun integrating internship with residency training, essentially turning ophthalmology residencies into four-year programs.

The Cole Eye Institute will begin its four-year residency program in July 2022. Planning, including administrative and scheduling changes, is already underway.

"We have a great opportunity to revamp ophthalmology training," says vitreoretinal surgeon Katherine Talcott, MD, who was recently named Associate Residency Program Director at the Cole Eye Institute. "We need to determine the best way to use this extra time with residents to enhance their education."

Dr. Talcott, who spent a year as Chief Resident at Massachusetts Eye and Ear before joining Cleveland Clinic in 2018, will work with Residency Program Director Jeffrey Goshe, MD, to determine the design of the new internship year (PGY1).

"In the past, ophthalmology programs had no control over internship training," says Dr. Talcott. "Now we will. At the Cole Eye Institute, our PGY1 residents still will be exposed to a mix of inpatient and outpatient services, but they'll also have three months of ophthalmology training. This earlier exposure to eye care will help increase their clinical exam skills and build a solid foundation for the three years of training to come."

Katherine Talcott, MD, Associate Residency Program Director at the Cole Eye Institute, helps train PGY2 resident Joseph Abraham, MD.

"WE NEED TO DETERMINE THE BEST WAY TO USE THIS EXTRA TIME WITH RESIDENTS TO ENHANCE THEIR EDUCATION."

– KATHERINE TALCOTT, MD

Over the other nine months of general medical training, PGY1 residents will be introduced to rheumatology, neurology, dermatology, infectious disease and other medical fields that often intersect with ophthalmology when caring for patients with eye conditions.

"We want to build trainees' knowledge about those conditions," says Dr. Talcott. "This new PGY1 experience also will help our ophthalmology faculty forge new clinical partnerships in those other fields."

NUMBER OF RESIDENTS PER YEAR GROWS FROM 4 TO 5

In addition to expanding the residency program from three years to four, the Cole Eye Institute will increase the number of residents per year from four to five.

"Our department has greatly expanded over the past decade, so it makes sense to expand our residency cohorts accordingly," says Dr. Goshe. "There are so many educational opportunities here, including many faculty members interested in teaching. We want to capitalize on that."

Additional residents will require additional educators, which will mean additional rotation options — still to be determined.

MORE CONTINUITY BENEFITS RESIDENTS

The newly integrated internship and residency program will offer trainees more continuity in their ophthalmic education, notes Dr. Talcott. Because trainees will be at Cleveland Clinic all four years, they can take advantage of educational opportunities sooner, including Grand Rounds and the numerous didactic conferences regularly held at the Cole Eye Institute.

"They'll have an extra year to start research projects and form relationships with mentors as well," says Dr. Talcott. "More time at the Cole Eye Institute will only improve their training experience."

VISION FIRST PROGRAM: DONORS HELP EXPAND SIGHT-SAVING SERVICES FOR CHILDREN IN NEED

NEW OPTOMETRY VAN HAS TWO EXAM AREAS

Pictured from left to right: Peter Kaiser, MD, retina physician and surgeon, Chaney Family Endowed Chair for Ophthalmology Research; Natalie Chaney; Jeff Chaney; Jeannie Chaney; Jim Chaney; Anita Chitluri, OD, Vision First optometrist; Daniel F. Martin, MD, Chair, Cole Eye Institute, Barbara and A. Malachi Mixon III Institute Chair of Ophthalmology; Rhonda Wilson, Vision First Manager.

TransDigm Group has teamed up with Cleveland Clinic to put at-risk children on the path to better vision. The aerospace company donated $1 million to Cleveland Clinic's Vision First program, a community outreach initiative that provides free vision screenings and eye examinations to local elementary students from a mobile optometry van.

The five-year investment will allow the Cole Eye Institute to reach more children in underserved communities throughout Northeast Ohio. Vision First helps improve access to preventive eye-care services in early childhood to protect kids from potential vision loss in adulthood and promote a lifetime of healthy eyesight.

In addition to the gift from TransDigm Group, a significant contribution from Jim and Jeannie Chaney in 2020 made it possible for Cleveland Clinic to purchase a new, customized van equipped with two exam areas.

The Vision First van — staffed by Cleveland Clinic optometrists Heather Cimino, OD; David Barnhart, OD; and Anita Chitluri, OD; and program manager Rhonda Wilson — visits more than 90 schools during the academic year. If a student fails an initial vision screening, the optometrist performs a complete eye examination, writes a prescription and provides a referral to a pediatric ophthalmologist for follow-up care. Children who need glasses can choose their frames on the same day as their exam.

Elias Traboulsi, MD, MEd, head of pediatric ophthalmology at the Cole Eye Institute, developed Vision First in 2002 in collaboration with the Cleveland Metropolitan School District. Over the years, the program has grown to include five additional school districts around Greater Cleveland.

"One of the single most important investments that one can make is in the health and future of our children," says Dr. Traboulsi. "This gift from the TransDigm Group will make an immeasurable impact in providing screenings to help combat vision impairment in children with limited access to these vital services."

Since its inception, Vision First has performed more than 97,000 free eye exams and provided 7,500 eyeglasses to children in need. Nearly 14% of children screened have been diagnosed and successfully treated for a variety of vision problems through the program.

"ONE OF THE SINGLE MOST IMPORTANT INVESTMENTS THAT ONE CAN MAKE IS IN THE HEALTH AND FUTURE OF OUR CHILDREN."

– ELIAS TRABOULSI, MD, MED

Top left: Heather Cimino, OD, performs an eye exam on a student at Cleveland Metropolitan School District's Campus International. Bottom left: Vision First van. Right: A student at Cleveland Metropolitan School District's Campus International receives a free eye exam through the Vision First program.

CLINICAL **TRIALS**

The following studies are either currently enrolling new patients or are pending approval by the Institutional Review Board and should be enrolling shortly.

RETINAL DISEASES

› ARCHER: A Phase 2, Multicenter, Randomized, Parallel-Group, Double-Masked, Four-Arm, Sham-Controlled Study of the Efficacy, Safety and Tolerability of ANX007 Administered by Intravitreal Injection in Patients with Geographic Atrophy Secondary to Age-Related Macular Degeneration

***Contacts*:** Katherine Talcott, MD (440.988.4040) | Thais Conti (216.445.3840)

› GALLEGO: A Phase 2, Multicenter, Randomized, Single-Masked, Sham-Controlled Study to Assess Safety, Tolerability and Efficacy of Intravitreal Injections of FHTR2163 in Patients with Geographic Atrophy Secondary to Age-Related Macular Degeneration

***Contacts*:** Sumit Sharma, MD (216.445.4904) | Pam Donati (216.444.3735)

› HORNBILL: A Study to Test Different Doses of BI 764524 in Patients Who Have Had Laser Treatment for a Type of Diabetic Eye Disease Called Diabetic Retinopathy with Diabetic Macular Ischemia

***Contacts*:** Katherine Talcott, MD (440.988.4040) | Pam Donati (216.444.3735)

› IONIS: A Phase 2, Randomized, Placebo-Controlled, Double-Masked Study to Assess Safety and Efficacy of Multiple Doses of IONIS-FB-LRX, an Antisense Inhibitor of Complement Factor B, in Patients with Geographic Atrophy Secondary to Age-Related Macular Degeneration

***Contacts*:** Sumit Sharma, MD (216.445.4904) | Theresa Kovacs (216.445.3762)

› BEACON: A Prospective, Randomized, Double-Masked, Active Comparator-Controlled, Multicenter, Two-Arm, Phase 3 Study to Evaluate the Efficacy and Safety of Intravitreal KSI-301 Compared with Intravitreal Aflibercept in Participants with Visual Impairment Due to Treatment-Naïve Macular Edema Secondary to Retinal Vein Occlusion

***Contacts*:** Sumit Sharma, MD (216.445.4904) | Theresa Kovacs (216.445.3762)

› GLIMMER: A Prospective, Randomized, Double-Masked, Active Comparator-Controlled, Multicenter, Two-Arm, Phase 3 Study to Evaluate the Efficacy and Safety of Intravitreal KSI-301 Compared with Intravitreal Aflibercept in Participants with Visual Impairment Secondary to Treatment-Naïve Diabetic Macular Edema

***Contacts*:** Sumit Sharma, MD (216.445.4904) | Theresa Kovacs (216.445.3762)

UVEITIS

› DOVETAIL: A Multicenter, Non-Randomized, Open-Label, Multiple Ascending Dose Study to Investigate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of RO7200220 in Monotherapy and in Combination with Ranibizumab Following Intravitreal Administration in Patients with Diabetic or Uveitic Macular Edema

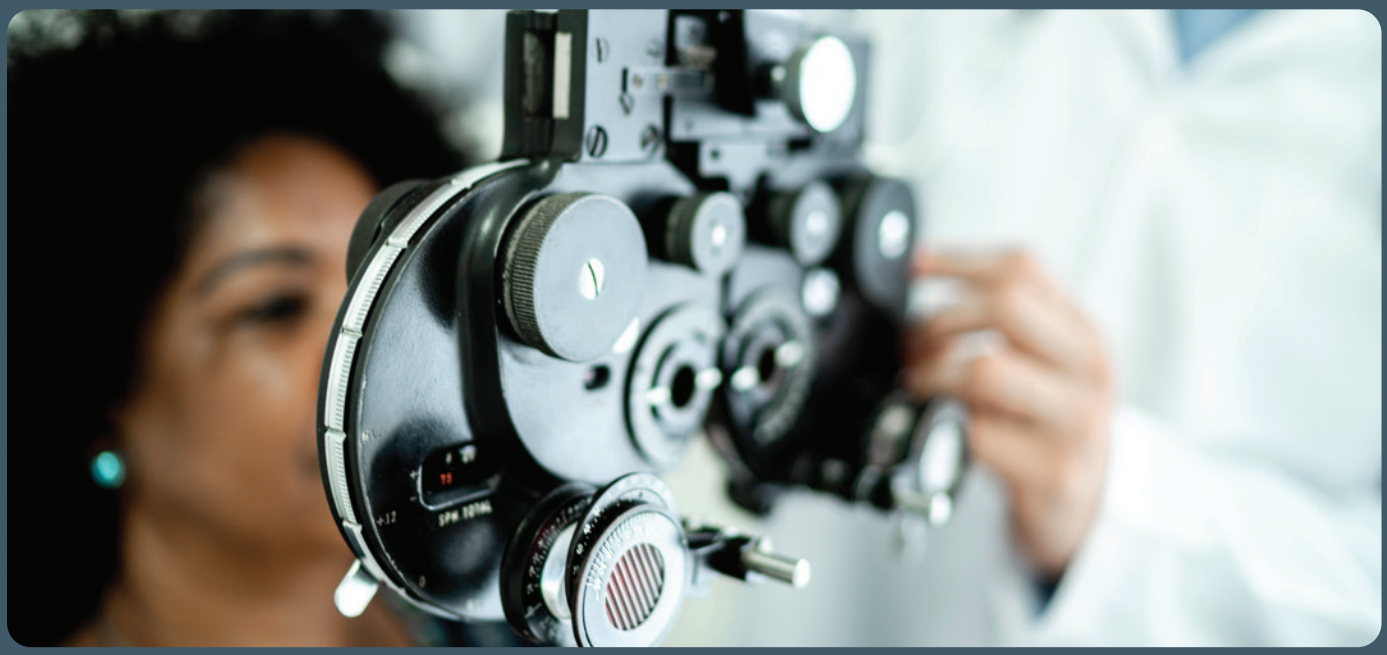
***Contacts*:** Sumit Sharma, MD (216.445.4904) | Danielle Burton (216.444.1765)

› LUMINA: A Phase 3, Multicenter, Sham-Controlled, Randomized, Double-Masked Study Assessing the Efficacy and Safety of Intravitreal Injections of 440 μg DE-109 for the Treatment of Active, Noninfectious Uveitis of the Posterior Segment of the Eye

***Contacts*:** Sumit Sharma, MD (216.445.4904) | Kim Baynes (216.444.2566)

› PANTHER: Prospective Imaging of the Intravitreal Fluocinolone Acetonide Implant Using Fluorescein Angiography and Optical Coherence Tomography in Uveitis Patients

***Contacts*:** Sunil Srivastava, MD (216.636.2286) | Danielle Burton (216.444.1765)



GENE THERAPY

› ATMOSPHERE: A Randomized, Partially Masked, Controlled, Phase 2b/3 Study to Evaluate the Efficacy and Safety of RGX-314 Gene Therapy in Participants with nAMD

***Contacts*:** Alex Yuan, MD, PhD (216.444.0079) | Theresa Kovacs (216.445.3762)

› HORIZON: A Phase 2, Open-Label, Outcomes-Assessor Masked, Multicenter, Randomized, Controlled Study to Evaluate the Safety and Efficacy of Two Doses of GT005 Administered as a Single Subretinal Injection in Subjects with Geographic Atrophy Secondary to Dry Age-Related Macular Degeneration

***Contacts*:** Alex Yuan, MD, PhD (216.444.0079) | Theresa Kovacs (216.445.3762)

› EXPLORE: A Phase 2, Open-Label, Outcomes-Assessor Masked, Multicenter, Randomized, Controlled Study to Evaluate the Safety and Efficacy of Two Doses of GT005 Administered as a Single Subretinal Injection in Subjects with Geographic Atrophy Secondary to Dry Age-Related Macular Degeneration [Note: Participants in EXPLORE also have a rare genetic variant of the *CFI* gene.]

***Contacts*:** Alex Yuan, MD, PhD (216.444.0079) | Theresa Kovacs (216.445.3762)

› SKYLINE: An Open-Label Dose Escalation Study to Evaluate the Safety and Efficacy of AGTC-501 (rAAV2tYF-GRK1-RPGR) in Subjects with X-Linked Retinitis Pigmentosa Caused by *RPGR* Mutations

***Contacts*:** Aleksandra Ratchitskaya, MD (216.445.9519) | Theresa Kovacs (216.445.3762)

CLINICAL **TRIALS** CONTINUED

CORNEA AND REFRACTIVE SURGERY

› **ZEDS: A Multicenter, Randomized, Double-Masked, Placebo-Controlled Clinical Trial of Suppressive Valacyclovir for One Year in Immunocompetent Study Participants with an Episode of Dendriform Epithelial Keratitis, Stromal Keratitis, Endothelial Keratitis and/or Iritis Due to Herpes Zoster Ophthalmicus in the Year Prior to Enrollment**

***Contacts*:** Craig See, MD (216.444.5898) | Thais Conti (216.445.3840)

RESOURCES FOR **PHYSICIANS**

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The Cole Eye Institute is one of the few dedicated, comprehensive eye institutes in the world. Our internationally recognized staff diagnoses and treats the entire spectrum of eye conditions, managing more than 310,000 clinical visits and performing more than 16,000 surgeries annually. The institute is part of Cleveland Clinic, a nonprofit, multispecialty academic medical center integrating outpatient and hospital care with research and education for better patient outcomes and experience. More than 4,500 staff physicians and researchers provide services through 20 patient-centered institutes. Cleveland Clinic is currently ranked as one of the nation's top hospitals by *U.S. News & World Report*.
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OPHTHALMOLOGY UPDATE

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21-EYE-2257061