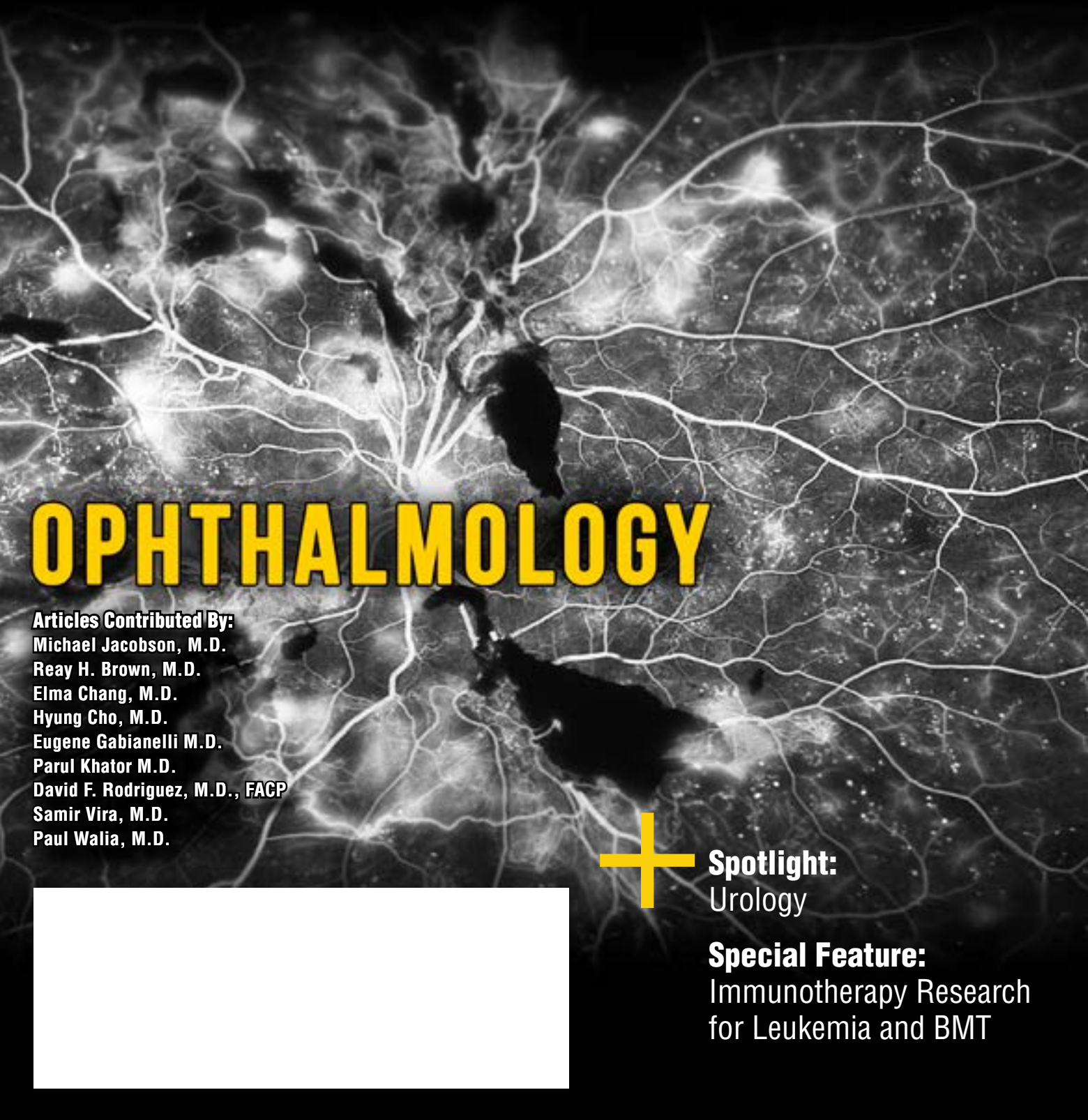
2017 Vol. 88, No. 3

# ATLANTA Medicine

JOURNAL OF THE MEDICAL ASSOCIATION OF ATLANTA



# OPHTHALMOLOGY

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Michael Jacobson, M.D.
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Elma Chang, M.D.
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Samir Vira, M.D.
Paul Walia, M.D.

**Spotlight:**
Urology

**Special Feature:**
Immunotherapy Research for Leukemia and BMT


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## Editorial Board

**Lisa C. Perry-Gilkes, MD FACS** is a solo private practice Otolaryngologist, who is currently on the board of the Atlanta Medical Association, Medical Associations of Georgia and the American Academy of Otolaryngology.

**Magda Hanafi, MD** Dr. Hanafi has had 10 years of training in the specialties of obstetrics and gynecology, infertility, surgery, and laparoscopic surgery. He has published manuscripts covering: fibroid tumors, adenomyosis, minimally invasive surgery (including robotic).

**Elizabeth Morgan MD PHD** is Director of Morgan Cosmetic Surgery, a plastic surgery practice limited to cosmetic plastic surgery. She is on staff at Northside Hosptial.

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ATLANTA Medicine is the journal of the Medical Association of Atlanta and is published by Sawyer Direct LLC at P.O. Box 49053, Colorado Springs, CO 80949

For subscription and advertising information, call 719.599.7220 or email info@sawyerdirect.com.

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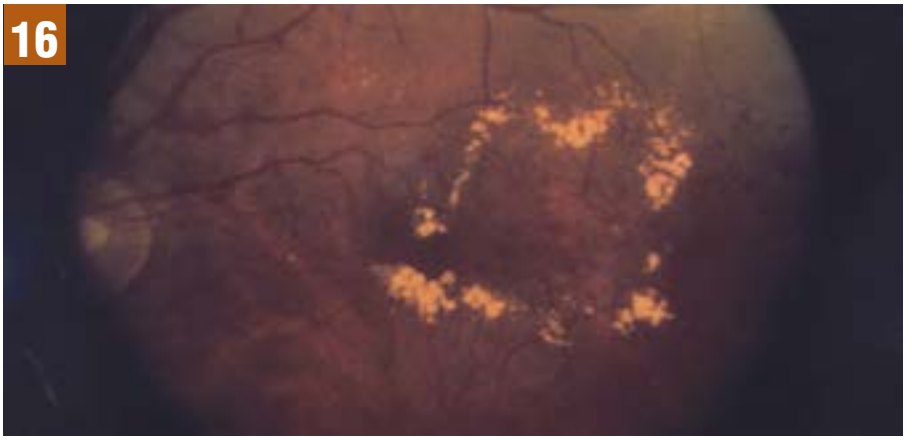



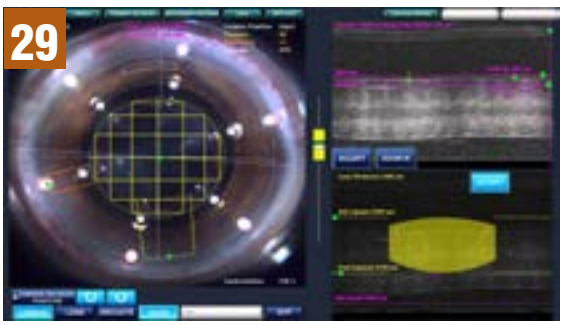




Cover photo: The cover photo is a fluourescein angiogram image of a 40 year old male diabetic with Proliferative Diabetic Retinopathy who has had diabetes for 18 years and also has hyperlipidemia and hypertension. A vegetable based dye (no iodine) is injected into the subject's arm and within 20 seconds the dye is visible in the retinal circulation. When subjected to a specific wavelength of light, the dye fluoresces at another wavelength. The use of filters allows us to only capture the fluorescent light. This allows the crisp visualization and contrast that you see in this image. No X-rays are required. The image reveals valuable information. The visible tiny white dots are microaneurysms. The cloudy leakage areas are retinal neovascularization. The black "paint swatches" are vitreous hemorrhage and the other subtle dark areas are ischemic zones of non-perfusion. This Georgia Retina photograph was acquired using an Optos wide field camera.

# Contributors

## GUEST EDITOR

**Michael Jacobson, M.D.**
Dr. Jacobson graduated from Dartmouth College and the University of Connecticut School of Medicine. He completed his residency at the University of Maryland and his fellowship at the University of Illinois. A cofounder of Georgia Retina, he has been a principal investigator of numerous clinical trials and a speaker at state, national and international meetings. He has authored a textbook chapter and published numerous articles, abstracts and papers in peer-reviewed journals.

**Hyung Cho, M.D.**
Dr. Cho graduated with honors from Dartmouth College. He completed his medical school and ophthalmology residency at the Albert Einstein College of Medicine and Montefiore Medical Center, where he was elected to serve as chief resident. He was a surgical retina fellow at Tufts New England Eye Center and Ophthalmic Consultants of Boston. He is currently a partner with Georgia Retina, one of the largest retina-only medical practices in the United States with 13 board-certified, fellowship-trained ophthalmologists.

**Paul Walia, M.D.**
Dr. Walia is a vitreoretinal surgeon at Georgia Retina. He received his undergraduate degree at the University of Florida and attended medical school at the University of South Florida. He performed his ophthalmology residency at Emory University and pursued a vitreoretinal surgery fellowship at Barnes Retina Institute in St. Louis. His clinical interests include diabetic retinopathy (DR), macular degeneration, retinal detachments, uveitis and pediatric retina. He is actively involved in clinical DR research.

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Dr. Brown is a cataract/glaucoma specialist who founded Atlanta Ophthalmology Associates with Dr. David A. Palay. He received his training at Harvard, Michigan, Johns Hopkins and Bascom Palmer and was previously Pamela Firman Professor of Ophthalmology at Emory. He has more than 25 patents for innovations in cataract and glaucoma surgery. He received the 2014 Innovator Award from the American Glaucoma Society and the 2017 Innovator Award from the American Society of Cataract and Refractive Surgery.

**Elma Chang, M.D.**
Dr. Chang is a glaucoma specialist at Atlanta Ophthalmology Associates. She received her B.A. from Emory University and M.D. from Washington University in St. Louis. She then completed her residency at Doheny Eye Institute and glaucoma fellowship at Bascom Palmer Eye Institute in Miami. Dr. Chang is board certified, and she specializes in glaucoma treatment, complex glaucoma surgery and cataract surgery.

**Samir Vira, M.D.**
Dr. Vira is a board-certified ophthalmologist who specializes in cataract, corneal and refractive surgery at Milan Eye Center. He earned his M.D. from the Medical College of Georgia and completed his residency in ophthalmology at Loyola University Medical Center in Chicago. He then completed fellowship training in cornea and refractive surgery at Emory. He is on staff at Northside Hospital-Forsyth, Northside Hospital–Cherokee, WellStar Windy Hill Hospital, WellStar North Fulton Hospital and Emory Johns Creek Hospital.

**Parul Khator M.D.**
Dr. Khator has practiced with Georgia Eye Partners in Atlanta for 8 years after completing her residency at Emory University and her glaucoma fellowship at the prestigious Wills Eye Hospital in Philadelphia. Dr. Khator specializes in glaucoma and has an extremely busy cataract and glaucoma surgical practice. She operates at The Eye Surgery Center of Georgia and Emory Midtown Hospital. She is Vice President for Medical Affairs at Georgia Eye Partners and a member of its executive board.

**Eugene Gabianelli M.D.**
Dr. Gabianelli founded Georgia Eye Partners in 1999 and has practiced in Atlanta for 25 years. He completed his residency at University of Chicago and his cornea fellowship at University of Connecticut. Dr Gabianelli specializes in the cornea and has a busy cataract and corneal surgery practice. He operates at The Eye Surgery Center of Georgia and serves as Medical Director of TLC Atlanta and Chief of the Ophthalmology Division at Emory/St Joseph's Hospital.

**David F. Rodriguez, M.D., FACP**
Dr. Rodriguez earned his Bachelor of Science and Medical Degree at Emory University. Subsequently, he completed his internship and residency in internal medicine at Emory University. He has been a practicing physician with Sandy Springs Internal Medicine since 1990. He has served on numerous committees and boards at Northside Hospital in Atlanta and is currently the Chairman of the Continuing Medical Education Advisory Committee.

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## MAA News

By David Waldrep, CAE, CEO/Executive Director

As I write this column, the Georgia legislature is wrapping up its session. This year, patients and physicians have been under attack from every direction. In conjunction with the MAG legislative team, we have been on the defense preserving access to care, the quality of care and the doctor-patient relationship.

Legislation to make writing opioid prescriptions without PDMP verification a felony has been amended to become more palatable, removing criminal penalties. The PDMP computer system has been unreliable and is not the solution to the opioid epidemic.

Optometrists are pushing forward to gain expanded scope of practice to include eye injections. And most importantly, insurance companies are pushing to solve the out-of-network emergency care issue by forcing out-of-network physicians to take a small fee and forego any billing to the patient.

On the positive side, State Rep. Betty Price (R-Roswell) introduced a bill inspired by the MAA to limit the handheld use of cell phones in an effort to reduce the number of fatalities caused in Georgia by distracted driving. This bill passed in sub-committee but failed to advance before Crossover Day – the final day to move bills from one chamber to the other.

We will continue to advocate for this and other issues facing our members and patients. We continue to have growth in membership and need to continue to encourage other physicians to get involved in the politics of medicine.

I want to invite all physicians in the Atlanta area to mark your calendar and attend our annual meeting, which will be held Saturday, June 17, 2017, at the Historic Wimbish House on Peachtree Street. This year's event is going to be a social event and an "Evening of Jazz."

With 163 years of history, the Medical Association of Atlanta continues to promote a healthier and safer community through physician leadership. This event will be a time for leaders in Atlanta medicine to celebrate our past and look to the future in a relaxed social environment. I hope to see you there.

## Healthcare Reform: Are you still straddling the fence?

By Thomas E. Bat, M.D., MAA President

Just when I thought I couldn't be more inundated with news, I awoke to the find the March 20 edition of *The Atlanta Journal -Constitution* (AJC) with two healthcare stories on the front page.

In the leading upper right corner was *"Even with new White House, Georgia faces old 'dilemma' over Medicaid."* Since 2010 and the passage of the Affordable Care Act, Georgia has chosen not to expand its Medicaid coverage as allowed under the new law. The U.S. Supreme Court upheld this tenet, and Georgia's political leaders agreed that expansion of a broken, expensive Medicaid system would not benefit our state.

There was a great deal of discourse on this topic and many opposing views. Our leaders felt adding 650,000 individuals to an overburdened Medicaid system would cost not only billions of dollars, but would decrease access to care. As other states expanded Medicaid, some with success, Georgia sat on the sidelines.

However, the recent American Healthcare Act or "AHCA," that was pulled before a scheduled vote on March 24 would have punished Georgia and other states that did not expand enrollment in Medicaid. Since the AHCA would have moved Medicaid to a block grant program with a fixed dollar amount, Georgia and 18 other states "could" have received less funding than states that have expanded their roles.

So now those same leaders would have been in a quandary of how to "expand" Medicaid to enhance the block grants and receive the maximum dollars for Georgia and its poorest citizens. How much more confusing can this get? What side of the fence to be on now?

In the lower front page was, *"Ryan: Healthcare bill likely to be changed. Speaker says older Americans should be given more assistance."* As the AHCA moved closer to a vote, Speaker of the House Ryan (R-Wis.), was caught between two factions in the majority party. One wanted to repeal all of the protections and regulations of Obamacare to keep political promises and keep our fiscal house in order. The other faction wanted more entitlement spending so no one currently getting coverage in the individual or Medicaid markets loses benefits.

That's a big fence to straddle. U.S. Secretary of Health and Human Services, Tom Price, M.D., rightfully declares "it's a fine needle that needs to be thread." I will not confuse you with the myriad of details between the ACA and the ACHA, because threading needles is not my management strength. I can only reflect that as a busy family physician, I am looking for a government who recognizes that patient-centric care requires physician leadership and engagement. At the Medical Association of Atlanta, our vision is "a healthier and safer community through physician leadership."

I am proud of MAA member Dr. Tom Price for his leadership, his vision and his tireless effort on behalf of our citizens, our patients, our profession and our country. We could not have a more devoted leader who is more thoughtful and diligent in everything he does. Even when we sit on opposite sides of the fence, he is able to communicate, listen and educate. For nearly three decades I have worked with Dr. Price on hospital committees, on the surgical floor, on outpatient consultations, at community events and even at political rallies. Even though all of our members do not know him as well, or perhaps sit on opposite sides of the proverbial fence, I hope we will support his leadership in efforts to fulfill the MAA vision.

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# Arrive Alive

## Smartphone regulations needed for distracted drivers to reduce fatalities and injuries

By Charles Wilmer, M.D. MAA President-elect, and Natalie Wilmer

Handheld smartphones – i.e., smartphones that the driver is able to touch while a vehicle is in motion – pose the greatest and most unprecedented form of danger ever seen on the road.

And smartphone ownership is growing. In 2011, 52 percent of drivers reported owning a smartphone, and by 2014 that number had grown to 80 percent. The greatest increases in smartphone ownership are among adults age 40 and older. However, our nation's youth are catching up, and their numbers are growing.

Distracted driving activities include things like using a cell phone, texting and eating. Using in-vehicle technologies (such as navigation systems) can also be sources of distraction. While any of these distractions can endanger the driver and others, texting while driving is especially dangerous because it combines all three types of distraction. (Text messaging requires visual, manual, and cognitive attention from the driver.)

Drivers allowed to manually operate a smartphone when driving are killing the innocent drivers next to them. When texting, the average time your eyes are off the road is five seconds. When traveling at 55 mph, that's enough time to cover the length of a football field blindfolded. It is not surprising then that distracted drivers veer out of their lane and into oncoming traffic.

At any given daylight moment across America, approximately 660,000 drivers are using cell phones or manipulating electronic devices while driving, a number that has held steady since 2010. A quick look at YouTube shows multiple examples of the tragedies that ensue.

Distracted driving is killing more people in Georgia, every year. More than 1,559 people died on Georgia's roads in 2016. That's 127 more than in 2015, and 389 more than in 2014. Twenty-five percent more people died in Georgia in 2016 compared to 2014 because of distracted driving.

The Georgia Department of Transportation (GDOT) found 74 percent of the above accidents were directly tied to the driver's behavior, often texting and driving. Sixty-five percent of the accidents were also caused by the driver failing to stay in their lane. In comparison, only 39 percent of fatalities had to do with car occupants not wearing any seat belts, according to GDOT.

These fatalities do not even take into account those "non-fatalities" in distracted-driving crashes, people who are never able to live a normal life as the result. Thousands of Americans struggle with back pain caused by motor vehicle accidents due to distracted driving, many of whom were the innocent victim.

Other states are enacting laws to prevent these fatalities and life-altering injuries.

- Talking on a handheld cellphone while driving is banned in 14 states and the District of Columbia.
- The use of all cellphones by novice drivers is restricted in 37 states and the District of Columbia.
- Text messaging is banned for all drivers in 46 states and the District of Columbia.

For example: In 2016, the Massachusetts Senate passed a bill banning the use of handheld cellphones while driving. The bill, S.2093, requires anyone who wants to use a phone while driving to use hands-free technology to both dial a number and to talk. The bill prohibits a driver from holding a phone while talking, inputting an address into a GPS, or composing or reading an electronic message.

The fines would be $100 for a first offense, $250 for a second offense and $500 for a third offense. These are the same fines that currently exist for texting while driving. There is an exception in case of an emergency.

When comparing data from other states or countries that have a handheld device ban, the U.S. appears to have the biggest death wish when it comes to driving while using cellphones, with Europe close behind. European governments are responding to the challenge with increasing fines and jail time. In London, the fine for a first-time offense is approximately $300 dollars and 6 points – the loss of a driver's license for a young driver.

This proposal is meant to save lives by banning the physical use of smartphones while the vehicle is being driven, not removing the use of cell phone capabilities (such as verbal communication and maps). The use of smart phones for non-physical capabilities (e.g phone calls, navigation, etc.) is still allowed via Bluetooth technology or verbal commands.

Fatalities and recklessness related to distracted driving is primarily the result of someone taking their eyes off the road to physically hold and operate a smartphone, resulting in loss of vision for the length of a football field while operating a two-ton missile. That is what needs to change. Unless there is a law in place that allows police to cite people for touching their phones while the vehicle is in operation, people will not voluntarily change what they find easy until they or a loved one are involved in a life-altering collision due to distracted driving.

Some of my patients have asked why doctors do not stand up for the safety of their patients and stop this carnage. I have come face-to-face with this issue myself. We lost one of our finest physicians this past year due to a distracted driver who ran over him while he was biking with friends. His wife lost a husband, his children lost their father, and the community lost one of their best physicians. More than 3,000 patients will be forced to find another doctor, never again to see the one they loved for so many years.

The time to act is now at hand. Let us be bold to realize our weakness with cellphones and put them down before another tragic loss of life occurs. It may just save our life or that of a loved one. ■

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## INDICATIONS AND IMPORTANT SAFETY INFORMATION

### INDICATIONS

- EYLEA® (aflibercept) Injection is indicated for the treatment of patients with Neovascular (Wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR) in Patients with DME.

### CONTRAINDICATIONS

- EYLEA® (aflibercept) Injection is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

### WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

### ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

***Please see brief summary of full Prescribing Information on the following page.***

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

TARGETED SCIENCE

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06/2016
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# EYLEA®
## (aflibercept) Injection
## For Intravitreal Injection

**BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION**

**FOR COMPLETE DETAILS, SEE FULL PRESCRIBING INFORMATION.**

**1 INDICATIONS AND USAGE**

EYLEA® (aflibercept) Injection is indicated for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR) in Patients with DME.

**2 DOSAGE AND ADMINISTRATION**

**2.1 Important Injection Instructions.** For ophthalmic intravitreal injection. EYLEA must only be administered by a qualified physician.

**2.2 Neovascular (Wet) Age-Related Macular Degeneration (AMD).** The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months).

**2.3 Macular Edema Following Retinal Vein Occlusion (RVO).** The recommended dose for EYLEA is (0.05 mL or 50 microliters) administered by intravitreal injection once every 4 weeks (monthly).

**2.4 Diabetic Macular Edema (DME).** The recommended dose for EYLEA is (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).

**2.5 Diabetic Retinopathy (DR) in Patients with DME.** The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).

**2.6 Preparation for Administration.** EYLEA should be inspected visually prior to administration. If particulates, cloudiness, or discoloration are visible, the vial must not be used. Using aseptic technique, the intravitreal injection should be performed with a 30-gauge x ½-inch injection needle. For complete preparation for administration instructions, see full prescribing information.

**2.7 Injection Procedure.** The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include surgical hand disinfection and the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a topical broad–spectrum microbicide should be given prior to the injection.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, a sterile paracentesis needle should be available.

Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay (*see Patient Counseling Information*).

Each vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter, and injection needles should be changed before EYLEA is administered to the other eye.

After injection, any unused product must be discarded.

**3 DOSAGE FORMS AND STRENGTHS**

Single-use, glass vial designed to provide 0.05 mL of 40 mg/mL solution (2 mg) for intravitreal injection.

**4 CONTRAINDICATIONS**

EYLEA is contraindicated in patients with

- Ocular or periocular infections
- Active intraocular inflammation
- Known hypersensitivity to aflibercept or any of the excipients in EYLEA.

Hypersensitivity reactions may manifest as severe intraocular inflammation.

**5 WARNINGS AND PRECAUTIONS**

**5.1 Endophthalmitis and Retinal Detachments.** Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments (*see Adverse Reactions*). Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately (*see Dosage and Administration and Patient Counseling Information*).

**5.2 Increase in Intraocular Pressure.** Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA (*see Adverse Reactions*). Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular edothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately (*see Dosage and Administration*).

**5.3 Thromboembolic Events.** There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

**6 ADVERSE REACTIONS**

The following adverse reactions are discussed in greater detail in the *Warnings and Precautions* section of the labeling:

- Endophthalmitis and retinal detachments
- Increased intraocular pressure
- Thromboembolic events

**6.1 Clinical Trials Experience.** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice. A total of 2711 patients treated with EYLEA constituted the safety population in seven phase 3 studies. Among those, 2110 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

**Neovascular (Wet) Age-Related Macular Degeneration (AMD).** The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, active-controlled clinical studies (VIEW1 and VIEW2) for 12 months.

**Table 1: Most Common Adverse Reactions (≥1%) in Wet AMD Studies**

| Adverse Reactions | EYLEA (N=1824) | Active Control (ranibizumab) (N=595) |
|---|---|---|
| Conjunctival hemorrhage | 25% | 28% |
| Eye pain | 9% | 9% |
| Cataract | 7% | 7% |
| Vitreous detachment | 6% | 6% |
| Vitreous floaters | 6% | 7% |
| Intraocular pressure increased | 5% | 7% |
| Ocular hyperemia | 4% | 8% |
| Corneal epithelium defect | 4% | 5% |
| Detachment of the retinal pigment epithelium | 3% | 3% |
| Injection site pain | 3% | 3% |
| Foreign body sensation in eyes | 3% | 4% |
| Lacrimation increased | 3% | 1% |
| Vision blurred | 2% | 2% |
| Intraocular inflammation | 2% | 3% |
| Retinal pigment epithelium tear | 2% | 1% |
| Injection site hemorrhage | 1% | 2% |
| Eyelid edema | 1% | 2% |
| Corneal edema | 1% | 1% |

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, and endophthalmitis.

**Macular Edema Following Retinal Vein Occlusion (RVO).** The data described below reflect 6 months exposure to EYLEA with a monthly 2 mg dose in 218 patients following CRVO in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following BRVO in one clinical study (VIBRANT).

**Table 2: Most Common Adverse Reactions (≥1%) in RVO Studies**

| Adverse Reactions | CRVO | | BRVO | |
|---|---|---|---|---|
| | EYLEA (N=218) | Control (N=142) | EYLEA (N=91) | Control (N=92) |
| Eye pain | 13% | 5% | 4% | 5% |
| Conjunctival hemorrhage | 12% | 11% | 20% | 4% |
| Intraocular pressure increased | 8% | 6% | 2% | 0% |
| Corneal epithelium defect | 5% | 4% | 2% | 0% |
| Vitreous floaters | 5% | 1% | 1% | 0% |
| Ocular hyperemia | 5% | 3% | 2% | 2% |
| Foreign body sensation in eyes | 3% | 5% | 3% | 0% |
| Vitreous detachment | 3% | 4% | 2% | 0% |
| Lacrimation increased | 3% | 4% | 3% | 0% |
| Injection site pain | 3% | 1% | 1% | 0% |
| Vision blurred | 1% | <1% | 1% | 1% |
| Intraocular inflammation | 1% | 1% | 0% | 0% |
| Cataract | <1% | 1% | 5% | 0% |
| Eyelid edema | <1% | 1% | 1% | 0% |

Less common adverse reactions reported in <1% of the patients treated with EYLEA in the CRVO studies were corneal edema, retinal tear, hypersensitivity, and endophthalmitis.

**Diabetic Macular Edema (DME).** The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) from baseline to week 52 and from baseline to week 100.

**Table 3: Most Common Adverse Reactions (≥1%) in DME Studies**

| Adverse Reactions | Baseline to Week 52 | | Baseline to Week 100 | |
|---|---|---|---|---|
| | EYLEA (N=578) | Control (N=287) | EYLEA (N=578) | Control (N=287) |
| Conjunctival hemorrhage | 28% | 17% | 31% | 21% |
| Eye pain | 9% | 6% | 11% | 9% |
| Cataract | 8% | 9% | 19% | 17% |
| Vitreous floaters | 6% | 3% | 8% | 6% |
| Corneal epithelium defect | 5% | 3% | 7% | 5% |
| Intraocular pressure increased | 5% | 3% | 9% | 5% |
| Ocular hyperemia | 5% | 6% | 5% | 6% |
| Vitreous detachment | 3% | 3% | 8% | 6% |
| Foreign body sensation in eyes | 3% | 3% | 3% | 3% |
| Lacrimation increased | 3% | 2% | 4% | 2% |
| Vision blurred | 2% | 2% | 3% | 4% |
| Intraocular inflammation | 2% | <1% | 3% | 1% |
| Injection site pain | 2% | <1% | 2% | <1% |
| Eyelid edema | <1% | 1% | 2% | 1% |

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.

**6.2 Immunogenicity.** As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.

In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

**6.3 Postmarketing Experience.** The following adverse reactions have been identified during postapproval use of EYLEA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hypersensitivity including rash, pruritus, and urticaria as well as isolated cases of severe anaphylactic/anaphylactoid reactions.

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy.** Pregnancy Category C. Aflibercept produced embryo-fetal toxicity when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days at subcutaneous doses ≥0.1 mg per kg. Adverse embryo-fetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was less than 0.1 mg per kg. Administration of the lowest dose assessed in rabbits (0.1 mg per kg) resulted in systemic exposure (AUC) that was approximately 10 times the systemic exposure observed in humans after an intravitreal dose of 2 mg.

There are no adequate and well-controlled studies in pregnant women. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Females of reproductive potential should use effective contraception prior to the initial dose, during treatment, and for at least 3 months after the last intravitreal injection of EYLEA.

**8.3 Nursing Mothers.** It is unknown whether aflibercept is excreted in human milk. Because many drugs are excreted in human milk, a risk to the breastfed child cannot be excluded. EYLEA is not recommended during breastfeeding. A decision must be made whether to discontinue nursing or to discontinue treatment with EYLEA, taking into account the importance of the drug to the mother.

**8.4 Pediatric Use.** The safety and effectiveness of EYLEA in pediatric patients have not been established.

**8.5 Geriatric Use.** In the clinical studies, approximately 76% (2049/2701) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 46% (1250/2701) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

**17 PATIENT COUNSELING INFORMATION**

In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist (*see Warnings and Precautions*). Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations (*see Adverse Reactions*). Advise patients not to drive or use machinery until visual function has recovered sufficiently.

***REGENERON***

Manufactured by:
**Regeneron Pharmaceuticals, Inc.**
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Tarrytown, NY 10591-6707

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Issue Date: June 2016
Initial U.S. Approval: 2011
June 2016

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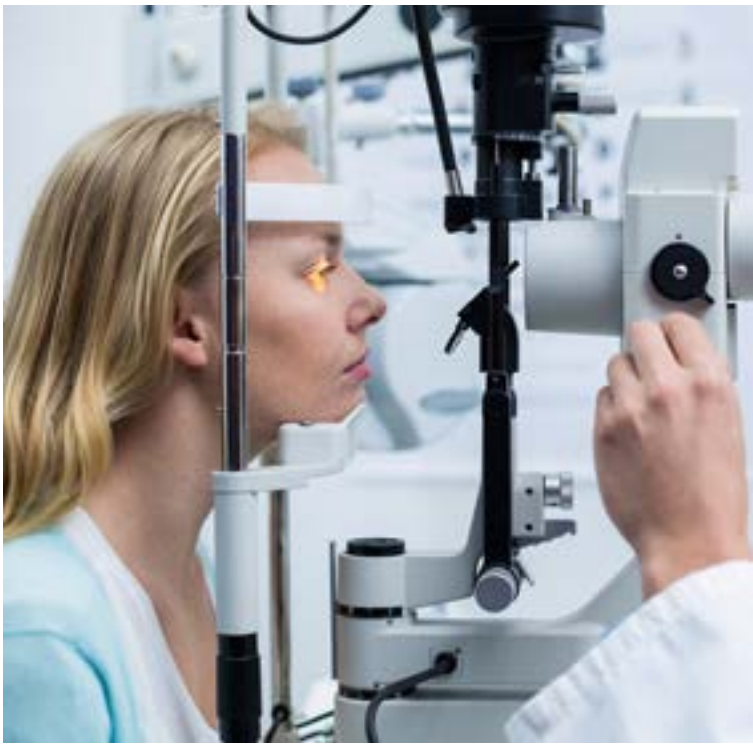
## WHAT'S HAPPENING IN OPHTHALMOLOGY?

# MORE THAN THE EYE CAN SEE.

By Michael Jacobson, M.D.



In this edition, we will explore and provide you insight into a wide range of ophthalmology topics. We will start at the front of the eye, the cornea, then delve deeper to discuss the lens and ciliary body. Lastly we'll finish our eye edition focused on the back of the eye, the retina.

Hold tight onto this issue, as we will give you a whirlwind tour of these wide-ranging and fascinating topics that have meaning for all of us, not just our patients. After all, if you live a long life, you will invariably develop one of these problems.

We will discuss the latest and most exciting developments when it comes to refractive surgery, which gives individuals the opportunity to reduce their dependency on glasses or contact lenses. We've come a long way since radial keratotomy (RK) surgery of the 1980s. With the advent of newer techniques like laser-assisted in situ keratomileusis (LASIK) and photorefractive keratectomy (PRK), we now have procedures that permit more consistent, predictable and sustained results.

This field is burgeoning, and the population of people that may be good candidates for some type of refractive procedure is enlarging. Even solutions for presbyopia, or farsightedness caused by loss of elasticity of the lens of the eye that compels most of us over age 40 to turn to reading glasses, is being addressed with surgical options. The future may even be more promising and is likely to surpass the vision correction results that we obtain with LASIK and PRK.

Did you know that 3 million people in the U.S. have glaucoma and that this blinding eye disease progresses insidiously because there are usually no symptoms?? Did you know you can have glaucoma but have normal pressure?

Increased pressure in the eye leads to blindness, and eye drops are usually the first line of treatment. New drug classes, each with a unique mechanism, has led to a diversity of eye drop options that we have used for the past 3 decades without any big developments. However there is a new drug class awaiting FDA approval which you can read more about in this issue.

Compliance has been a major obstacle in treating glaucoma patients with drops. Innovative sustained drug delivery devices may lead to improved outcomes, and these are addressed.

For those in whom drops are not enough, laser therapy remains effective to increase outflow or decrease inflow, but there have not been new big breakthroughs here. A momentous advance in glaucoma treatment has been the discovery that cataract surgery lowers pressure. This has been very good news for glaucoma patients as that can sometimes be enough of a drop in pressure to make a difference.

If that is not thought to be enough pressure reduction, then the opening of the eye during cataract surgery now affords the opportunity to insert micro-incisional devices to facilitate the drainage of fluid out of the eye. Our authors have been involved in their development. Additional novel approaches in this micro-incisional surgery arena will be highlighted.

More advanced glaucoma damage requires larger scale, macro surgery. These procedures create a pathway – essentially a hole – from inside the eye to a bleb (a fluid-filled bump) on the ocular surface, and they can achieve profound pressure reduction. Alternate fluid pathways procedures continue to evolve year by year now. If patients undergo frequent eye exams as they grow older as recommended and when necessary, and we use the aforementioned treatments, we can hopefully prevent blindness from this terrible disease.

A cataract is formed as the lens of the eye becomes dense and opacified with age. Less light is able to enter the eye, causing diminished light perception, dulling of colors and blurry vision. Light becomes diffracted, resulting in glare. As the No. 1 cause of reversible vision loss worldwide, a great deal of time and effort has been spent on developing a safe, efficient and accurate surgical treatment.

The evolution of cataract surgery to become the operation it is today is one of the most interesting stories in all of medicine, and that journey is what the authors will share with you,

taking you from ancient couching to incisional surgery where the entire cataract was removed.

The invention of intraocular implants allowed the "Coke bottle" glasses of your great grandparents to disappear. Techniques advanced allowing partial removal of the lens. Then ultrasonic dissolution and aspiration evolved to permit smaller and smaller incisions.

Very recently, a unique laser has enhanced and "simplified" the surgical technique whereby the laser can make precise computer-designed incisions and dissolve the cataract. Incision size can be as small as 2mm (less than 1/10 inch), still large enough to remove the old cataract and insert a foldable lens implant substitute. Anesthesia has evolved from required general anesthesia to retrobulbar shots and now simply topical. That makes it infinitely safer for all patients.

While risks of surgery exist, this surgery offers very high levels of postoperative satisfaction. Astigmatism-correcting intraocular lenses (IOLs), refractive multifocal IOLs and presbyopia-correcting ones are available. Models have improved rapidly particularly over the past decade, and there is an excellent chance of finding a precise internal vision correction that makes the patient much less eyeglass-dependent. Essentially, a patient with healthy retina can request and choose crisp near vision or crisp distance vision. If that is not the desired endpoint, then there are multifocal IOL options that try to achieve a hybrid of both. The authors explain how cataract surgery of 2017 should preserve one's active lifestyles like never before.

Diabetic retinopathy (DR) affects nearly one-third of all patients, and diabetes is the leading cause of blindness in our working-age population. This disease is epidemic, particularly here in Georgia.

A retina specialist will provide you with a succinct understanding of how this condition is managed. He emphasizes how all of us need to work collectively to get our patients motivated to not only achieve good A1c levels, but to address the other factors that accelerate this disease, particularly hyperlipidemia, hypertension and tobacco use.

All of us now know that what was considered an acceptable A1c of 8 in the past is not acceptable and the postponement of nephropathy, neuropathy and retinopathy depend on true tight control. Today he will report that compliant patients seldom end up blind, thanks to more tools in the retinal surgical tool box (small gauge surgery, improved preop pharmacology).

I recall during my fellowship and will never forget that one of my friends, in the midst of his neuroradiology fellowship, developed Type I diabetes mellitus. He diagnosed himself. It was ironic that he came down with this, given that his father, a professor of endocrinology, was also the president of the American Diabetes Association. Initially, he went into a deep depression concerned that he ultimately would lose the ability to read X-rays and catastrophizing how his life was doomed. Today such thinking hopefully is truly a thing of the past.

Age-related macular degeneration (AMD) is a very big deal because the aggressive forms of the disease lead to legal blindness (20/200 vision). This represents a severe handicap to our aging population who will lose the ability to drive, read or recognize faces.

Unless you are a pediatrician, you will encounter these visually handicapped patients. Now over 9 million people here in the U.S. have AMD, but 18 million people will have this condition by 2050. That is staggering! Knowing that QALY surveys find that people would rather have AIDS or advanced congestive heart failure than face the prospect of blindness, I am pleased to report that we have made great strides in managing this horrific condition, and a retinal specialist will share the good news with you and what we hope to achieve tomorrow.

No longer are ophthalmologists serving like psychiatrists trying to help these patients cope with their depression that such visual loss brings. Intravitreal injections of anti-VEGF drugs remain the standard of care for wet AMD. Yes, shots directly into the eye. Ninety percent of patients benefit, and of those, almost half experience some vision improvement. Considering 10 years ago when we relied on laser, we could only help 10 percent of patients, this is a revolutionary breakthrough. However, there is still room for improvement in AMD treatments since only the minority of patients experience significant visual gains and the treatment burden of frequent injections is high.

Breakthroughs for patients blinded by retinitis pigmentosa (RP) may include a retinal prosthetic device akin to a cochlear implant, called the Argus. In a different direction, we soon may be able to repopulate compromised/degenerated retinal cells using stem cell replacement, injected under the retina. 3-D printers using living cells placed on a substrate may even build networks of retinal cells that mimic the complex retinal hierarchal structure. Gene therapy provided by a viral vector (adeno-associated virus) has been recently used successfully in Leber's Congenital Amaurosis (LCA), a blinding eye disease of children, and now may be modified to insert enhanced cells that may suppress natural VEGF production and allow our body to better defend against the onset of wet AMD.

As a consequence of the human genome project, each day more single-nucleotide polymorphisms (SNPs) of DNA are being investigated to find their relationship to eye disease. These discoveries will allow us to explore how we can synthesize protein inhibitors or promoters to prevent or cure disease.

Such research is robustly underway, including biotech company Spark Therapeutics, which is screening large populations to attack some rarer but devastating blinding eye disease such as choroideremia, RP and LCA. Enjoy this eye edition. ■

# Age-related Macular Degeneration
# THE BASICS AND BEYOND

By Hyung Cho, M.D.

Age-related macular degeneration (AMD) is a medical condition that may result in blurred or no vision in the center of the visual field. While it does not result in complete blindness, loss of central vision can make it hard to recognize faces, drive, read or perform other activities of daily life.

AMD is the primary cause of vision loss and legal blindness in patients over the age of 65 in developed countries. In 2010, 9.1 million people were reported to have AMD. That number will nearly double to 17.8 million people by 2050.[1]

Early AMD often does not exhibit any symptoms. The first symptom of AMD is usually noticed when straight lines appear wavy. This may lead to a gradual loss of central vision. Other symptoms of AMD include the following:

- Objects, print may become blurry or distorted
- A dark or blank spot in the center of the vision
- The size or color of something looks different when viewed through different eyes
- Trouble recognizing people's faces
- More light may be required to read

The exact cause of AMD is not known; however, some people are at greater risk. The greatest risk factor for AMD is age. At age 50, you have just a 2 percent risk, but that risk increases to 30 percent by age 75.[2]

**Risk factors for AMD that cannot be controlled include:[2]**

- **Family History:** The risk of AMD is three times higher if an immediate family member has the condition
- **Skin/eye color:** People with light-colored skin and eyes are more likely to develop AMD
- **Gender:** Women get AMD more often than men

**Risk factors for AMD that can be controlled:**

- **Smoking:** Smokers are three to four times more likely to develop AMD compared to non-smokers
- **Nutrition:** Importance of a nutritionally balanced diet. Fruits, green leafy vegetables and fish will supply the nutrients that are necessary to maintain healthy eyes
- **Obesity:** Overweight patients with AMD are more than twice as likely to develop advanced forms of the disease compared with people of normal body weight[3]
- **High blood pressure/cholesterol:** Linked to the development of advanced AMD
- **Excessive exposure to sunlight:** Research has shown that excessive ultraviolet light may increase the risk of developing AMD[4]

The disorder is classified into two forms: non-neovascular (dry) AMD and neovascular (wet) AMD. The dry form of AMD affects about 90 percent of AMD patients and usually begins when tiny yellow deposits called drusen appear in the macula (Figure 1). Drusen usually do not cause serious loss of vision but can distort it. In advanced stages, dry AMD can lead to tissue breakdown/atrophy and patients may lose their central vision.

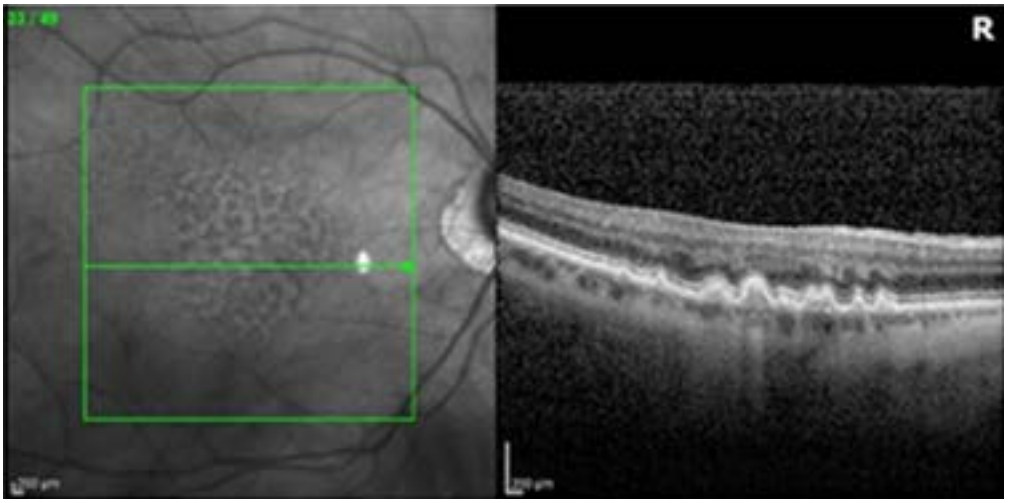



Figure 1. OCT of dry AMD with drusen without evidence of fluid/hemorrhage

Neovascular AMD is characterized by choroidal neovascularization (CNV), which is a growth of abnormal blood vessels beneath the macula that can leak fluid and blood into the eye. Although only roughly 10 percent of patients with AMD have the neovascular form, it accounts for around 90 percent of the severe loss of vision.[5] The longer these abnormal vessels leak or grow, the greater risk you have of losing more of your detailed vision.

The wet form of AMD usually causes major vision problems, such as blind spots and loss of central vision in the affected eye, and can advance rapidly. These abnormal blood vessels and chronic fluid eventually scar, leading to permanent retinal damage and loss of central vision.

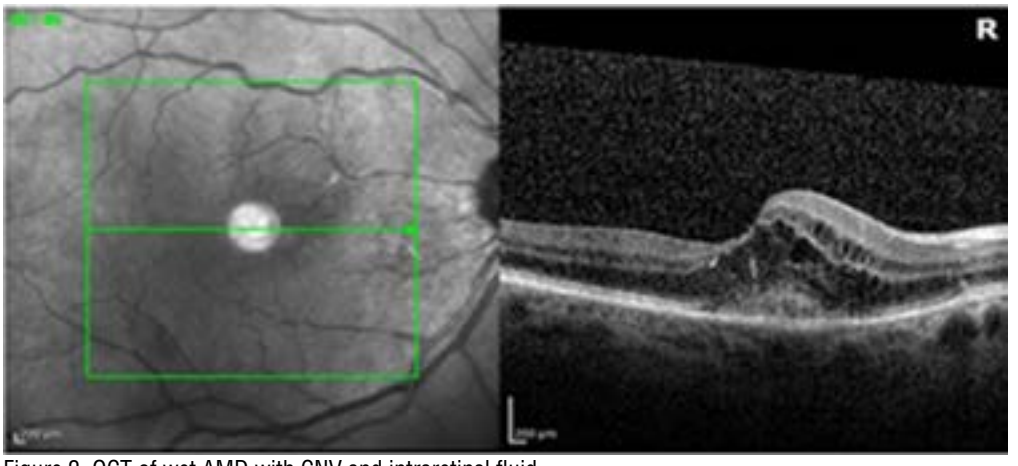


Figure 2. OCT of wet AMD with CNV and intraretinal fluid

Because the dry form can change into the wet form, it is very important for people with AMD to monitor their eyesight carefully and see their eye doctor on a regular basis. Your eye doctor can see these drusen during a routine eye exam. Often, an optical coherence tomography (OCT) picture will be taken. OCT shows how thick the retina is and can identify accumulated fluid from abnormal blood vessels (Figure 2).

People with AMD can check their own vision with a simple test called the Amsler grid (Figure 3). The Amsler grid is a pattern of straight lines that make perfect squares. The patient covers one eye and looks at a dot in the middle of the grid and notices any areas where the lines look blurry, wavy, or broken. Early detection of AMD is very important because there are treatments that can delay or reduce the severity of the disease.

Unfortunately, at this time there is no single proven treatment for the dry form of AMD. However, a large scientific study has shown that antioxidant vitamins and zinc may reduce the impact of macular degeneration in some people by slowing its progression toward more advanced stages.

- **Vitamin C** – 500 mg
- **Vitamin E** – 400 IU
- **Lutein** – 10 mg
- **Zeaxanthin** – 2 mg
- **Zinc Oxide** – 25 mg
- **Copper (as cupric oxide)** – 2 mg

The Age-Related Eye Disease Study (AREDS) found that taking vitamin and mineral supplements can decrease the vision loss in patients with intermediate to advanced dry AMD. The newest versions of vitamins tend to have "AREDS2" in the name or on the label. They have not been shown to prevent the disease but may slow the worsening of progression to advanced stages by at least 25 percent. The study also found that there was a 19 percent reduction in the risk of vision loss among moderate to advanced AMD patients when this vitamin supplement was taken.[6] The supplements did not appear to provide a benefit for people with minimal macular degeneration or people without evidence of the disease.

Treatment strategies for neovascular AMD have progressed from thermal laser photocoagulation to a cold laser treatment called photodynamic therapy (PDT). Pharmacotherapy, in particular, those that inhibit vascular endothelial growth factor (VEGF), has become first-line and revolutionized the treatment for exudative AMD.

VEGF is a protein that promotes the growth of new abnormal blood vessels, and anti-VEGF injection therapy blocks this growth. Since 2004, three of the most common anti-VEGF drugs introduced were ranibizumab (Lucentis; Genentech/Roche), aflibercept (Eylea; Regeneron Pharmaceuticals) and bevacizumab (Avastin; Genentech/Roche).

Bevacizumab, a monoclonal VEGF-specific antibody, has been developed for the use of various cancers but has been widely used off-label for the treatment of neovascular AMD. Many physicians have preferred low-cost bevacizumab – over the higher cost ranibizumab or aflibercept – for the initial treatment of AMD, although only recently has bevacizumab (administered monthly) been shown to produce improvements in vision that are comparable to ranibizumab.[7]

Bevacizumab only can be secured from a compounding pharmacy, thus there is potential increased risk for contamination or adulteration. The more expensive drugs were designed for the eye and have been investigated more exhaustively in studies, so bevacizumab is considered off label. Frequent lifelong intravitreal injections remain the standard of care for wet AMD. However, there is still room for improvement since only the minority of patients experience significant visual gains and the treatment burden of frequent injections is high. However, 90 percent of patients benefit and of those almost half experience some vision improvement.

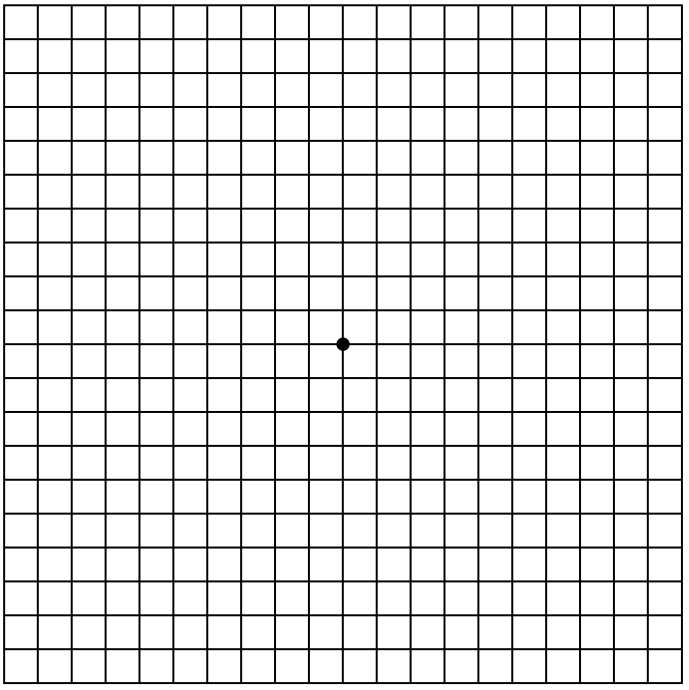


Figure 3. Amsler grid

1. Be sure to wear your bifocals or reading glasses
2. Hold the grid at your normal reading distance
3. Cover one eye and then only look at the center dot
4. While looking at the center dot, all of the lines should appear straight and all of the squares should be the same
5. Perform the test for each eye separately, not with both eyes open at the same time

People with wet or dry AMD who cannot be treated will rarely become completely blind, as they will still have peripheral vision. If it is partial, the result is a vision impairment known as low vision. These patients may be helped with low-vision aids. A common misconception is that there is going to be one pair of glasses that will solve the low vision visual impairment. Typically, more than one device is needed, such as:

- High-powered reading glasses
- Handheld and spectacle-mounted telescopic lens systems
- Handheld and/or stand magnifiers
- Closed-circuit television systems
- Computers

Low-vision aids help people with partial vision make the most of their remaining vision by learning new strategies to accomplish daily activities. For some patients with end-stage AMD, an Implantable Miniature Telescope (IMT) may be an option. This FDA-approved device can help restore some lost vision by focusing images onto a healthier part of the retina. After surgery to implant the IMT, patients participate in an extensive vision rehabilitation program.

Few ocular diseases are so prevalent and devastating to daily life as AMD. Fortunately, considerable research has made notable advances in attempting to unravel the complexities associated with this maculopathy. The field of ophthalmology has witnessed an unparalleled degree of progress over the last decade in the diagnosis and management of AMD thanks to advances from anti-VEGF treatment and enhanced imaging.

**AMD is the primary cause of vision loss and legal blindness in patients over the age of 65 in developed countries. In 2010, 9.1 million people were reported to have AMD.**

However, very little progress has been made to prevent or slow down the disease and treat the mounting population of patients who suffer vision loss from advanced dry AMD. Advanced dry ARMD is also called geographic atrophy (GA), and it represents the other 10 percent of severe vision loss that occurs with macular degeneration.

Fortunately, the majority of patients with common dry ARMD have a slow vision loss over decades, but those with GA experience a very rapid decline of central acuity, sometimes in just two to three years.

We are doing active research in this regard that we hope will change and expand understanding of the pathobiology on dry AMD and point us toward new therapeutic strategies and targets for this desperate group of patients, especially now that we have so effectively neutralized the advancement of wet ARMD. ■

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GEORGIA RETINA

# DIABETIC RETINOPATHY UPDATE

By Paul Walia, M.D.

Diabetic retinopathy affects nearly one-third of all patients with diabetes and is the leading cause of visual impairment and blindness in working-aged adults. The Centers for Disease Prevention and Control (CDC) estimates that currently the healthcare costs associated with the treatment for diabetic retinopathy is around $500 million annually. Projections forecast that from 2010 to 2050, the number of Americans with diabetic retinopathy is expected to nearly double, from 7.7 million to 14.6 million, mirroring trends with obesity and metabolic syndrome.

Diabetic retinopathy often begins without symptoms. It invariably affects both eyes and is usually symmetric. If asymmetric disease is present with one eye having severe changes and the other eye not showing manifestation, the ophthalmologist must be alerted to unilateral hypoperfusion, specifically carotid artery insufficiency or blockage.

Patients may have relatively good and even perfect vision at initial presentation. However as the disease progresses, patients may experience distortion of vision, floaters and decrease of vision from mild diminution to total loss of vision.

The pathophysiology of diabetic retinopathy is complex. Hyperglycemia induces vascular pericyte deficiency, which leads to an increased vascular permeability and leakage and release of pro-inflammatory cytokines. This leads to local ischemia. Clinically, increased vascular permeability is most evident as microaneurysms, cotton-wool spots, intraretinal hemorrhages, the presence of exudates and macular edema. Ischemia is discernible as the presence of neovascularization.

The two sight-threatening consequences are diabetic macular edema and proliferative diabetic retinopathy. Diabetic macular edema (Figure 1) affects the macula, and thus the central vision is reduced. Focal laser treatment to photocoagulate the leaking microaneurysms has long been proven an effective therapy. Advances in pharmacotherapy have allowed intravitreal injections of medication to revolutionize the treatment paradigm. (See Figure 2.)

Medications such as anti-VEGF monoclonal antibodies and corticosteroids are vital tools in the retina specialists' tool chest to treat diabetic macular edema. A challenge with these medications, however, is that they require multiple and ongoing injections at various intervals based on their pharmacokinetics. Promising research is ongoing about other drug-delivery vehicles, such as implantable biodegradable implants, that can allow sustained delivery of medication and reduce the frequency of injections. Additionally, there are several oral medications being studied that in conjunction with intravitreal injections may reduce the treatment burden.

Proliferative diabetic retinopathy is marked by the presence of neovascularization. (See Figure 3.) The new compensatory vessels that develop in response to ischemia lack structural integrity. They can burst and result in massive vitreous hemorrhage or fibrose and cause traction retinal detachments. Treatment options include intravitreal injection, pan-retinal laser photocoagulation of ischemic retina and vitrectomy

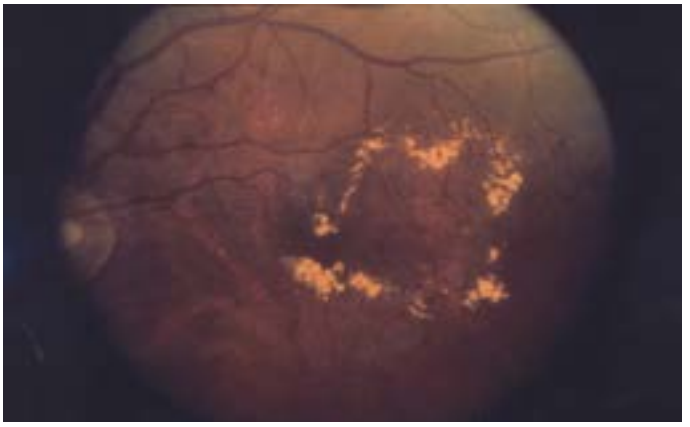

Photo courtesy of the Wills Eye Manual

Figure 1 Macular Edema

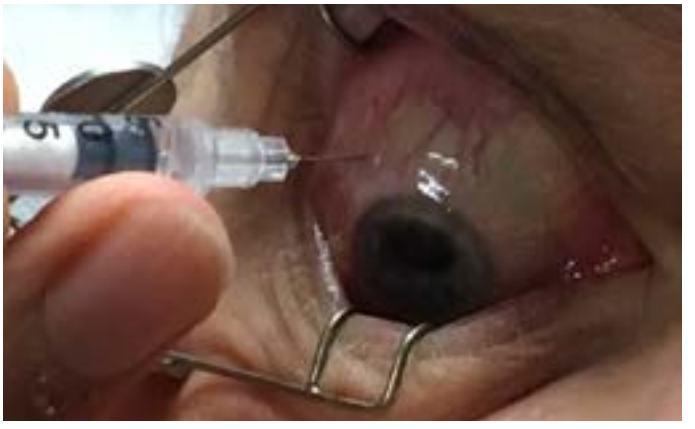

Figure 2 Intravitreal Injection

**NOW APPROVED** FOR PATIENTS WITH MYOPIC CHOROIDAL NEOVASCULARIZATION (mCNV)


# STRENGTH IN EVIDENCE

The efficacy and safety of LUCENTIS were rigorously studied in 9 pivotal trials[1-9]

LUCENTIS®
RANIBIZUMAB INJECTION

Approved for wet AMD, DME, DR with DME, macular edema following RVO, and mCNV.

## INDICATIONS

LUCENTIS® (ranibizumab injection) is indicated for the treatment of patients with:

- Neovascular (wet) age-related macular degeneration (wAMD)
- Macular edema following retinal vein occlusion (RVO)
- Diabetic macular edema (DME)
- Diabetic retinopathy (Non Proliferative DR (NPDR) and Proliferative DR (PDR)) with diabetic macular edema (DME)
- Myopic choroidal neovascularization (mCNV)

## IMPORTANT SAFETY INFORMATION

### CONTRAINDICATIONS

- LUCENTIS is contraindicated in patients with ocular or periocular infections or known hypersensitivity to ranibizumab or any of the excipients in LUCENTIS

### WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis, retinal detachment, and iatrogenic traumatic cataract. Proper aseptic injection technique should always be utilized when administering LUCENTIS. Patients should be monitored following the injection to permit early treatment, should an infection occur
- Increases in intraocular pressure (IOP) have been noted both pre-injection and post-injection (at 60 minutes) with LUCENTIS. Monitor intraocular pressure prior to and following intravitreal injection with LUCENTIS and manage appropriately
- Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause)
- Fatal events occurred more frequently in patients with DME and DR at baseline treated monthly with LUCENTIS compared with control. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded

### ADVERSE EVENTS

- Serious adverse events related to the injection procedure that occurred in <0.1% of intravitreal injections included endophthalmitis, rhegmatogenous retinal detachment, and iatrogenic traumatic cataract
- In the LUCENTIS Phase III clinical trials, the most common ocular side effects included conjunctival hemorrhage, eye pain, vitreous floaters, and increased intraocular pressure. The most common non-ocular side effects included nasopharyngitis, anemia, nausea, and cough

*Please see Brief Summary of LUCENTIS full Prescribing Information on adjacent page.*

The following randomized, double-masked pivotal trials were conducted for the 5 LUCENTIS indications: **wAMD:** *MARINA*—Phase III, multicenter, 2-year, sham injection–controlled study; primary end point at 1 year. *ANCHOR*—Phase III, multicenter, 2-year, active treatment–controlled study; primary end point at 1 year. *PIER*—Phase IIIb, 2-year, sham injection–controlled study; primary end point at 1 year. *HARBOR*—Phase III, multicenter, 2-year, active treatment–controlled dose-response study; primary end point at 1 year. **RVO:** *BRAVO*—Phase III, multicenter, 1-year, sham injection–controlled study; primary end point at 6 months. *CRUISE*—Phase III, multicenter, 1-year, sham injection–controlled study; primary end point at 6 months. **DME and DR in patients with DME:** *RISE*—Phase III, multicenter, 3-year, sham injection–controlled study; primary end point at 2 years. *RIDE*—Phase III, long-term, 3-year, sham injection–controlled study; primary end point at 2 years. **mCNV:** *RADIANCE*—Phase III, multicenter, 1-year, active treatment–controlled study; key clinical outcomes at month 3.[1-9]

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# LUCENTIS®
## RANIBIZUMAB INJECTION

**Brief summary–please see the LUCENTIS® package insert for full prescribing information.**

## 1 INDICATIONS AND USAGE
LUCENTIS is indicated for the treatment of patients with:

**1.1** Neovascular (Wet) Age-Related Macular Degeneration (AMD)

**1.2** Macular Edema Following Retinal Vein Occlusion (RVO)

**1.3** Diabetic Macular Edema (DME)

**1.4** Diabetic Retinopathy (Non Proliferative Diabetic Retinopathy (NPDR), Proliferative Diabetic Retinopathy (PDR)) in patients with Diabetic Macular Edema (DME)

**1.5** Myopic Choroidal Neovascularization (mCNV)

## 4 CONTRAINDICATIONS

### 4.1 Ocular or Periocular Infections
LUCENTIS is contraindicated in patients with ocular or periocular infections.

### 4.2 Hypersensitivity
LUCENTIS is contraindicated in patients with known hypersensitivity to ranibizumab or any of the excipients in LUCENTIS. Hypersensitivity reactions may manifest as severe intraocular inflammation.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Endophthalmitis and Retinal Detachments
Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique should always be used when administering LUCENTIS. In addition, patients should be monitored following the injection to permit early treatment should an infection occur *[see Dosage and Administration (2.7, 2.8) in the full prescribing information and Patient Counseling Information (17)]*.

### 5.2 Increases in Intraocular Pressure
Increases in intraocular pressure have been noted both pre-injection and post-injection (at 60 minutes) while being treated with LUCENTIS. Monitor intraocular pressure prior to and following intravitreal injection with LUCENTIS and manage appropriately *[see Dosage and Administration (2.8 in the full prescribing information)]*.

### 5.3 Thromboembolic Events
Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).

*Neovascular (Wet) Age-Related Macular Degeneration*
The ATE rate in the three controlled neovascular AMD studies (AMD-1, AMD-2, AMD-3) during the first year was 1.9% (17 of 874) in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS compared with 1.1% (5 of 441) in patients from the control arms *[see Clinical Studies (14.1 in the full prescribing information)]*. In the second year of Studies AMD-1 and AMD-2, the ATE rate was 2.6% (19 of 721) in the combined group of LUCENTIS-treated patients compared with 2.9% (10 of 344) in patients from the control arms. In Study AMD-4, the ATE rates observed in the 0.5 mg arms during the first and second year were similar to rates observed in Studies AMD-1, AMD-2, and AMD-3.

In a pooled analysis of 2-year controlled studies (AMD-1, AMD-2, and a study of LUCENTIS used adjunctively with verteporfin photodynamic therapy), the stroke rate (including both ischemic and hemorrhagic stroke) was 2.7% (13 of 484) in patients treated with 0.5 mg LUCENTIS compared to 1.1% (5 of 435) in patients in the control arms (odds ratio 2.2 (95% confidence interval (0.8-7.1))).

*Macular Edema Following Retinal Vein Occlusion*
The ATE rate in the two controlled RVO studies during the first 6 months was 0.8% in both the LUCENTIS and control arms of the studies (4 of 525 in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS and 2 of 260 in the control arms) *[see Clinical Studies (14.2 in the full prescribing information)]*. The stroke rate was 0.2% (1 of 525) in the combined group of LUCENTIS-treated patients compared to 0.4% (1 of 260) in the control arms.

*Diabetic Macular Edema and Diabetic Retinopathy*
Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline *[see Clinical Studies (14.3, 14.4 in the full prescribing information)]*.

In a pooled analysis of Studies D-1 and D-2 *[see Clinical Studies (14.3 in the full prescribing information)]*, the ATE rate at 2 years was 7.2% (18 of 250) with 0.5 mg LUCENTIS, 5.6% (14 of 250) with 0.3 mg LUCENTIS, and 5.2% (13 of 250) with control. The stroke rate at 2 years was 3.2% (8 of 250) with 0.5 mg LUCENTIS, 1.2% (3 of 250) with 0.3 mg LUCENTIS, and 1.6% (4 of 250) with control. At 3 years, the ATE rate was 10.4% (26 of 249) with 0.5 mg LUCENTIS and 10.8% (27 of 250) with 0.3 mg LUCENTIS; the stroke rate was 4.8% (12 of 249) with 0.5 mg LUCENTIS and 2.0% (5 of 250) with 0.3 mg LUCENTIS.

### 5.4 Fatal Events in Patients with DME and DR at baseline
*Diabetic Macular Edema and Diabetic Retinopathy*
Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline *[see Clinical Studies (14.3, 14.4 in the full prescribing information)]*.

A pooled analysis of Studies D-1 and D-2 *[see Clinical Studies (14.3 in the full prescribing information)]*, showed that fatalities in the first 2 years occurred in 4.4% (11 of 250) of patients treated with 0.5 mg LUCENTIS, in 2.8% (7 of 250) of patients treated with 0.3 mg LUCENTIS, and in 1.2% (3 of 250) of control patients. Over 3 years, fatalities occurred in 6.4% (16 of 249) of patients treated with 0.5 mg LUCENTIS and in 4.4% (11 of 250) of patients treated with 0.3 mg LUCENTIS. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded.

## 6 ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the label:
- Endophthalmitis and Retinal Detachments *[see Warnings and Precautions (5.1)]*
- Increases in Intraocular Pressure *[see Warnings and Precautions (5.2)]*
- Thromboembolic Events *[see Warnings and Precautions (5.3)]*
- Fatal Events in patients with DME and DR at baseline *[see Warnings and Precautions (5.4)]*

### 6.1 Injection Procedure
Serious adverse reactions related to the injection procedure have occurred in < 0.1% of intravitreal injections, including endophthalmitis *[see Warnings and Precautions (5.1)]*, rhegmatogenous retinal detachment, and iatrogenic traumatic cataract.

### 6.2 Clinical Studies Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in one clinical trial of a drug cannot be directly compared with rates in the clinical trials of the same or another drug and may not reflect the rates observed in practice.

The data below reflect exposure to 0.5 mg LUCENTIS in 440 patients with neovascular AMD in Studies AMD-1, AMD-2, and AMD-3; in 259 patients with macular edema following RVO. The data also reflect exposure to 0.3 mg LUCENTIS in 250 patients with DME and DR at baseline *[see Clinical Studies (14 in the full prescribing information)]*.

Safety data observed in Study AMD-4 and in 224 patients with mCNV were consistent with these results. On average, the rates and types of adverse reactions in patients were not significantly affected by dosing regimen.

*Ocular Reactions*
Table 1 shows frequently reported ocular adverse reactions in LUCENTIS-treated patients compared with the control group.

**Table 1** Ocular Reactions in the DME and DR, AMD, and RVO Studies

| | DME and DR 2-year | | AMD 2-year | | AMD 1-year | | RVO 6-month | |
|---|---|---|---|---|---|---|---|---|
| | LUCENTIS 0.3 mg | Control | LUCENTIS 0.5 mg | Control | LUCENTIS 0.5 mg | Control | LUCENTIS 0.5 mg | Control |
| Adverse Reaction | n=250 | n=250 | n=379 | n=379 | n=440 | n=441 | n=259 | n=260 |
| Conjunctival hemorrhage | 47% | 32% | 74% | 60% | 64% | 50% | 48% | 37% |
| Eye pain | 17% | 13% | 35% | 30% | 26% | 20% | 17% | 12% |
| Vitreous floaters | 10% | 4% | 27% | 8% | 19% | 5% | 7% | 2% |
| Intraocular pressure increased | 18% | 7% | 24% | 7% | 17% | 5% | 7% | 2% |
| Vitreous detachment | 11% | 15% | 21% | 19% | 15% | 15% | 4% | 2% |
| Intraocular inflammation | 4% | 3% | 18% | 8% | 13% | 7% | 1% | 3% |
| Cataract | 28% | 32% | 17% | 14% | 11% | 9% | 2% | 2% |
| Foreign body sensation in eyes | 10% | 5% | 16% | 14% | 13% | 10% | 7% | 5% |
| Eye irritation | 8% | 5% | 15% | 15% | 13% | 12% | 7% | 6% |
| Lacrimation increased | 5% | 4% | 14% | 12% | 8% | 8% | 2% | 3% |
| Blepharitis | 3% | 2% | 12% | 8% | 8% | 5% | 0% | 1% |
| Dry eye | 5% | 3% | 12% | 7% | 7% | 7% | 3% | 3% |
| Visual disturbance or vision blurred | 8% | 4% | 18% | 15% | 13% | 10% | 5% | 3% |
| Eye pruritus | 4% | 4% | 12% | 11% | 9% | 7% | 1% | 2% |
| Ocular hyperemia | 9% | 9% | 11% | 8% | 7% | 4% | 5% | 3% |
| Retinal disorder | 2% | 2% | 10% | 7% | 8% | 4% | 2% | 1% |
| Maculopathy | 5% | 7% | 9% | 9% | 6% | 6% | 11% | 7% |
| Retinal degeneration | 1% | 0% | 8% | 6% | 5% | 3% | 1% | 0% |
| Ocular discomfort | 2% | 1% | 7% | 4% | 5% | 2% | 2% | 2% |
| Conjunctival hyperemia | 1% | 2% | 7% | 6% | 5% | 4% | 0% | 0% |
| Posterior capsule opacification | 4% | 3% | 7% | 4% | 2% | 2% | 0% | 1% |
| Injection site hemorrhage | 1% | 0% | 5% | 2% | 3% | 1% | 0% | 0% |

*Non-Ocular Reactions*
Non-ocular adverse reactions with an incidence of ≥ 5% in patients receiving LUCENTIS for DR, DME, AMD, and/or RVO and which occurred at a ≥ 1% higher frequency in patients treated with LUCENTIS compared to control are shown in Table 2. Though less common, wound healing complications were also observed in some studies.

**Table 2** Non-Ocular Reactions in the DME and DR, AMD, and RVO Studies

| | DME and DR 2-year | | AMD 2-year | | AMD 1-year | | RVO 6-month | |
|---|---|---|---|---|---|---|---|---|
| | LUCENTIS 0.3 mg | Control | LUCENTIS 0.5 mg | Control | LUCENTIS 0.5 mg | Control | LUCENTIS 0.5 mg | Control |
| Adverse Reaction | n=250 | n=250 | n=379 | n=379 | n=440 | n=441 | n=259 | n=260 |
| Nasopharyngitis | 12% | 6% | 16% | 13% | 8% | 9% | 5% | 4% |
| Anemia | 11% | 10% | 8% | 7% | 4% | 3% | 1% | 1% |
| Nausea | 10% | 9% | 9% | 6% | 5% | 5% | 1% | 2% |
| Cough | 9% | 4% | 9% | 8% | 5% | 4% | 1% | 2% |
| Constipation | 8% | 4% | 5% | 7% | 3% | 4% | 0% | 1% |
| Seasonal allergy | 8% | 4% | 4% | 4% | 2% | 2% | 0% | 2% |
| Hypercholesterolemia | 7% | 5% | 5% | 5% | 3% | 2% | 1% | 1% |
| Influenza | 7% | 3% | 7% | 5% | 3% | 2% | 3% | 2% |
| Renal failure | 7% | 6% | 1% | 1% | 0% | 0% | 0% | 0% |
| Upper respiratory tract infection | 7% | 7% | 9% | 8% | 5% | 5% | 2% | 2% |
| Gastroesophageal reflux disease | 6% | 4% | 4% | 6% | 3% | 4% | 1% | 0% |
| Headache | 6% | 8% | 12% | 9% | 6% | 5% | 3% | 3% |
| Edema peripheral | 6% | 4% | 3% | 5% | 2% | 3% | 0% | 1% |
| Renal failure chronic | 6% | 2% | 0% | 1% | 0% | 0% | 0% | 0% |
| Neuropathy peripheral | 5% | 3% | 1% | 1% | 1% | 0% | 0% | 0% |
| Sinusitis | 5% | 8% | 8% | 7% | 5% | 5% | 3% | 2% |
| Bronchitis | 4% | 4% | 11% | 9% | 6% | 5% | 0% | 2% |
| Atrial fibrillation | 3% | 3% | 5% | 4% | 2% | 2% | 1% | 0% |
| Arthralgia | 3% | 3% | 11% | 9% | 5% | 5% | 2% | 1% |
| Chronic obstructive pulmonary disease | 1% | 1% | 6% | 3% | 3% | 1% | 0% | 0% |
| Wound healing complications | 1% | 0% | 1% | 1% | 1% | 0% | 0% | 0% |

### 6.3 Immunogenicity
As with all therapeutic proteins, there is the potential for an immune response in patients treated with LUCENTIS. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to LUCENTIS in immunoassays and are highly dependent on the sensitivity and specificity of the assays.

The pre-treatment incidence of immunoreactivity to LUCENTIS was 0%-5% across treatment groups. After monthly dosing with LUCENTIS for 6 to 24 months, antibodies to LUCENTIS were detected in approximately 1%-9% of patients.

The clinical significance of immunoreactivity to LUCENTIS is unclear at this time. Among neovascular AMD patients with the highest levels of immunoreactivity, some were noted to have iritis or vitritis. Intraocular inflammation was not observed in patients with DME and DR at baseline, or RVO patients with the highest levels of immunoreactivity.

### 6.4 Postmarketing Experience
The following adverse reaction has been identified during post-approval use of LUCENTIS. Because this reaction was reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.
- Ocular: Tear of retinal pigment epithelium among patients with neovascular AMD

## 7 DRUG INTERACTIONS
Drug interaction studies have not been conducted with LUCENTIS.

LUCENTIS intravitreal injection has been used adjunctively with verteporfin photodynamic therapy (PDT). Twelve (12) of 105 (11%) patients with neovascular AMD developed serious intraocular inflammation; in 10 of the 12 patients, this occurred when LUCENTIS was administered 7 days (± 2 days) after verteporfin PDT.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy
Risk Summary
There are no adequate and well-controlled studies of LUCENTIS administration in pregnant women.

Administration of ranibizumab to pregnant monkeys throughout the period of organogenesis resulted in a low incidence of skeletal abnormalities at intravitreal doses 13-times the predicted human exposure (based on maximal serum trough levels [$C_{max}$]) after a single eye treatment at the recommended clinical dose. No skeletal abnormalities were observed at serum trough levels equivalent to the predicted human exposure after a single eye treatment at the recommended clinical dose *[see Animal Data]*.

Animal reproduction studies are not always predictive of human response, and it is not known whether ranibizumab can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for ranibizumab *[see Clinical Pharmacology (12.1 in the full prescribing information)]*, treatment with LUCENTIS may pose a risk to human embryofetal development.

LUCENTIS should be given to a pregnant woman only if clearly needed.

Data
*Animal Data*
An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received intravitreal injections of ranibizumab every 14 days starting on Day 20 of gestation, until Day 62 at doses of 0, 0.125, and 1 mg/eye. Skeletal abnormalities including incomplete and/or irregular ossification of bones in the skull, vertebral column, and hindlimbs and shortened supernumerary ribs were seen at a low incidence in fetuses from animals treated with 1 mg/eye of ranibizumab. The 1 mg/eye dose resulted in trough serum ranibizumab levels up to 13 times higher than predicted $C_{max}$ levels with single eye treatment in humans. No skeletal abnormalities were seen at the lower dose of 0.125 mg/eye, a dose which resulted in trough exposures equivalent to single eye treatment in humans. No effect on the weight or structure of the placenta, maternal toxicity, or embryotoxicity was observed.

### 8.2 Lactation
Risk Summary
There are no data available on the presence of ranibizumab in human milk, the effects of ranibizumab on the breastfed infant or the effects of ranibizumab on milk production/excretion.

Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, caution should be exercised when LUCENTIS is administered to a nursing woman.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LUCENTIS and any potential adverse effects on the breastfed child from ranibizumab.

### 8.3 Females and Males of Reproductive Potential
Infertility
No studies on the effects of ranibizumab on fertility have been conducted. and it is not known whether ranibizumab can affect reproduction capacity. Based on the anti-VEGF mechanism of action for ranibizumab, treatment with LUCENTIS may pose a risk to reproductive capacity.

### 8.4 Pediatric Use
The safety and effectiveness of LUCENTIS in pediatric patients have not been established.

### 8.5 Geriatric Use
In the clinical studies, approximately 76% (2449 of 3227) of patients randomized to treatment with LUCENTIS were ≥ 65 years of age and approximately 51% (1644 of 3227) were ≥ 75 years of age *[see Clinical Studies (14 in the full prescribing information)]*. No notable differences in efficacy or safety were seen with increasing age in these studies. Age did not have a significant effect on systemic exposure.

## 10 OVERDOSAGE
More concentrated doses as high as 2 mg ranibizumab in 0.05 mL have been administered to patients. No additional unexpected adverse reactions were seen.

## 17 PATIENT COUNSELING INFORMATION
Advise patients that in the days following LUCENTIS administration, patients are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise the patient to seek immediate care from an ophthalmologist *[see Warnings and Precautions (5.1)]*.

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Initial US Approval: June 2006
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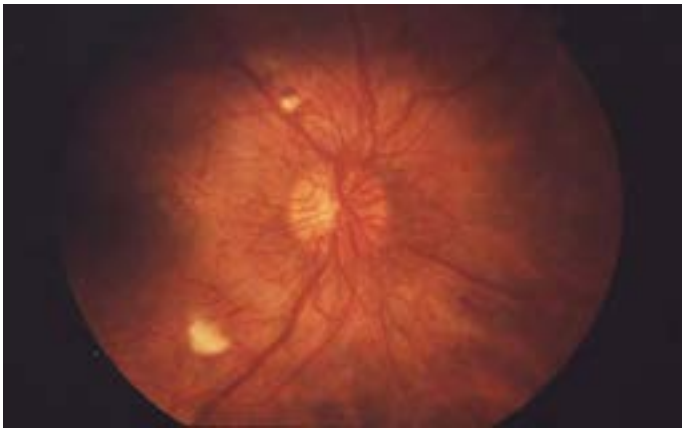

Photo courtesy of the Wills Eye Manual

Figure 3 proliferative diabetic retinopathy

to remove vitreous hemorrhages and delaminate the tractional tissue from the retinal surface. Improvements in vitreoretinal surgery, including small-gauge incisions, improving viewing systems and enhancements to microsurgical instruments, have allowed retina surgeons to achieve superior outcomes.

While specialists who care for retinal diseases have a variety of treatment options to address diabetic retinopathy, prevention remains crucial. Early detection is essential to reducing the devastating consequences that can occur. Estimates suggest that a routine comprehensive dilated eye exam at least once a year can reduce the risk of eye disease by 54 percent to 76 percent and lead to the early detection of eye disease.

Of paramount importance in the treatment of diabetic retinopathy is the optimization of hyperglycemia. According to The Diabetes Control and Complications Trial, controlling diabetes and maintaining the HbA1c level in the 6 percent to 7 percent range can delay the onset or substantially reduce the progression of diabetic retinopathy. Additional risk factors for progression of diabetic retinopathy include male sex, longer duration of diabetes, insulin use and higher systolic blood pressure as well as African-American or Hispanic ethnicity.

As the number of patients with diabetes escalates, all physicians taking care of diabetic patients will be faced with the challenge of managing this chronic disease. With early detection, systemic control and retinal therapeutics, ophthalmologists who focus on retinal care are prepared to handle the fight against diabetic retinopathy. ■

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# GLAUCOMA

INCREASINGLY COMMON AS THE POPULATION AGES BUT TREATMENT HAS NEVER BETTER!

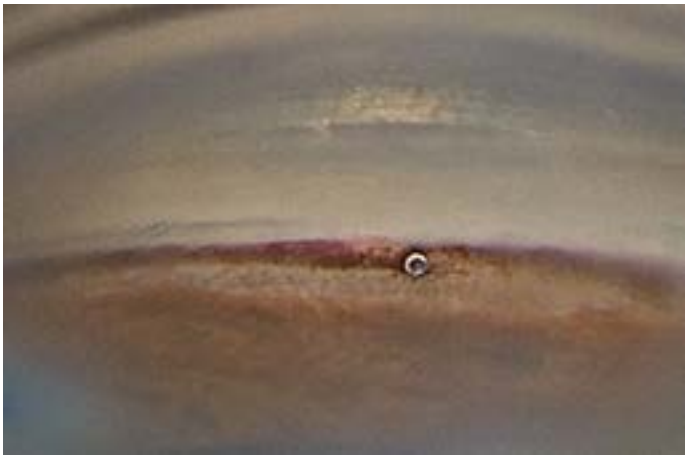
By Elma Chang, M.D. and Reay Brown, M.D.

Three million people in the U.S have glaucoma – an asymptomatic, blinding eye disease. At least 1 million of these victims don't even know they have it, which is why glaucoma is called the "Thief in the Night." Detecting glaucoma is one of the main reasons we recommend an eye exam every 1 or 2 years, even for people who feel like they are seeing very well.

The fluid inside the eye has a natural circulation designed to achieve a normal internal pressure. Normal pressure should be defined as any pressure that does not cause optic nerve damage with a corresponding visual field defect. Using this argument, the previously accepted thought that a patient cannot have glaucoma if the eye pressure is below 21 is false. In the same way, if a patient has an eye pressure above 21 but no coexisting optic nerve damage, the patient is diagnosed with ocular hypertension and not glaucoma.

In a patient where it has been established that the optic nerve has thinning that corresponds with a visual field loss, visual fields are obtained on an annual basis. Peripheral vision is slowly – and imperceptibly – lost. If undetected and untreated, the eye may become totally blind. Since glaucoma is usually bilateral, patients too often present with blindness in one eye and advanced visual loss in the other. However, this progressive damage can be slowed or stopped completely by treatments that reduce the eye pressure to a normal level.

Fortunately, we have many excellent treatments for glaucoma. Eye drops are usually the first line of treatment. These lower pressure by enhancing outflow and reducing the fluid production. The next step is laser treatment – a very safe and effective option that is performed in the office and only takes a few minutes.



(Image1) Stent in canal: The iStent is a right-angled tube that is implanted into Schlemm's canal. [see round silver lumen revealed in this magnified gonioscopic view of the anterior chamber angle.] The open end of the stent is pointing into the anterior chamber and the longer portion is running along the canal. The stent lowers intraocular pressure by opening the drainage canal so that aqueous can bypass the resistance in the trabecular meshwork and follow a direct path to the distal outflow channels.

Cataract surgery has been found to be a very effective intervention for lowering eye pressure even though its main goal is to improve vision. We also have several devices (iStent, CyPass, and Xen implants) that we can place at the time of cataract surgery, and these have been breakthroughs in glaucoma treatment. Patients who need further pressure lowering will receive a trabeculectomy or a tube-shunt.

## Medications – Both Now and the Future

Eye drops that decrease fluid production are beta-blockers (timolol maleate, Betimol, Timoptic), adrenergic agonists (brimonidine, Alphagan) or topical and oral carbonic anhydrase inhibitors (dorzolamide, Azopt, acetazolamide, Diamox). Medicines that promote outflow are cholinergic agonists (Pilocarpine), adrenergic agonists and prostaglandin analogs (latanoprost, Lumigan, Travatan, and Xalatan).

Rhopressa is a newer topical medication that is awaiting final FDA approval and will be available soon. It acts via rhokinase inhibition. This has been found to increase both aqueous outflow through the trabecular meshwork and reduce episcleral venous pressure.

## Newer Delivery Systems

Eye drops require that patients use them once or twice daily. Compliance has been a major obstacle in treating glaucoma patients. Studies have shown that as many as 80 percent of patients forget to take their eye drops. Sustained drug delivery devices may be one key to improving compliance.

One device is a ring that is placed under the upper and lower lids. Another device is placed in the tear punctum in the lower lid. These devices are in studies and have shown good results in reducing intraocular pressure (IOP) for up to 6 months.

Other studies have examined the use of particulate drug delivery systems or injectable formulations such as microspheres, liposomes and nanospheres/nanoparticles. This involves trapping the drug in the nanocarrier matrix and releasing the bioactive agent in a controlled fashion after administration.

It is impossible to know which of these technologies will emerge as the best option, but it is clear that longer duration treatments are a critical unmet need. We will continue to see rapid improvement in these technologies.

## Laser Surgery

Laser surgery has traditionally been used as an intermediate step between topical therapy and incisional surgery. Laser therapy can increase outflow of fluid through the trabecular meshwork (laser trabeculoplasty) or decrease aqueous production from the ciliary body (diode laser

cyclophotocoagulation). Laser trabeculoplasty can easily be performed in the office setting.

The Micropulse laser is a newer laser technology that seeks to improve the safety of the traditional diode cyclophotocoagulation while preserving the pressure-lowering.

### Cataract Surgery with MIGS

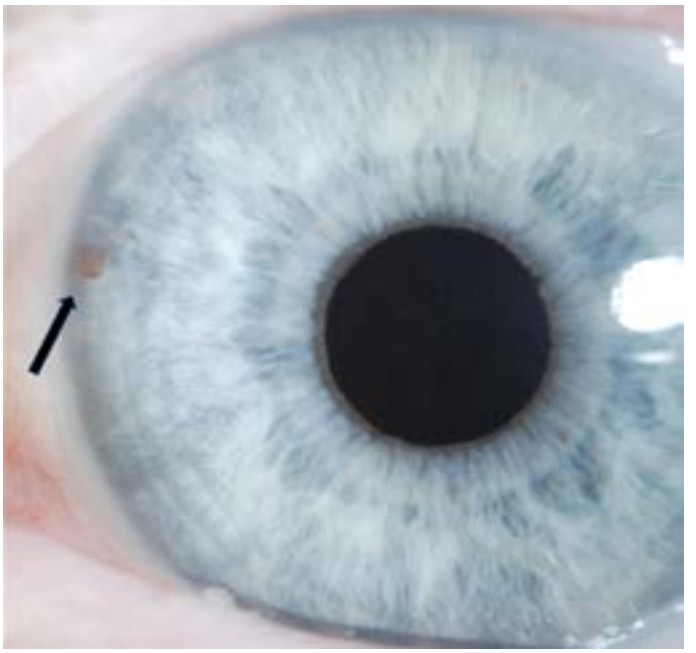
One of the major recent advances in glaucoma treatment has been the discovery that cataract surgery lowers pressure and that the magnitude of pressure reduction was proportional to the pre-op intraocular pressure. In other words, cataract surgery is also a glaucoma operation that lowers pressure best in patients who need it the most.

There are 3.5 million cataract operations each year in the U.S., and studies show that as many as 20 percent of these patients have a concurrent diagnosis of glaucoma. So, this is all very good news for glaucoma patients.

Cataract and glaucoma are also linked because the two new devices that have been approved for glaucoma treatment – the iStent and CyPass – are restricted for use only at the time of cataract surgery. They can be used "off-label" as stand-alone procedures, but insurance coverage is more uncertain.

The iStent (Image 1) and CyPass (Image 2) are the first devices in the category of micro-incisional glaucoma surgery or MIGS. MIGS is a revolution in glaucoma treatment. MIGS approaches are much safer than conventional glaucoma surgery.

One of the key differences between MIGS and traditional glaucoma surgeries is the approach to the eye's outflow system. Specifically, an ab interno approach is used in MIGS where the surgeon is able to access the trabecular meshwork (iStent) or suprachoroidal space (CyPass) via a corneal incision. Previously, the outflow system was approached via an ab externo approach, which meant that the outflow system was accessible only after resecting back conjuntival and scleral tissues.



(Image 2) The CyPass microstent is seen at the left edge of the iris-scleral junction. [see bold arrow] The CyPass lowers intraocular pressure by enhancing drainage of aqueous into the supraciliary space.


There are many new approaches in the MIGS category. These include the ability to thread a catheter in the space behind the trabecular meshwork (canaloplasty) and then pull the catheter through the meshwork and creating an opening in the trabecular meshwork (goniotomy). A similar goniotomy effect can be achieved with several new technologies – the Trabectome, the Kahook blade and the Trab360 device.

### Incisional Surgeries – Now and What's on the Horizon

In some cases, treatment with eye drops, laser, cataract surgery and MIGS may not be enough to halt glaucoma damage. The next step is a trabeculectomy or a tube implant. These procedures create a pathway – essentially a hole – from inside the eye to a bleb (a fluid-filled bump) on the ocular surface. This can achieve profound pressure reduction but has a greater risk of infection, IOP being too low for clear vision, double vision and failure.

Finally, the newest device to achieve FDA approval is the Xen gel implant. This device is also implanted ab interno via a corneal incision. It is a newer and less invasive way to perform the trabeculectomy. The goal is to implant a gel-like Xen material in the subconjunctival space. The implant itself maintains a passageway between the anterior chamber and the subconjunctival space. The hope is that this will be safer than a traditional trabeculectomy but just as effective in lowering IOP.

The pace of innovation in glaucoma treatment is accelerating – both for topical therapy and for surgery. Most glaucoma surgeons still perform traditional glaucoma surgeries (trabeculectomies and tube implantations), but the acceptance of MIGS devices and technology is growing.

Our practice has been involved with some of the research that led to the development of the iStent and with the studies that led to the approval of the CyPass. We believe that MIGS is fundamentally changing the glaucoma treatment paradigm with surgical approaches becoming more common.

But these innovations are just the beginning. We have never had so many outstanding options for treating glaucoma and tailoring the approach to each patient. No one should ever become blind from glaucoma. ■

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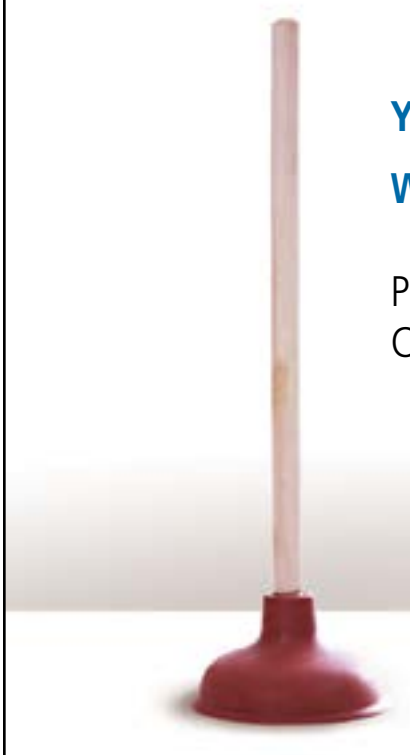

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INNOVATIONS IN REFRACTIVE SURGERY

# LASIK, PRK AND BEYOND

By Samir Vira, M.D.

Refractive surgery gives individuals the opportunity to reduce their dependency on glasses or contact lenses. With the advent of new technologies over the last 10 to 15 years, refractive surgery has become increasingly popular for our patients.

For the majority of young patients, there are two primary types of refractive surgeries through laser vision correction – LASIK and PRK.

**The field of refractive surgery continues to grow beyond the initial bounds of laser vision correction seen with LASIK and PRK.**

LASIK – laser-assisted in situ keratomileusis – is the most commonly performed refractive surgery with more than 700,000 procedures done in 2014 by surgeons in the United States. During LASIK, a thin flap is initially created in the cornea, then the underlying corneal bed is reshaped with an excimer laser based on the patient's prescription, or refractive error.

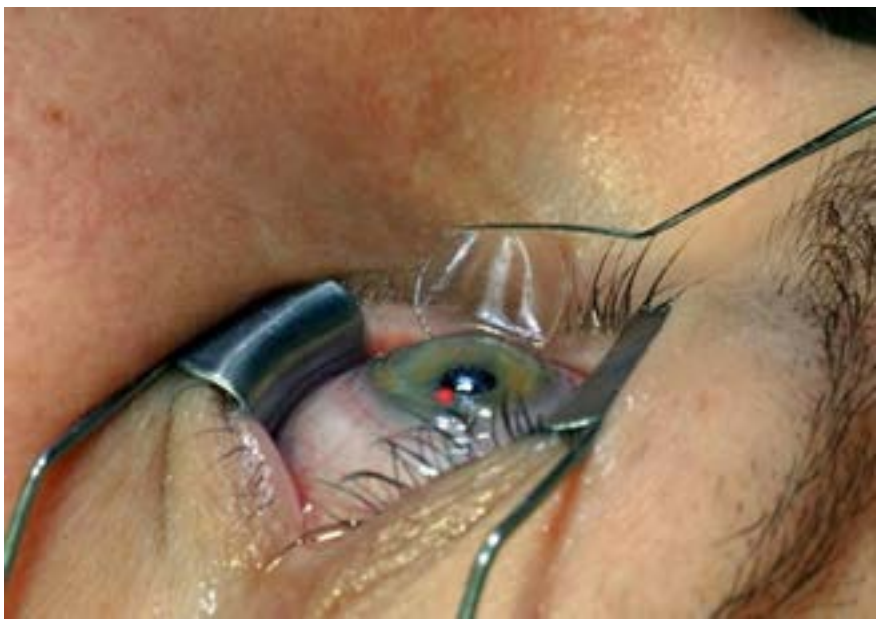

Image 1 - LASIK Flap created by Femtosecond Laser

For years, the flap was created using a microkeratome blade. However, with the introduction of a femtosecond laser for flap creation, most surgeons are now only performing "bladeless" LASIK (Image 1). Once the treatment has been completed with the excimer laser, the flap is placed back into its original position.

PRK – photorefractive keratectomy – is an alternative procedure and actually the predecessor to LASIK. As opposed to the creation of a flap, the corneal epithelium is denuded. The same excimer laser is then used to reshape the cornea. After this, a contact lens is placed on the eye as a bandage to allow the corneal surface to re-epithelialize over 3 to 5 days.

Either procedure takes about 15 minutes to perform. While most patients choose LASIK due to the faster visual recovery, some are not suitable candidates for LASIK due to thin corneas or irregular corneal shapes that is determined with testing during the initial consultation; those patients subsequently undergo PRK.

Final visual outcomes with LASIK and PRK are very comparable based on long-term studies. Patient satisfaction after LASIK worldwide is more than 95 percent.

In some instances, such as patients with high myopia or extremely thin corneas, patients are not candidates for either LASIK or PRK. For these individuals, phakic intraocular lenses (IOLs) are a safer alternative. These implantable lenses are placed within the eye and are typically performed in the operating room.

There are currently two FDA-approved phakic IOLs in the United States – Verisyse (rigid plastic PMMA) and Visian ICL (implantable collamer lens, a foldable collagen copolymer lens). These are both approved for use in patients with moderate to severe myopia of up to –20 diopters.

**LASIK – laser-assisted in situ keratomileusis – is the most commonly performed refractive surgery with more than 700,000 procedures done in 2014 by surgeons in the United States.**

Verisyse is an iris-fixated implant, while the Visian ICL is a posterior chamber implant placed between the iris and the eye's natural lens. While phakic IOLs are more invasive, the procedure can produce excellent results with the distinct advantage of not removing any corneal tissue. Additionally, these implants are reversible and thus can be removed at any time.

While LASIK and PRK may make the most sense for patients with myopia and mild hyperopia, newer refractive surgical approaches have been developed for patients with presbyopia. Presbyopia is caused by loss of elasticity of the lens of the eye, whereby an individual loses the ability to see objects up close. This natural aging phenomenon typically starts in the mid-40s and occurs due to hardening and progressive inflexibility of the natural lens. For presbyopic patients, LASIK or PRK can be combined with monovision, whereby the patient uses the one dominant eye for distance targets and the other non-dominant eye for near targets.

Recently, corneal inlays have been developed for presbyopia. Approved by the FDA in 2015, the AcuFocus Kamra inlay is an implant placed under a corneal flap in the non-dominant eye. A corneal pocket is created by the same femtosecond laser used for LASIK. Unlike LASIK, no tissue is ablated.

The Kamra inlay uses a small aperture or opening to create the pinhole concept and allow patients to have increased depth of focus. This enables the patient to not only see objects at a distance target but also at intermediate and near targets without the need for reading glasses.

In June 2016, FDA approved the Revision Optics Raindrop corneal inlay for presbyopia. This inlay is also an implant placed under a corneal femtosecond laser flap in the



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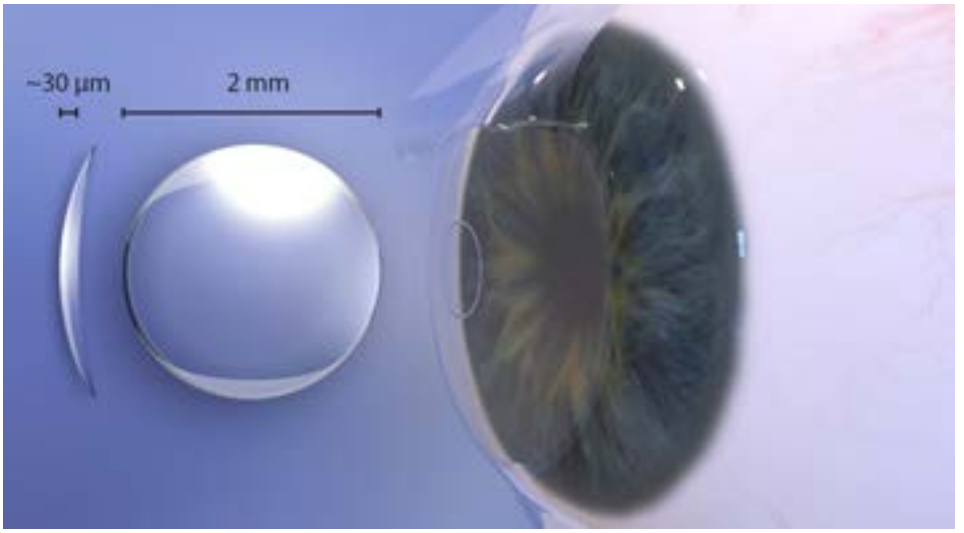


Image 2 - Raindrop Corneal Inlay for Presbyopia

non-dominant eye. Made of the same hydrogel material as a contact lens, the Raindrop inlay reshapes the central cornea to provide increased power for near vision (Image 2). Both the Kamra and Raindrop corneal inlays can be reversibly removed.

Refractive lens exchange (RLE), or clear lens exchange, is another surgical option for presbyopic patients. Presbyopic patients not only struggle with their ability to see objects up close but also complain about the quality of their vision. As the natural lens ages, it develops optical aberrations that degrade image quality. Patients may complain of glare and halos while driving at night or increasing difficulty with reading small print. With RLE, each eye's natural lens is removed and replaced with a lens implant. In essence, this procedure is done for an "immature cataract" and is very similar to cataract surgery.

RLE is not only a viable option for presbyopic patients but also for patients with moderate to severe hyperopia who are not candidates for LASIK, PRK or phakic IOLs. Several presbyopia-correcting lens implants, including accommodative and multifocal implants, have been developed over the last 10-15 years so that patients can see clearly with independence from glasses or contact lenses.

Accommodative implants (Bausch and Lomb Crystalens IOL) and multifocal implants (Alcon Restor IOL and Tecnis Multifocal IOL) provide good options for these patients. However, both categories of implants have their limitations. Accommodative implants do not provide adequate near vision for most individuals and still require the need for reading glasses. Multifocal implants usually provide good vision for intermediate and near tasks, such as working on the computer or reading a book; however, patients can rarely experience halos while driving, especially at night.

The newest presbyopic-correcting lens implant that received FDA approval in July 2016 is the Tecnis Symfony IOL. This implant, categorized as the only "Extended Depth of Focus" implant, provides a broad range of vision from distance to near for patients. Additionally, the Symfony implant has been engineered to correct spherical and chromatic aberrations of the eye.

By reducing these aberrations, the Symfony implant aims to improve the quality of a patient's vi-

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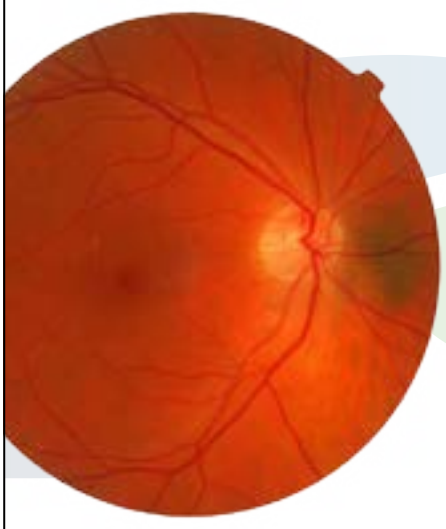

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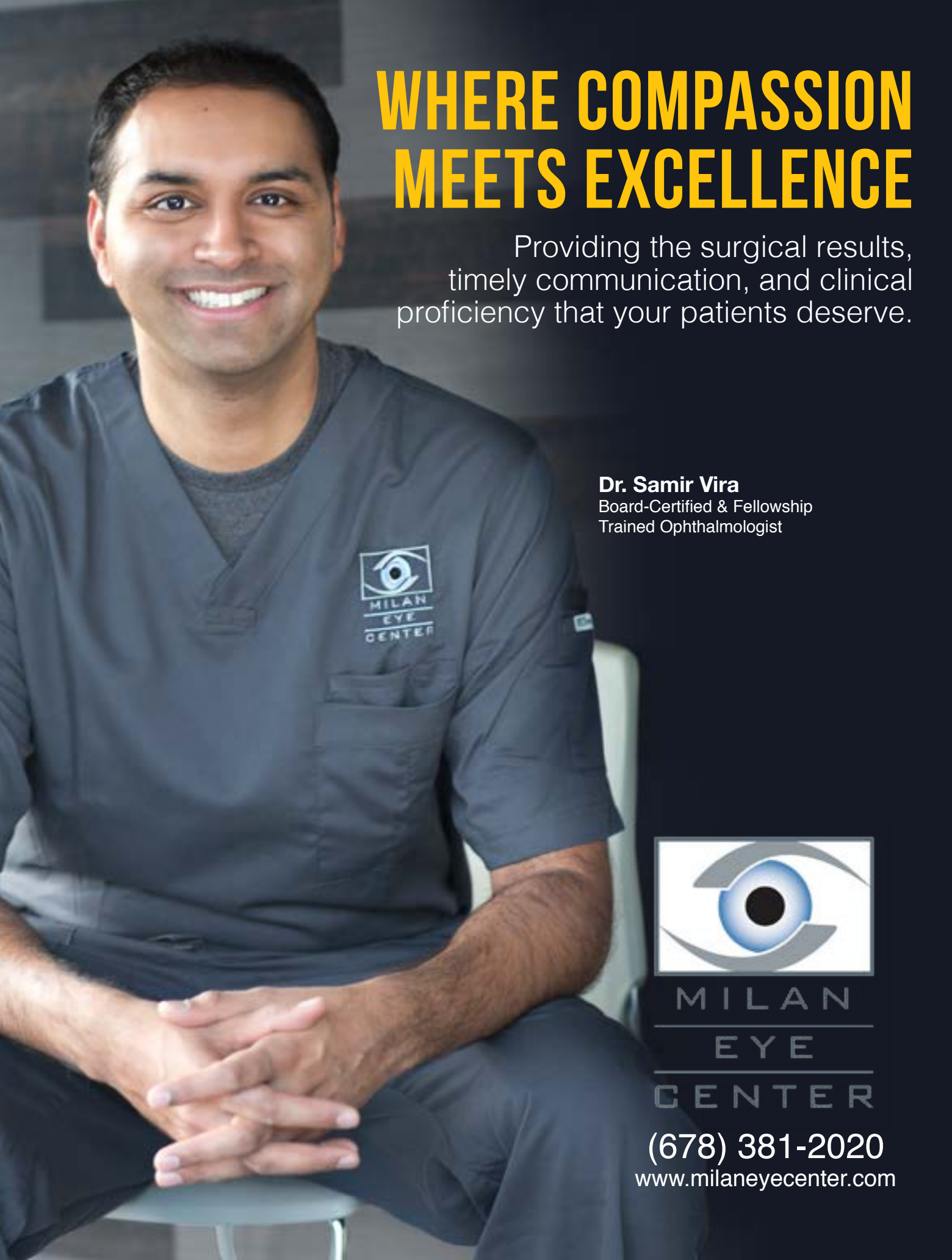


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**PRK – photorefractive keratectomy – is an alternative procedure and actually the predecessor to LASIK. As opposed to the creation of a flap, the corneal epithelium is denuded.**

sion. Furthermore, with a reduced incidence of glare and halos with this implant, patients are more likely to be satisfied with their visual outcomes. The Symfony implant is also available for astigmatic correction, unlike the previous multifocal implants, in the United States.

The field of refractive surgery continues to grow beyond the initial bounds of laser vision correction seen with LASIK and PRK. While these procedures continue to be the mainstay for young patients with myopia in their 20s and 30s, phakic IOLs, corneal inlays and refractive lens exchange are emerging techniques that should be considered for our patients.

Phakic IOLs are a great option for patients with high myopia who are not candidates for LASIK or PRK. Corneal inlays are proving to be viable for presbyopic patients in their 40s and early 50s. Refractive lens exchange, especially when done with multifocal IOLs or the newest extended-depth-of-focus IOL, is an excellent long-lasting solution for many patients, especially those with moderate to high hyperopia and presbyopia who are experiencing symptoms of a dysfunctional lens.

As these innovative refractive technologies continue to evolve and become safer, they will allow us to tailor solutions based on our patients' visual demands. ■

**Suggested Reading:**


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# CATARACT SURGERY ACROSS THE AGES

By Parul Khator, M.D., and Eugene Gabianelli, M.D.

India, 798 B.C.: After an early-morning hot spring bath and full-body oil massage, Reyansh lowered himself into a cross-legged sitting position on the mud floor. He faced the Ocularist and drew a cleansing breath.

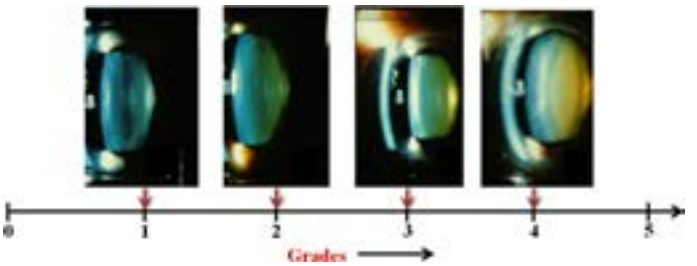
The blow came swiftly, rocking his head backwards. Flashing lights and a wave of nausea. The sharpened metal instrument had punctured his eye and pierced his lens, driving it back into the vitreous jelly.

He struggled to right himself as the assistant held his shoulders. Suddenly, another thrust and indescribable pain. The healer was yelling now.

Reyansh covered one nostril and blew with all his force, bile burning his throat. Bloody gel oozed through the puncture wound. The light was instantly brighter.

The word cataract derives from the ancient Greek word kataraktes, which translates to "I rush down," and subsequently the Latin word cataracta, meaning waterfall. During ancient times, a cataract was recognized only once it became opaque, converting the normal red reflex of the pupil to a bright white. These hypermature cataracts resembled the sheet of white water that is seen in a forceful waterfall.

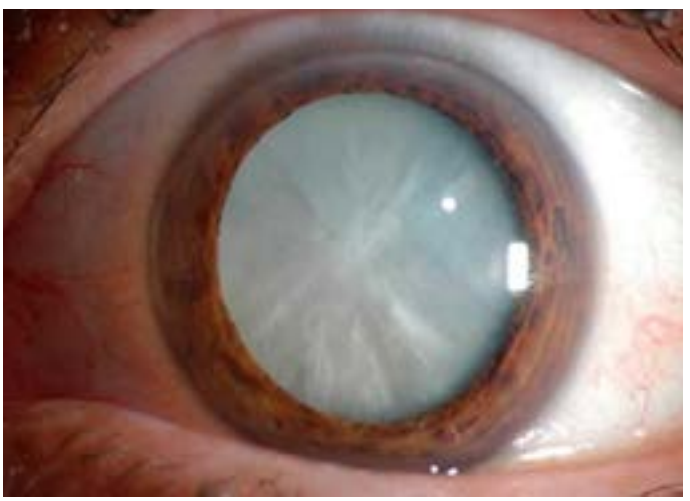
These days, we diagnose cataracts at a much earlier stage and recognize that they do not represent a disease of the eye, but rather a natural aging process. A cataract is formed as the lens of the eye, transparent when we are born, becomes dense and opacified with age.



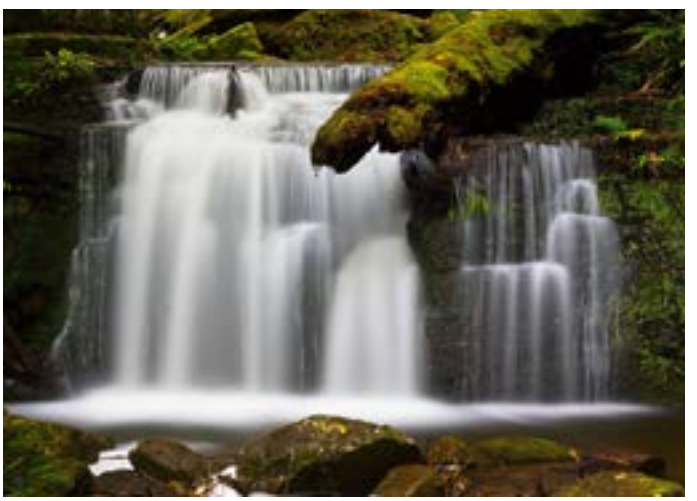

Today, we grade cataracts on a scale of zero to four, with the lens becoming increasingly opacified as one moves up the scale. An aging lens will also change colors, from green-yellow to bronze to white.

As the lens becomes more opaque, less and less light is able to enter the eye, causing diminished light perception, dulling of colors and blurry vision. As light hits the opaque lens it becomes diffracted, and this results in glare symptoms that a patient will particularly notice while driving at night.

As the No.1 cause of reversible vision loss worldwide, a great deal of time and effort has been spent on developing a



Hyper mature cataract



Cataracta - meaning is waterfall; fall.

safe, efficient and accurate surgical treatment. The evolution of cataract surgery is one of the most interesting stories in all of medicine, spanning centuries and consisting of dramatic innovations. The oldest documented example of a cataract can be seen in a small but famous statue from 2457-2467 B.C. that is now housed in the Egyptian Museum in Cairo.

The statue, made of wood, shows the figure of a priest reader. Careful examination of the eyes reveals a normal pupil in the right eye, but a purposefully crafted white reflex in the pupil of the left eye. Historians believe the subject of this art piece had a mature cataract in his left eye.

Artwork, including wall paintings and reliefs from Egypt around 1200 B.C., suggest Egyptians were performing eye surgery. The first well-documented evidence of cataract surgery lies in the Sanskrit document "Sushruta Samhita, Uttar Tantra," which describes "couching," one of the most ancient surgical techniques in the world.

Translated, this text reads much like a modern-day surgical guide, replete with preoperative, operative and postoperative care for the patient. Preoperatively, the patient was required to have an oily massage and a hot bath. The patient would then face the surgeon and the surgeon would insert a sharp needle into the patient's eye to push the lens repeatedly until it broke free of its attachments to the wall of the eye. The lens would fall to the back of the eye and out of the patient's visual axis, and the patient would notice an immediate brightening of vision, though a significant amount of clarity would not be restored.

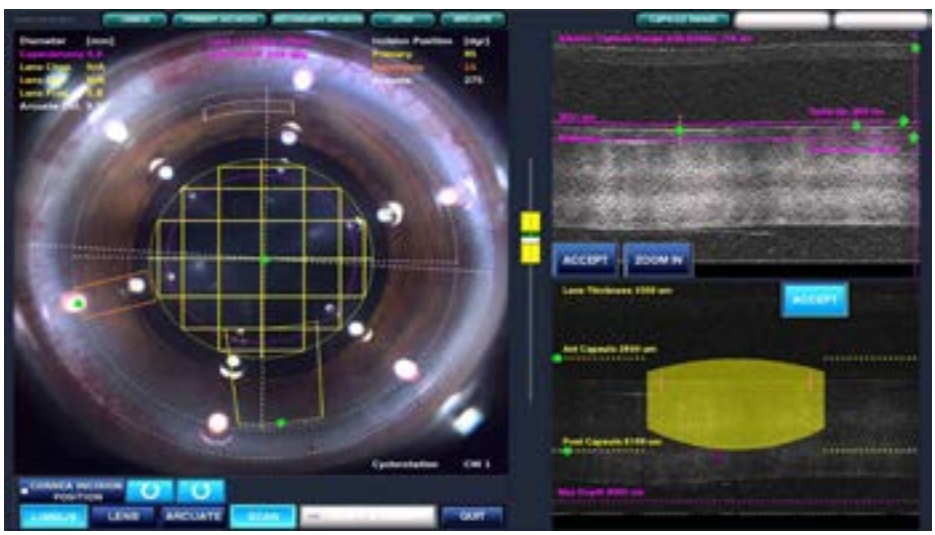
The patient would then cover one nostril and blow forcefully out of the other. This would cause any remaining lenticular tissue still in the visual axis to extravasate out of the eye through the needle track. Postoperatively, the eye was treated with roots, clarified butter and sometimes breast milk. The eye was then bandaged, and the patient was instructed to lie flat on his back for several days without moving. This technique was recommended only for severe cases as it would often result in blindness.

Couching became widespread throughout India and then travelled West via Greek travelers and East to China via the Silk Road; it was the primary method of cataract removal for centuries. It is still used in remote portions of Africa today.

Sometime around the 2nd century A.D., a technique called "cataract suction" arose. The procedure was detailed by a Persian physician in the 10th century. Cataract suction began with a large incision in the patient's eye. A hollow cylinder was placed into the cataract, and an assistant with "an extraordinary lung capacity" would suction the cataract out of the eye, often swallowing it.

As barbaric as couching and cataract suction seem today, they would often provide vision superior to the bare light perception of patients with mature cataracts. However, these techniques often blinded patients, especially if a large blood vessel was punctured during the procedure.

By the 1700s, patients were being operated on with more refined instruments in surgical theaters. "Mesmerism," or hypnosis, was the prime method of intraoperative pain control. Jaques Daviel, a French ophthalmologist, pioneered cataract removal through a large incision, rather than dis-




HD ophthalmic surgery series by JH Lee Web. 3 April 2017.

placement within the eye. His first case of removal was April 8, 1747. He happily reported a 50 percent success rate with his new procedure.

In the mid 1900s, cataracts were removed en toto, with a large incision followed by a cryoprobe pulling the lens from the eye. Enzymes were injected to soften the internal lens attachments prior to the cryoextraction. This was called intracapsular cataract removal because the cataract and the entire lens capsule complex was removed in one motion. Patients were left without a lens in the eye, necessitating strong "cataract glasses."

Following the "intracapsular" technique, in the late 1970s cataracts began to be removed with an "extracapsular" technique, which allowed the lens capsule to remain in position so it could support an intraocular lens implant made of plastic or glass. Cataract lens implants were the brainchild of Sir Thomas Ridley at Moorfield Eye Hospital in London. Ridley was frustrated by the need for "coke bottle glasses" in patients whose cataractous lenses had been removed. A medical student commented to him one day that a lens placed in the eye would be a great innovation.

Ridley observed pilots from the Royal Air Force of London returning from war with shards of Polymethyl Methacrylate (PMMA) in their eyes from windshield damage in their planes. He observed that PMMA caused no immune reaction in the eye, as long as it was not touching the iris. Thus, the era of intraocular lenses was born, and cataract results took another great leap forward.

In the late 1980s, ultrasound, also called phacoemulsification, became the standard way to remove a cataract. "Phaco" allowed for smaller incisions and quicker recovery and launched a generation of excellent cataract outcomes and tens of millions of satisfied cataract patients.

While risks of surgery continued to exist, for the most part this became routine surgery with very high postoperative satisfaction levels. By this point, anesthesia had progressed from general to a small injection below the eye to simply topical drops with light IV sedation.

As baby boomers enter the retirement years, demand for medical care of all types is rising. Cataract surgery is no exception. We are presented with a wave of active seniors not willing to accept decreased vision and who seek independence from corrective eyewear. Fortunately, advances in technology allow us to offer a modern suite of cataract surgery options to meet their desires.

LASIK (Laser-Assisted In Situ Keratomileusis) surgery in the United States began in 1995. The high level of success with LASIK became baked into the American conscious. As many of the same folks who had Lasik in the late 90s developed cataracts during the last 10 years, they brought along high expectations of glasses independence.

Technology kept pace with this demand with the advent of astigmatism-correcting intraocular lenses (IOLs) and presbyopia correcting IOLs, allowing for glasses-free near and distance vision. These extra options have remained uncovered by most insurance plans, however, thrusting cataract surgery into the elective surgery arena with self-pay options relating to glasses independence.

Within the last 5 years, femtosecond lasers have come into the mainstream as an alternate way of dissolving the cataract and making incisions in the eye. Further refinement of the Toric and Multifocal IOLs have propelled us to a higher level of post-cataract eyewear independence and a higher level of patient expectations. The excimer laser can now also be used in a LASIK-type approach to deliver glasses-free results in essentially all post-cataract patients who desire it.

Today, your patients, many of whom are active baby boomers, will encounter a cataract surgical menu not remotely resembling the cataract surgery of the past. Please encourage them to have a healthy discussion with their eye care providers, and keep in mind that cataract surgery in 2017 should help preserve the active lifestyles that your patients cherish. They will achieve this in a convenient outpatient setting, and these days any hot tub baths and full body oil massages are strictly optional. ■


Exceeding Expectations

# IMMUNOTHERAPY RESEARCH LEADS TO BETTER OUTCOMES FOR **LEUKEMIA** AND **BMT PATIENTS**

By Helen K. Kelley

For patients in need of a blood or bone marrow stem cell transplant, a program operating out of an Atlanta community hospital, rather than an academic medical center, is making a difference. Since 2009, the Blood and Marrow Transplant (BMT) Program at Northside Hospital has consistently been recognized for achieving among the best survival rates in the nation for bone marrow transplants and is one of the largest clinical transplant programs in the United States.

According to Leslie Kerns, Director of Northside's BMT Program, the recognition is based on annual data released by the Be the Match registry and the Center for International Blood and Marrow Transplant Research (CIBMTR) regarding outcomes for transplant programs across the country.

"The survey takes into account weighted risk factors to predict what a one-year survival rate should be after an allogeneic transplant based on patient characteristics," she explained. "For the last eight years, our patient outcomes are higher than those predicted and our program is ranked in the 'exceeds expectations' category."

One hundred and seventy-nine centers, virtually all of the accredited transplant centers in the nation, are surveyed to find out the characteristics of patients transplanted at each site. This data is used to predict expected one-year survival for each center. Each year only about 10-20 centers exceed their predicted survival. Northside has been in this elite group for eight consecutive years. Only one other center in the country has been in this group more than eight straight years.

### Northside's BMT Program recognized for quality of research in state, nation

The Blood and Marrow Transplant Program is one of the nation's 20 elite BMT programs. The high quality of its research program has been recognized by the National Institutes of Health (NIH), as demonstrated by its designation as a primary core clinical center for the Blood and Marrow Transplant Clinical Trials Network (BMT-CTN).

### Patient-centric focus, robust research are keys to program's success

Lawrence Morris, M.D., who serves as Medical Director of the Leukemia Program and Medical Director of the Inpatient Bone Marrow Unit at Northside, says that robust research is one reason for the program's continued high rankings.

"Having an active research program is a standard of care in this rapidly changing field. Our research-focused program is a big draw for patients and referrals," he said. "If you're not engaged in research, you can't offer the best new therapies."

Asad Bashey, Director of Clinical Research for Northside's BMT Program, adds that research goes hand-in-hand with a commitment to excellence in patient care.

"Our transplant outcomes are among the very best in the country and I believe that has to do with how we set the program up," he said. "We focus on two issues: patient care and clinical research. While research is not the primary driver of the program, it is an integral part of serving our patients and one of the reasons for our success in outcomes."

### Manipulating T-cells to fight myeloma

Northside's BMT Program has numerous clinical trials under way at any given time, including some promising research on immunotherapy. Morris cites one study in multiple myeloma, a common bone marrow cancer, as an example.

"Most people with myeloma receive an autologous stem cell transplant, meaning that some of the patient's own bone marrow stem cells are removed first and frozen before the patient receives a large dose of chemotherapy to try and eradicate the myeloma, but which also eradicates the patient's normal bone marrow. After chemotherapy, the stem cells are thawed out and reintroduced to the patient to help regrow their bone marrow," he explained. "In our current trial, we are collecting additional immune cells called T-Cells from the patient's bone marrow that have the potential to fight the myeloma. These cells are sent to a laboratory at Johns Hopkins, where they are expanded and activated to become 'killer T-cells.' A few days after the transplant, patients receive these activated cells. We hope to prove that these activated T-cells will kill myeloma cells and improve the outcome of the transplant."

## Using antibodies to fight cancer

Dr. Bashey says that antibodies play an important role in mobilizing the immune system to fight blood and marrow cancers, and that there are several ongoing trials that are focused on using antibodies to deliver immunotherapy.

"We are studying various ways that target the cancer either by activating the body's own immune system or by delivering drugs directly with 'weaponized' antibodies," he said.

The immune system has the ability to distinguish between normal cells in the body and what it sees as "foreign" cells. Using "checkpoints" — molecules that need to be activated or inactivated to start an immune response — the immune system attacks the foreign cells. Bashey cites one particular study of antibodies as immune checkpoint inhibitors as having great promise.

"This trial is pioneering," he said. "We know that cancer can augment the 'brakes' or 'checkpoints' that the immune system has in place to prevent it from being overactive, essentially making those brakes invisible. What we're studying now is how to use antibodies that inhibit the checkpoints, thereby taking the brakes off the immune system and activating it."

## Continuously studying new ways to attack blood and marrow cancers

The physicians and researchers of Northside's BMT Program are constantly looking for new approaches to attack blood and marrow cancers and improve the lives of different populations of patients.

For example, one current clinical trial focuses on treating patients with leukemia who are not candidates for an allogeneic transplant, a procedure in which a person receives blood-forming stem cells from a genetically similar, but not identical, donor.

"These patients need a transplant, but are not candidates because of reasons like their age, medical or other issues, or inability to find a suitable donor. We can try using their own stem cells, but that's usually not effective in fighting leukemia," explained Morris. "So we're studying a powerful injectable drug called Pembrolizumab, which has the potential to activate the T-cells and make them fight the leukemia. This immune therapy has been used to treat other cancers like solid tumors, but there has been little research using it to treat leukemia."

Bashey says that new trials involving different ways to attack cancer are constantly opening for enrollment.

"We have just opened a trial for leukemia that uses a bispecific antibody to target leukemia cells. The antibody serves as a bridge between leukemia cells and immune system cells," he said. "Additionally, we have a trial opening soon that will study a new drug, not yet approved, to deliver antibodies directly to the cancer."

Clinical trials are the reason for advances in treatment for patients with blood and marrow cancers, says Morris.

"Thousands of patients who have participated in clinical trials are why we have better treatments today and why we will continue to have better treatments in the future," he said. "That's the only way we can ever improve treatments, including ones that are effective for patients for whom traditional therapies are not effective."

**To learn more about open Blood & Marrow Transplant trials/protocols at Northside, visit http://www.bmtga.com/clinicaltrials2.htm**

## Northside participates in groundbreaking clinical research partnership

The Blood and Marrow Transplant Program at Northside Hospital is one of only 10 sites that have been selected to participate in a prestigious partnership with the Leukemia & Lymphoma Society (LLS) and the Dana-Farber Cancer Institute to provide clinical trial testing of innovative blood cancer therapies in community oncology settings across the country. This groundbreaking Blood Cancer Research Partnership (BCRP) brings clinical trials closer to where patients live and helps to address one of the primary bottlenecks in the development of new cancer therapies: the need for more patients to take part in trials.

Asad Bashey, M.D.

Lawrence Morris, M.D.

# UROLOGY

Advancing technologies and noninvasive treatments, along with more open communication between physicians and patients, are improving the lives of people with urological conditions and diseases, from incontinence to cancer. *Atlanta Medicine* recently spoke with specialists who are excited to share their knowledge of the changing landscape of urology.

## Minimally invasive procedures for benign prostatic hyperplasia

A growing number of older and younger adults are willing to seek out treatment for chronic conditions that have had a long-term negative impact on their quality of life, says Drew Freilich, M.D., a urologist with Urology Specialists of Atlanta.

"We're seeing a trend of patients of all ages who are willing to be more aggressive in the treatments they want. They don't want to continue using catheters, and they are more open to accept the risks of undergoing anesthesia for procedures that can help them," he says. "We're also finding that cardiologists are more open to clearing older and sicker patients to go into the O.R."

One example is men who suffer from an enlarged prostate, which causes an inability to urinate and often requires them to stay catheterized and/or to take multiple medications. Freilich cites some minimally invasive procedures that are effectively reducing prostate size in cases of benign prostatic hyperplasia (BPH).

"Historically, in cases of benign prostatic hyperplasia, if the prostate grew to a certain size — over 80 grams — open surgery would be performed to remove it. Today, we use a GreenLight laser to remove prostate tissue," he explains. "The laser technology has been around for several years now. The procedure involves inserting a small fiber into the urethra through a cystoscope and basically 'vaporizing' the tissue. The procedure has lower risk of bleeding than previous treatments and improves urinary flow immediately."


Drew Freilich, M.D.


Mehrdad Alemozaffar, M.D.


John G. Pattaras, M.D.

**In 2017, more than 161,000 new cases of prostate cancer are expected to be diagnosed in the U.S., and about 26,730 deaths from the disease are anticipated.**

Freilich says two newer procedures — UroLift and Rezūm — are also effective treatments for relieving the symptoms of BPH with minimal risks for the patient.

"UroLift is sort of a 'glorified stapler.' We place implants that hold the enlarged prostate tissue out of the way to relieve compression on the urethra," Freilich says. "Rezūm is an ablation procedure that uses radiofrequency general thermal therapy, or 'hot steam,' to destroy the extra prostate tissue that is causing the symptoms."

Freilich says both procedures quickly improve urinary flow and have minimal side effects.

"UroLift and Rezūm both have good long-term outcomes," he says. "The low risks and fast recovery time make this procedure popular with both older and younger men."

Freilich adds that a large part of his practice is comprised of people who have finally sought help after suffering long-term from conditions such as BPH, urinary incontinence and erectile dysfunction.

"Many of them don't know there is help for their conditions or have been too embarrassed to bring it up," he says. "As physicians, we must be more proactive about having open discussions so that patients will understand there are options available to them that can improve their quality of life."

## Robotics improve cancer treatments

"Almost every case I've done this week has used a scope," says John G. Pattaras, M.D., associate professor of urology at the Emory University School of Medicine and chief of Emory Urology services at Emory Saint Joseph's Hospital. Pattaras, who started the laparoscopic and robotic urologic surgery at Emory 17 years ago, adds that technology has evolved to make a wide variety of surgeries — including those for kidney, prostate and bladder cancers — more effective.

"Robotics allow us to see better inside the patient. It's not just diagnostic; it's changed our ability to do reconstructive surgery," he says.

Pattaras says that robotic surgery has made treatment of kidney cancer, in particular, more successful.

"In the last several years, we have seen mounting evidence that if we could remove the cancerous tumor from the kidney and spare the organ itself, the patient has a longer life expectancy. For certain size and stage tumors, removing the kidney itself has equal outcomes as far as cancer control. But this is not a good option for people who have only one kidney," he says. "Robotic surgery gives us the precision to remove tumors, curing the cancer while preventing further deterioration of the kidney."

For prostate cancer surgery, which has employed robotics for years, improvements have also occurred as the technology has evolved.

"This is a very compact operation, with a complex reconstruction process to restore urination and erectile function. The robot became popular about 10 years ago as an alternative to open surgery for prostate cancer," Pattaras says. "With today's technology, we are able to do bigger surgeries with the same number of small holes and we're managing more aggressive cancer. Robotics allow less invasive, lower morbidity surgeries."

## New methods for detecting and treating cancer

Mehrdad Alemozaffar, M.D., urologic oncology surgeon and assistant professor of urology at the Emory School of Medicine, says there are several recent technologies that now allow urologists to more easily detect and successfully treat various cancers.

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"Bladder cancer is a good example of how a new technology is helping us locate and treat cancers more effectively. Sometimes we have difficulty finding tumors in the bladder because they can be very small and might not be readily seen using a standard cystoscope," he says. "But we now have blue light cystoscopy, which is an enhanced imaging procedure that increases our ability to detect cancers that might be missed under regular light. It involves injecting a fluorescent agent into the bladder an hour before the procedure. The blue light cystoscope then picks up areas where the fluorescence has been taken up, which is preferentially cancerous cells."

Alemozaffar cites another technology, targeted biopsies, as a very important tool in diagnosing prostate cancer.

"When a patient comes in with an elevated PSA [prostate-specific antigen] level, the only way we can truly diagnose cancer is with a biopsy. Traditionally, the way we have done that is to take tissue samples from 12 different areas of the prostate in a somewhat 'blind' method," he says. "Today, we have the ability to target actual lesions seen on an MRI. The MRI determines the probability of cancer using the prostate imaging reporting and data system [PI-RADS]. We are then able to see inside the prostate using a combination of the MRI and ultrasound imaging and can zoom in on the targeted area to obtain a much more precise biopsy."

Alemozaffar adds that the targeted biopsy, which allows him to see 3-D images of the prostate lesions, has been a game changer for detecting prostate cancer.

"I'm able to find more clinically significant cancers using this technology than I did in the past with the blind sampling biopsy," he says.

## Fluciclovine PET/CT improves radiotherapy targeting for recurrent prostate cancer

A clinical investigation article in the March 2017 issue of the *Journal of Nuclear Medicine* demonstrates that the PET radiotracer fluciclovine (fluorine-18; F-18) can help guide and monitor targeted treatment for recurrent prostate cancer, allowing for individualized, targeted therapy.

"This is the first study of its kind demonstrating changes in post-surgery radiotherapy target design with advanced molecular imaging in recurrent prostate cancer, with no demonstrated increase in early radiotherapy side effects," explains Ashesh B. Jani, M.D., of the Winship Cancer Institute of Emory University.

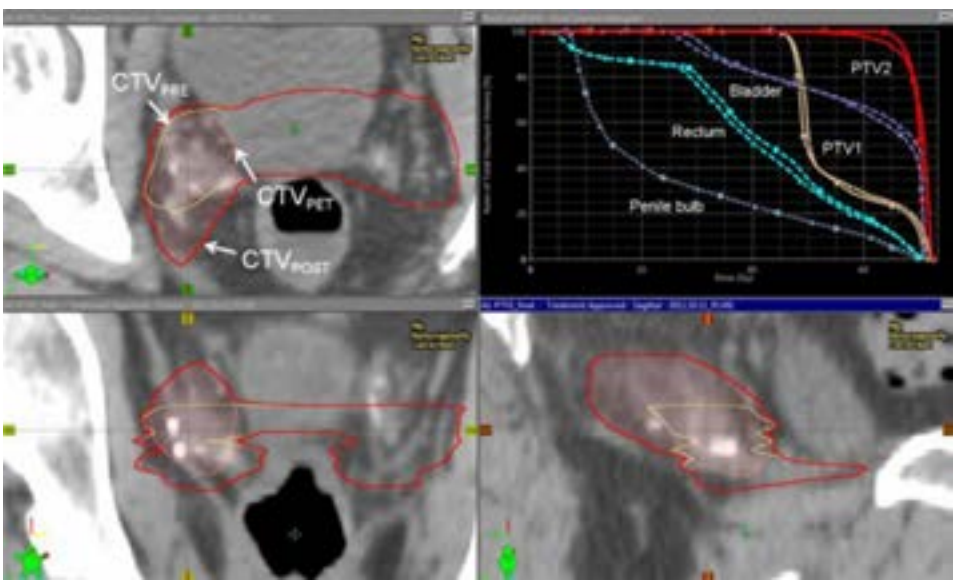
According to the American Cancer Society, one in seven men will develop prostate cancer in his lifetime. In 2017, more than 161,000 new cases of prostate cancer are expected to be diagnosed in the U.S., and about 26,730 deaths from the disease are anticipated.

For the study, 96 patients were enrolled in a clinical trial of radiotherapy for recurrent prostate cancer after prostatectomy. All patients underwent initial treatment planning based on results from conventional abdominopelvic imaging (CT or MRI). Forty-five of the patients then underwent treatment-planning modification (better defining the tumor-targeted area) after additionally undergoing abdominopelvic F-18-fluciclovine PET/CT. No increase in toxicity was observed with this process.

The Emory researchers determined that the inclusion of F-18-fluciclovine PET information in the treatment planning process leads to significant differences in target volumes (the areas to receive radiotherapy). It did result in a higher radiation dose delivered to the penile bulb, but no significant differences in bladder or rectal radiation dose or in acute genitourinary or gastrointestinal toxicity.

These are preliminary results in a three-year study, which hypothesizes that there will be an increase in disease-free survival for patients in the F-18-fluciclovine-modified treatment group over those in the standard treatment group.

This study could have implications beyond prostate cancer. Jani points out, "Our methodology is readily applicable to other novel imaging agents, and it may potentially facilitate improvement of cancer control outcomes." ■




Credit: Ashesh B. Jani, MD, and David Schuster, MD, Emory University.

CTVPOST (red) = CTVPRE (yellow) union CTVPET (pink). Also shown (upper right corner) are the PRE (square) vs POST (triangle) dose volume histograms for PTV1, PTV2, rectum, bladder, and penile bulb, showing minimal impact on target coverage or organs at risk dose with the modified targets.

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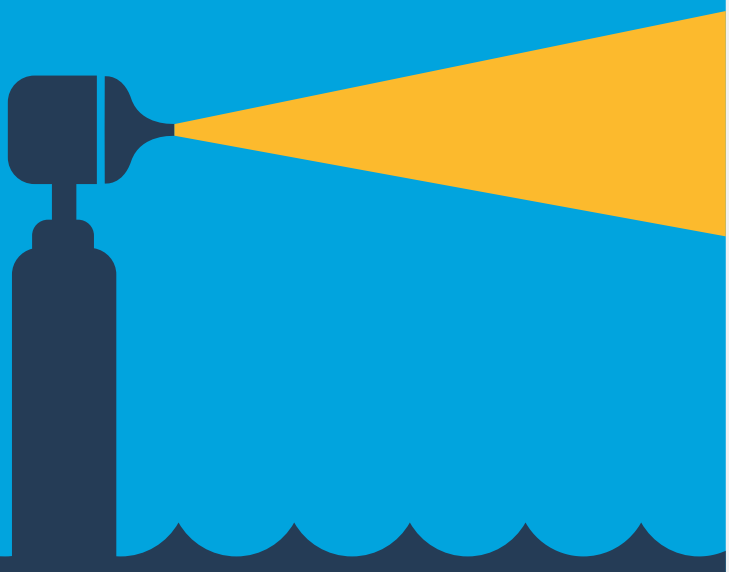

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# "Yes, I am a **DOCTOR** and I Can Help."

By David F. Rodriguez, M.D., FACP, Sandy Springs Internal Medicine, PC Atlanta

My father was a naturalized American medical trailblazer who used his surgical expertise to impact countless lives. After his death, I learned from his handwritten autobiography (inspired by my niece – a Boston University graduate) many details of his life and medical training that remind us that medicine is a calling.

He was born in 1931 in Monterrey, Mexico. When he was in elementary school, his mother would tell friends, relatives and acquaintances that he was going to be a doctor. When he was in high school, in the summers he would travel to San Antonio, Texas, with his parents to deliver milk at 5 a.m. Each summer his cousins would tease him asking, "Are you a doctor, yet?"

The 1930s in Mexico brought the great economic depression with unprecedented factory closings, bankrupt railroads and failed businesses. The casualties included my grandfather's car repair shop. My father and his family lost their home and moved to an apartment.

During this time, two infant siblings died of pneumonia related to poor nutrition and inability to pay for medications. Not surprisingly, my father's mother contracted tuberculosis. Early in her illness, she remained strong and was able to board the bus to the city where she would sell fruits and vegetables to supplement the family income.

Gold shots were tried as treatment for his mother's condition but they were ineffective. Isoniazid (INH) had not yet been discovered, and effective treatment for tuberculosis was unavailable in Mexico at that time. Unfortunately, his mother's illness progressed. She was terminally ill with the family at her bedside during his high school graduation. It should have been a time of shared joy and celebration, not sadness and death. I can only imagine the intense pride that he felt years later when he and my mother attended my graduation from Emory University School of Medicine.

My father was always a good student and spent many hours reading into the late hours of the night, frequently by candlelight since they could not always afford electricity. Following the European model, he was accepted to medical school upon graduation from high school. One week later, his mother died from "consumption" (tuberculosis) after a relentless pulmonary progression, as if waiting to be sure that her son was on the right track and her dream would be fulfilled before she left this world.

Shortly before beginning medical school, Dad began working with a plastic surgeon

who directed a burn unit. This physician taught him to use scalpels and sutures and how to harvest and place skin grafts. Dad was 19 years old, and as he wrote in his own hand, "I performed all those things very well." Dad continued, "I became the surgeon's assistant in private practice. We would operate at the largest private hospital in Monterrey. He would give me money after each surgery and would drive me home when we finished the hospital work."

**My father was a naturalized American medical trailblazer who used his surgical expertise to impact countless lives.**

After medical school, he took extra classes in English and wrote to many U.S. hospitals requesting internship applications.

He arrived for internship in January (the middle of winter from sunny Mexico) to Camden Clark Hospital in Parkersburg, W.Va. He met a nurse (my mother) in the emergency room. They courted, fell in love and later married. After internship, they moved to Ohio Valley General Hospital in Wheeling, W.Va., for his general surgery residency.

As fate would have it, his U.S. visa was scheduled to expire prior to full completion of his final surgical year. He contacted a congressman in Wheeling whom he had met when he performed a tracheotomy on the congressman's son in the course of caring for the child after an auto accident. At the time he was the Chief Surgical Resident, and the congressman had read about him in the local paper after he took care of two indigent boys who had suffered 3rd degree burns and required extensive skin grafting. The congressman had Dad's U.S. visa extended.

Eventually, the U.S. visa expired, and Dad, his wife and two young boys (my older brother and I) moved back to Mexico where he found a job in a local clinic. He reapplied for a U.S. visa but needed a U.S. job for it to be granted. He found an ER position in Wilmington, Del., at a Catholic hospital.

After working there for 8 months, he received a call from the West Virginia congressman that he had met in Wheeling. The congressman was now running for Governor of West Virginia, and he was looking for a physician to relocate to Grantsville, W.Va., a medically underserved area of the state. The soon-to-be Governor mentioned the U.S. visa and the possibility of naturalization to U.S. citizenship. My parents decided to move immediately.

Dad was the only surgeon in town and quickly became very busy, performing four to six major surgeries per day in addition to daily office hours performing primary, secondary and tertiary care. There were two nurses and one general practitioner that assisted in the operating room. Mom was his office manager, nurse, bookkeeper, scheduler and problem solver.

In the summers, I would help out in the office doing odd jobs. One summer I organized his bookshelves, and I was amazed to see the variety of medical and surgical journals. Only after I went through medical school did I realize that the American College of Surgery has 14 recognized surgical specialties; Dad handled all but Ophthalmology.

Dad placed the first cardiac pacemaker in Calhoun County, W.V.a, in the 1960s. He organized a "walking blood bank" in which all townspeople were asked to come to the hospital to have their blood typed and logged. When blood was needed, these people were contacted (by land lines – no cell phones in those days – or by sending a 4-wheel drive vehicle to their home) and asked to come to the hospital.

While practicing medicine and surgery in Grantsville, W.Va., in the 1960s, Dad would travel to Massachusetts General Hospital periodically to attend surgical conferences. He learned new surgical techniques there including flexible, fiber-optic endoscopy/colonoscopy. He was present when Japanese-born Hiromi Shinya became the first physician in the world to reach the cecum during a colonoscopy. In addition, he was one of the first in West Virginia to learn percutaneous insertion of central venous catheters via the subclavian vein.


**My father was always a good student and spent many hours reading into the late hours of the night, frequently by candlelight since they could not always afford electricity.**

Going to Harvard continuing education programs stimulated his interest in cancer screening and treatment. He organized free breast and cervical cancer screening programs and convinced the state of West Virginia (it's good to know the Governor) to provide a trailer with a laboratory and examination table. He subsequently organized the first Calhoun County Cancer Society. During this time, Dad became a naturalized United States citizen; there was no prouder patriot.

After vacationing in Florida on several occasions, my mother (a native West Virginian) had grown weary of the winters and we moved to St. Cloud, Fla. (just south of Orlando). Disney World had just opened (1972), and the area was ripe for extensive growth. Doctors were in short supply in Osceola County, and Dad was a doctor; he could help.

Once again, Dad organized free cancer screenings. Now, however, he became concerned about end-stage, terminal cancer patients who could not be cured, were in pain and did not have financial resources. He learned about hospice care and its origins in England. He formed a volunteer group and treated people at home for no cost.

In 1976 he started Hospice of Osceola County, the first hospice group in Central Florida. A few years later, the neighboring counties of Orange and Seminole counties requested assistance and joined Osceola to form Hospice of Central Florida.

This became a large institution with more than 1,000 active patients, a large board of directors of prominent business people, numerous departments, nurses, therapists, administrative staff, clergy and volunteers. All care, medications and services were donated and were provided without cost to the patients. Dad performed surgeries on patients who could not pay and was happy to donate his time, energy and expertise.


During this time, Dad was elected to Fellowship in the American College of Surgeons (FACS) after submitting the requisite surgical case histories. This would not have happened without Mom's dedicated and detail-oriented administrative skills. This represented a crowning achievement in his proud, surgical career.

Subsequently, Hospice of Central Florida was sold to Vitas Hospice. Dad retired from general surgery in 2000 after practicing for more than 35 years. He then became the Inpatient Hospice Director for Vitas Hospice of Central Florida in Orlando, Fla., where he served for 8 years teaching palliative care to physicians and residents.

He retired again in August 2008 to help care for my mother, who had paroxysmal atrial fibrillation, but she ended up caring for him when he developed Alzheimer's dementia.

Dad's life came full circle in the end when he was cared for by a Hospice physician from the same Vitas Hospice program that he founded.

I am privileged to have been inspired by my father's life, and thanks to him I can say, "Yes, I, too, am a doctor, and I can help." ■

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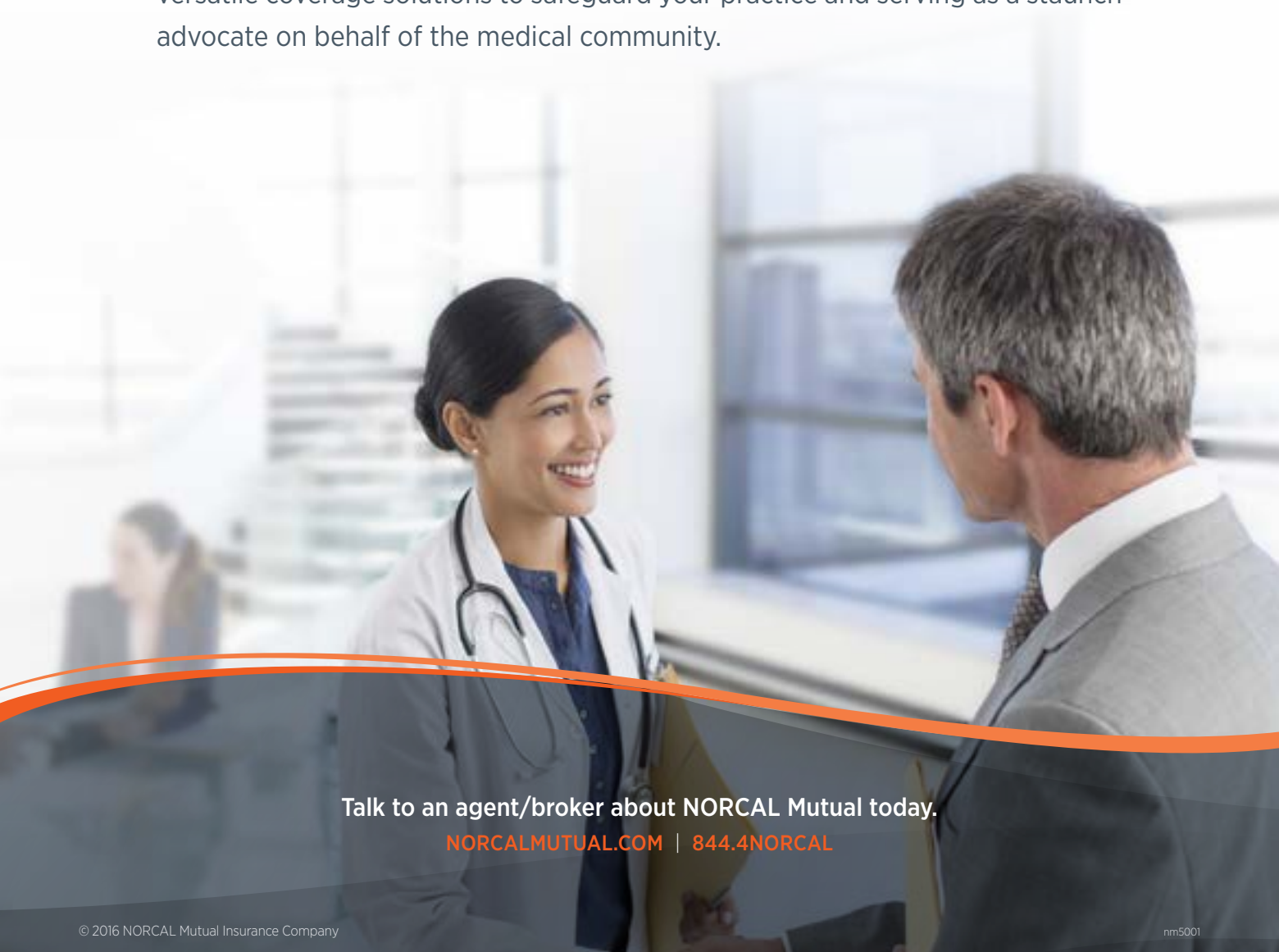

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