Applying AI in fundus images

FDA decision changes scope of healthcare delivery; increases patient access to early detection of DR

By Steve Lenier;
Reviewed by Michael D. Abramoff, MD, PhD

A DECISION by the FDA in April 2018 changed the game for identifying patients at risk of vision loss. Its decision authorized the marketing of an AI system (IDx-DR), that enables the automated detection of diabetic retinopathy in primary care, and marked the first time the agency has granted clearance for an autonomous AI diagnostic system that does not require a physician to interpret results.

This advancement will lead to changes in healthcare delivery by increasing patient access to early detection of diabetic retinopathy, noted Michael D. Abramoff, MD, PhD, the Robert C. Watzke, MD Professor in Retina Research, Department of Ophthalmology and Visual Sciences, University of Iowa Carver College of Medicine, Iowa City.

The autonomous AI diagnostic system makes a diagnosis by itself for DR. It requires no human oversight, and, importantly, it aligns with clinical standards. The system has been designed and tested for use in a primary-care setting, where it can provide a point-of-care diagnosis in a few minutes.

The system includes a robotic camera and there-
(Continues on page 27: AI analysis)
Achieving IOP control

What makes once-daily Rhopressa® different¹

- Consistent IOP reduction up to 5 mmHg in patients across a range of baseline IOPs
- Once-daily dosing to simplify dosing regimens
- Mild ocular adverse events and no known contraindications opens up treatment options
- Unique mechanism of action for patients who may benefit from improved trabecular aqueous outflow

Rhopressa® is covered for the majority of patients nationwide.²

Visit Rhopressa.com to learn more about this innovative IOP-lowering treatment.

INDICATION AND IMPORTANT SAFETY INFORMATION

INDICATION
Rhopressa® (netarsudil ophthalmic solution) 0.02% is a Rho kinase inhibitor indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

Dosage and Administration: The recommended dosage is one drop in the affected eye(s) once daily in the evening.

IMPORTANT SAFETY INFORMATION

Dosage and Administration: Twice a day dosing is not well tolerated and is not recommended. If Rhopressa® is to be used concomitantly with other topical ophthalmic drug products to lower IOP, administer each drug product at least 5 minutes apart.

Warnings and Precautions:

Bacterial Keratitis: There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

Adverse reactions: The most common ocular adverse reaction observed in controlled clinical studies with Rhopressa® dosed once daily was conjunctival hyperemia which was reported in 53% of patients. Other common (approximately 20%) adverse reactions were: corneal verticillata, instillation site pain, and conjunctival hemorrhage. Instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, and reduced visual acuity were reported in 5-10% of patients. The corneal verticillata seen in Rhopressa®-treated patients were first noted at 4 weeks of daily dosing. This reaction did not result in any apparent visual functional changes in patients. Most corneal verticillata resolved upon discontinuation of treatment.

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

RHOPRESSA® (netarsudil ophthalmic solution) 0.02%
Rx Only

BRIEF SUMMARY
Consult the Full Prescribing Information for complete product information.

INDICATIONS AND USAGE
RHOPRESSA® (netarsudil ophthalmic solution) 0.02% is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

DOSAGE AND ADMINISTRATION
The recommended dosage is one drop in the affected eye(s) once daily in the evening.

If one dose is missed, treatment should continue with the next dose in the evening. Twice a day dosing is not well tolerated and is not recommended. If RHOPRESSA is to be used concomitantly with other topical ophthalmic drug products to lower IOP, administer each drug product at least 5 minutes apart.

WARNINGS AND PRECAUTIONS
Bacterial Keratitis
There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been previously contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

Use with Contact Lenses
RHOPRESSA contains benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of RHOPRESSA and may be reinserted 15 minutes following its administration.

ADVERSE REACTIONS
Clinical Trials Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The most common ocular adverse reaction observed in controlled clinical studies with RHOPRESSA dosed once daily was conjunctival hyperemia which was reported in 53% of patients. Other common (approximately 20%) ocular adverse reactions reported were: corneal verticillata, instillation site pain, and conjunctival hemorrhage. Instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, and reduced visual acuity were reported in 5-10% of patients.

Corneal Verticillata
Corneal verticillata occurred in approximately 20% of the patients in controlled clinical studies. The corneal verticillata seen in RHOPRESSA-treated patients were first noted at 4 weeks of daily dosing. This reaction did not result in any apparent visual functional changes in patients. Most corneal verticillata resolved upon discontinuation of treatment.

USE IN SPECIFIC POPULATIONS
Pregnancy
There are no available data on RHOPRESSA use in pregnant women to inform any drug associated risk; however, systemic exposure to netarsudil from oculic administration is low. Intravenous administration of netarsudil to pregnant rats and rabbits during organogenesis did not produce adverse embryofetal effects at clinically relevant systemic exposures.

Animal Data
Netarsudil administered daily by intravenous injection to rats during organogenesis caused abortions and embryofetal lethality at doses ≥0.3 mg/kg/day (126-fold the plasma exposure at the recommended human ophthalmic dose [RHOD], based on Cmax). The no-observed-adverse-effect-level (NOAEL) for embryofetal development toxicity was 0.1 mg/kg/day (40-fold the plasma exposure at the RHOD, based on Cmax).

Netarsudil administered daily by intravenous injection to rabbits during organogenesis caused embryofetal lethality and decreased fetal weight at 5 mg/kg/day (1480-fold the plasma exposure at the RHOD, based on Cmax). Malformations were observed at ≥3 mg/kg/day (1330-fold the plasma exposure at the RHOD, based on Cmax), including thoracogastroschisis, umbilical hernia and absent intermediate lung lobe. The NOAEL for embryofetal development toxicity was 0.5 mg/kg/day (214-fold the plasma exposure at the RHOD, based on Cmax).

Lactation
There are no data on the presence of RHOPRESSA in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to netarsudil following topical ocular administration is low, and it is not known whether measurable levels of netarsudil would be present in maternal milk following topical ocular administration. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for RHOPRESSA and any potential adverse effects on the breastfed child from RHOPRESSA.

Pediatric Use
Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

Geriatric Use
No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have not been performed to evaluate the carcinogenic potential of netarsudil. Netarsudil was not mutagenic in the Ames test, in the mouse lymphoma test, or in the in vivo rat micronucleus test. Studies to evaluate the effects of netarsudil on male or female fertility in animals have not been performed.

Manufactured for: Aerie Pharmaceuticals, Inc., Irvine, CA 92614, U.S.A.

For more information, go to www.RHOPRESSA.com or call 1-855-AerieRx (1-855-237-4379).

RHOPRESSA is a registered trademark of Aerie Pharmaceuticals, Inc.
U.S. Patent Nos.: 8,450,344; 8,394,826; 9,096,569; 9,415,043
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Watch Doug Katsev, MD, discuss atopic dermatitis and cataract development at http://bit.ly/1rOQAED

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Watch Doug Katsev, MD, discuss atopic dermatitis and cataract development at http://bit.ly/1rOQAED

Video courtesy of the Medical News Minute

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IN DESIRED OUTCOMES

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Ophthalmology Times
Livin’ in the real world

Real-world outcomes often throw curveball at clinical trial data

By Peter J. McDonnell, MD

NEW FDA Commissioner Scott Gottlieb, MD, has made a number of changes that have been widely recognized as being positive.

One innovation that I think most people believe moves us in the right direction is the use of “real-world outcomes” to look at the results of our therapies and develop data regarding the efficacy and associated adverse events after a therapy has reached the market.

Real-world data (RWD) and real-world evidence (RWE), according to the FDA, “can better inform regulatory decisions. Because they include data covering the experience of physicians and patients with the actual use of new treatments in practice, and not just in research studies, the collective evaluation of these data sources has the potential to inform clinical decision making by patients and providers, develop new hypotheses for further testing of new products to drive continued innovation and inform us about the performance of medical products.”

RWD and RWE make the FDA’s job of post-market evaluation of safety timelier and more effective, giving answers sooner at a fraction of the cost of traditional post-market studies.

WHY EMPHASIS ON REAL WORLD?

If you have ever been involved in formal, randomized, controlled trials, you know that patients are carefully selected, with a typically lengthy list of inclusion criteria (patients must have all these things) and an equally long list of exclusion criteria (including comorbidities) that might make it more difficult to interpret the effect of the therapy being tested. Study coordinators cheerfully, but persistently, contact patients to make sure they take their medications (or placebo) exactly as directed and return as scheduled for follow-up and testing.

In the real world, we rely on patients to remember to take their pills as prescribed and there is no study coordinator to watch over their shoulders. In the real world, patients who don’t have a ride to the doctor’s office miss their appointment and treatment window, whereas in the artificial world of trials a car might be dispatched to pick up patients, deliver them to the doctor, and return them home after testing and/or follow-up treatment.

Does this real-world stuff make a difference? We have data to say the answer to this question is a definite “yes—and more than you might think.” In a recent study, the results of treating more than 15,000 eyes of patients with diabetic macular edema with anti-VEGF agents by retina specialists in the real world was compared with the published results of randomized controlled trials for the same condition.

Overall, after a year of treatment, real-world patients experienced less than half of the benefit from the “scientific trials”—eyes initiated on aflibercept, bevacizumab, and ranibizumab gained 5.5, 5.5, and 4.0 letters, respectively, compared with the published gains of 13.3, 9.7, and 11.2 letters. Real-world patients who started out with 20/40 or better, lost 2.5, 2.0, and 2.7 letters over a 12-month period, compared with gains of 7.4, 6.0, and 6.1 letters with the same three drugs in published papers.

The inescapable conclusion seems to be there are therapies that might work nicely in the rarified world of trials only to prove much less effective—or actually detrimental—in the real world of our offices/operating rooms. The FDA is wise to look at real-world evidence, and we physicians should share that information with patients when discussing risks/benefits of therapies, rather than relying solely on published results from the unreal world of clinical trials.

References

- https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm627760.htm
- https://www.ophthalmologyretina.org/article/S2468-6530(18)30265-3/fulltext
XIIDRA MAY INTERRUPT THE CYCLE OF INFLAMMATION CENTRAL TO DRY EYE DISEASE1,2

The exact mechanism of action of Xiidra in Dry Eye Disease is not known.1

Xiidra blocks the interaction of ICAM-1 and LFA-1, which is a key mediator of the inflammation central to Dry Eye Disease. In vitro studies have shown that Xiidra may inhibit the recruitment of previously activated T cells, the activation of newly recruited T cells, and the release of pro-inflammatory cytokines.1

Indication
Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of signs and symptoms of dry eye disease (DED).

Important Safety Information
Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients.

In clinical trials, the most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

To avoid the potential for eye injury or contamination of the solution, patients should not touch the tip of the single-use container to their eye or to any surface.

Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.

Safety and efficacy in pediatric patients below the age of 17 years have not been established.

Check out Xiidra-ECP.com

For additional safety information, see accompanying Brief Summary of Safety Information on the adjacent page and Full Prescribing Information on Xiidra-ECP.com.

References:
BRIEF SUMMARY:
Consult the Full Prescribing Information for complete product information.

INDICATIONS AND USAGE
Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of the signs and symptoms of dry eye disease (DED).

DOSAGE AND ADMINISTRATION
Instill one drop of Xiidra twice daily (approximately 12 hours apart) into each eye using a single-use container. Discard the single-use container immediately after using in each eye. Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.

CONTRAINDICATIONS
Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation.

ADVERSE REACTIONS
Clinical Trials Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical conditions, adverse reaction rates observed in clinical studies because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in clinical studies cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In five clinical studies of dry eye disease conducted with lifitegrast ophthalmic solution, 1401 patients received at least 1 dose of lifitegrast (1287 of which received lifitegrast 5%). The majority of patients (84%) had ≤3 months of treatment exposure. 170 patients were exposed to lifitegrast for approximately 12 months. The majority of the treated patients were female (77%). The most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

Postmarketing Experience
The following adverse reactions have been identified during postapproval use of Xiidra. 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. Rare cases of hypersensitivity, including anaphylactic reaction, bronchospasm, respiratory distress, pharyngeal edema, swollen tongue, and urticaria have been reported. Eye swelling and rash have been reported.

USE IN SPECIFIC POPULATIONS
Pregnancy
There are no available data on Xiidra use in pregnant women to inform any drug associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from pre-mating through gestation day 17, did not produce teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocele at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD], based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear.

Animal Data
Lifitegrast administered daily by intravenous (IV) injection to rats, from pre-mating through gestation day 17, caused an increase in mean preimplantation loss and an increased incidence of several minor skeletal anomalies at 30 mg/kg/day, representing 5,400-fold the human plasma exposure at the RHOD of Xiidra, based on AUC. No teratogenicity was observed in the rat at 10 mg/kg/day (460-fold the human plasma exposure at the RHOD, based on AUC). In the rabbit, an increased incidence of omphalocele was observed at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the RHOD, based on AUC), when administered by IV injection daily from gestation days 7 through 19. A fetal No Observed Adverse Effect Level (NOAEL) was not identified in the rabbit.

Lactation
There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lifitegrast from ocular administration is low. The developmental and health benefits of breastfeeding should be considered, along with the mother’s clinical need for Xiidra and any potential adverse effects on the breastfed child from Xiidra.

Pediatric Use
Safety and efficacy in pediatric patients below the age of 17 years have not been established.

Geriatric Use
No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis: Animal studies have not been conducted to determine the carcinogenic potential of lifitegrast. Mutagenesis: Lifitegrast was not mutagenic in the in vitro Ames assay. Lifitegrast was not clastogenic in the in vivo mouse micronucleus assay. An in vitro chromosomal aberration assay using mammalian cells (Chinese hamster ovary cells), lifitegrast was positive at the highest concentration tested, without metabolic activation. Impairment of fertility: Lifitegrast administered at intravenous (IV) doses of up to 30 mg/kg/day (5400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD] of lifitegrast ophthalmic solution, 5%) had no effect on fertility and reproductive performance in male and female treated rats.
Celebrating retina research, future generation of EyeMDs

Fifteen fellows, residents showed just why research in retina is on the cutting edge

By Michelle Dalton, ELS

The Research Scholar Honoree Program featured a wide range of research topics, from biosimilars to retinal changes during migraine episodes to retinal morphology and its effect on refractive lens exchange. They also included research on ascorbic acid and diabetic retinopathy (DR), bile acid metabolites, and a validation of smartphone-based photography for DR screening.

Chairman Rishi P. Singh, MD, (Cleveland, OH) said he wanted the finalists to have “a really good sense of how much of a contribution you all have made to the field just by being here.”

Dr. Singh and fellow judges Darius M. Moshfeghi, MD (Stanford, CA); Judy E. Kim, MD (Milwaukee, WI); and Charles C. Wykoff, MD, PhD (Houston), had pre-vetted 15 presenters from among 50 entrants—including one from Africa and one from Italy.

Each presenter was allowed 7 minutes to discuss his or her research, including what role he or she played in the research. The remaining 3 minutes were left for a question-and-answer session by the judges.

said, improving to 0.4, 0.7, and 1.3 logMAR, respectively. “We think this was related to patients who were able to reperfuse their central retinal artery,” with the IV infusion helping the patient maintain that perfusion, he said. (The remaining patients improved to 2.3 or 2.7 logMAR.)

Though winning was an honor, Dr. Malbin said, “it’s great to have something that we can offer patients with acute CRAO. To finally have something that we can offer patients with such a devastating disease is nice.”

Dr. Malbin acknowledged both Xihui Lin, MD, as the principal investigator, as well as the Kresge Eye Institute and the Department of Neurology at the Detroit Medical Center.

‘During the time when you are a resident or a fellow, you have a unique opportunity to do research with your faculty mentors. I would encourage all of you to take advantage of this time.’ — Harry W. Flynn Jr., MD

The remaining top five finalists (in alphabetical order):

John Chancellor, MD, MS, (Little Rock, AR) who is researching the influence of diabetic retinopathy on the visual outcomes of cataract surgery;

Kenneth C. Fan, MD, MBA, (Miami), who is researching in vitro susceptibilities of vitreous Candida isolates to novel and traditional antifungal agents;

IN THE TOP FIVE

The second annual Ophthalmology Times Research Scholar Honoree Program featured a wide range of research topics, from biosimilars to retinal changes during migraine episodes to retinal morphology and its effect on refractive lens exchange.
Nimesh A. Patel, MD, (Miami), who is research-
ing the rapid detection of pathogens with fluo-
rescence in situ hybridization (FISH), and
Tapan P. Patel, MD, PhD, (Ann Arbor, MI), who is
researching smartphone-based fundus photog-
raphy for the screening of plus-disease retinopa-
thy of prematurity.

FOR THE LOVE
OF RESEARCH
Dr. Singh said “one of the most impressive things”
about keynote speaker Harry W. Flynn Jr., MD
(Miami) “has been his commitment in the field
of endophthalmitis and infectious diseases.” Dr.
Flynn has been the author or co-author of more
than 550 peer-review publications and 104 book
chapters, and has edited or co-edited more eight
books.

Dr. Flynn said “during the time when you are
a resident or a fellow, you have a unique oppor-
tunity to do research with your faculty mentors.
I would encourage all of you to take advantage
of this time so that you can put your name on
research projects and present that data at local
and national meetings.”

Research (both basic science and clinical re-
search) is a process of three steps, he said: 1) Pos-
ing a question, 2) collecting the data, to an-
swer the question and 3) reporting the answer
to the question.

For example, “you could add multimodal im-
aging using optical coherence tomography an-
giography images in your paper to describe new
and unique findings,” he said. “Or you can re-
view outcomes of treatment in a large clinical
series.” Dr. Flynn also noted researchers may
need financial help, and they should be prepared
to reach out for help “and persevere when you
face frustrations.”

Paraphrasing Sherlock Holmes, Dr. Flynn
said: “One should not twist the facts to suit
theories, instead propose theories to reflect
the facts.”

He recommended interacting with colleagues
at conferences—adding he often learns more
while at lunch or dinner than he learns from
podium presentations because of the “give-
and-take” interaction.

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Since the FDA approval of a high-definition wavefront aberrometer (iDesign Advanced WaveScan, Johnson & Johnson Vision) in 2015, this technology affords a broader range of patients—including those with higher astigmatism—to be treated with custom, wavefront-guided ablations. In the FDA clinical trial, 64% of 344 eyes had monocular uncorrected visual acuity (UCVA) of 20/16 or better at six months.

Robert Maloney, MD, Stephen Coleman, MD, and I wanted to evaluate whether we could reproduce the FDA clinical trial results in a real-world clinical practice setting and determine the impact on patient satisfaction.

We conducted a multicenter, open-label study with a target enrollment of 100 patients, who were to be examined at baseline, 1 day, and at 30, 60, 90, and 180 days postoperatively.1

The study was open to patients with a wide range of myopic refractive error, from –0.25 D to –11.00 D, with or without astigmatism of up to 5.00 D. All subjects had to have best-corrected visual acuity (BCVA) of 20/20 or better preoperatively, no uncontrolled ophthalmic disease (including severe dry eye), and no prior corneal surgery. All were slated for plano corrections (no monovision).

All patients were treated with iDesign-guided LASIK treatments using the VISX Star S4 IR laser and the iFS femto-second laser for flap creation (Johnson & Johnson Vision). Flap thickness and architecture were at the surgeon’s discretion. 

**STUDY RESULTS**

The mean age of patients enrolled was 30 (range: 18 to 47). Sixty subjects were male and 35 female. Preoperative manifest refraction sphere ranged from –0.25 to –7.75 D (mean: –3.40 D). At six months the mean sphere had been reduced to 0.11 ±0.263 D. Preoperative manifest refraction cylinder ranged from 0 to –5.00 D at baseline (mean: –0.87 D) and was reduced to –0.22 ±0.263 D. The mean spherical equivalent was reduced from –3.83 ±1.92 D to plano (0.00 ± 0.242 D).

At six months, our visual acuity results were even better than those reported in the FDA clinical trial for iDesign. Nearly all eyes (97%) had 20/20 or better UCVA, and 77% were 20/16 or better (Figure 1).

When we looked at binocular vision, 93% could see 20/16 or better at six months and one in 10 patients had 20/10 vision (Figure 2).

These are some of the best visual acuity results we’ve seen in any multicenter clinical trial. At six months, patients were asked how often their eyes felt dry or gritty; 99% said “none of the time” or “sometimes,” an improvement over the percentage that answered this way preoperatively.

The proportion of people saying they were bothered by starbursts, halo, glare, or double vision more than “none of the time” or “sometimes” was very low but also decreased from

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**Finding value in real-world aberrometry outcomes**

Researchers explore clinical and patient-reported outcomes after WFG LASIK for myopia

By Colman R. Kraff, MD; Special to Ophthalmology Times

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**TAKE-HOME**

Use of high-definition wavefront aberrometry may improve the chance of better-than-20/20 results and high patient satisfaction, according to Colman R. Kraff, MD.
Primary lens extraction rivals iridotomy in primary angle closure
Approach more cost-effective, considered as option for first-line therapy, suggests surgeon

By Fred Gebhart; Reviewed by Paul J. Harasymowycz, MD

A THREE-YEAR follow-up to the landmark EAGLE study in patients with primary angle closure confirms initial findings that primary lens extraction produces better clinical outcomes and better quality of life compared with standard care with laser peripheral iridotomy plus topical medical treatment. Clear lens extraction is more cost-effective than primary iridotomy and should be considered as an option for first-line treatment, said Paul J. Harasymowycz, MD.

“Based on the evidence, one should not jump straight to iridotomy when a patient presents with narrow angles,” said Dr. Harasymowycz, chief of glaucoma, University of Montreal, and director, Montreal Glaucoma Institute. “Clear lens extraction is not necessarily right for every patient, but ophthalmologists should be having this discussion about clear lens extraction with their primary angle closure (PAC) or primary angle-closure glaucoma (PACG) patients.”

EAGLE FOLLOW-UP
Dr. Hayramowycz discussed the three-year, follow-up analysis of EAGLE patients. The initial study, published in The Lancet in 2016, concluded that clear lens extraction was both more effective than primary laser iridotomy and more cost effective. Follow-up analysis focusing on long-term visual acuity was published in The British Journal of Ophthalmology in 2018.

The findings that favor clear lens extraction follow World Glaucoma Association angle-closure staging criteria that divide angle closure into three categories:

■ Primary angle closure suspect, (PACS), with 180° of appositional closure;
■ Primary angle closure (PAC) with peripheral anterior synchiae (PAS) or high IOP shows trabecular meshwork dysfunction; and
■ Primary angle-closure glaucoma (PACG), shows signs of structural or functional glaucoma damage.

The EAGLE trial randomly assigned 419 PAC and PACG patients with an IOP of 30 mm Hg or higher to either clear lens extraction or standard care. Of the group, 155 patients had PAC and 263 had PACG. None of the patients had existing cataracts and all were age 50 and older. Quality of life was assessed using three scales: National Eye Institute 25-Item Visual Function Questionnaire, the European Quality of Life-5 Dimensions Questionnaire, and the Glaucoma Utility Index.

After treatment, clear lens extraction patients were on a mean of 0.4 medications versus 1.3 medications for iridotomy patients (p < 0.0001) and had an IOP of 16.6 mm Hg versus 17.9 mm Hg (p < 0.004). Only one clear lens extraction required additional surgery, whereas 24 iridotomy patients need additional treatment. Patient-reported quality of life was significantly higher for the clear lens extraction group, and the incremental cost effectiveness ratio was £14,284, about $18,300 at current exchange rates, in favor of clear lens extraction.

Study authors noted: “Laser peripheral iridotomy as the initial treatment for angle-closure glaucoma should be reconsidered. This study provides robust evidence that initial clear lens extraction is associated with better clinical and patient reported outcomes and that this approach is likely to be cost effective in a publicly funded health system.”

Three years later, corrected distance visual acuity for the clear lens extraction group was virtually unchanged, 79.9 letters compared with 77.9 letters at baseline. Slightly over half of eyes, 59.9%, were within 0.5 D of predicted refraction and 85% of eyes were within 1 D. “The major conclusion is the clear lens extraction is beneficial to both the patient and the healthcare system,” Dr. Harasymowycz said. “The vast majority of patients that have a narrow angle are already presbyopic and can benefit from the different types of multifocal or extended-depth-of-focus IOLs that are available, depending on where they live or if glaucoma damage is present. But the three-year results tell us not to overpromise that patients will not need glasses. Only 85% of patients were within 1 D of emetropia, and a discussion of effective lens position is crucial in this patient demographic.”

TAKE-HOME
Clear lens extraction is not necessarily right for every patient, but surgeons should have this discussion with their primary angle closure (PAC) or primary angle-closure glaucoma (PACG) patients.

Dr. Harasymowycz

Paul J. Harasymowycz, MD
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This article was adapted from Dr. Harasymowycz’s presentation during Glaucoma Subspecialty Day at the 2018 meeting of the American Academy of Ophthalmology.
He is a speaker/consultant with Aerie Pharmaceuticals, Alcon Laboratories, Allergan, Bausch + Lomb, GlaxoSmithKline, Johnson & Johnson Vision, and Novartis.
WFG LASIK

(Continued from page 12)

preoperative to six months postoperative. By six months, 97% of subjects said they could function without glasses or contact lenses with no difficulty (Figure 3) and 98% saw an overall improvement in their quality of life since LASIK surgery. (No one said their quality of life was worse.)

Not surprisingly, 99% said they would recommend the procedure for friends or family.

LESSONS LEARNED

Even as technology has steadily improved, the lessons of the past 20 years of refractive surgery still hold true. We must choose good candidates with healthy eyes, and be sure to treat pre-existing conditions such as dry eye and meibomian gland dysfunction (MGD) before refractive surgery. Dry eye and MGD are extremely common in patients presenting for LASIK, given that contact lens intolerance due to MGD and evaporative dry eye was often the catalyst driving them to seek refractive surgery in the first place.

The ability of new aberrometry devices to image and capture more aberrated eyes does not mean every eye that can be captured should be treated. Surgeons have to be rigorous in evaluating more aberrated eyes and those requiring large corrections and be mindful of tissue consumption in treatment planning.

Patients with high astigmatism can now be treated with very good clinical outcomes.

However, extremely high astigmatism is uncommon and does require careful assessment of refractive stability and of corneal cylinder. I want to see inter- and intraocular topographic symmetry on Placido disc analysis as well as normal indices on Pentacam (Oculus), including symmetrical anterior and posterior elevations and a normal Belin Ambrosio analysis. It is also important to consider any family history of ectatic disease and discuss the potential for night-vision issues with patients with these unusual corrections.

The average age of patients in the study discussed here (30) reflects the reality that today’s laser vision correction patients are generally younger than the average patient a decade or more ago.

The millennial generation represents a great opportunity for refractive surgery centers, simply because it is so large. These patients can be challenging to reach through traditional advertising so practices must delve more into social media outreach.

This generation also has the advantage of having seen older friends and family reap the rewards of successful LASIK. In my experience, they are more confident in the procedure and less fearful of complications than earlier generations.

CONCLUSION

A new version of the iDesign aberrometer was just approved and will be commercially available soon. It provides surgeons with additional maps and analyses and is likely to further incorporate topographical and keratometric data into the treatment planning.

Additionally, it increases the range of hyperopic astigmatism that can be treated.

We are fortunate that our refractive surgery technology continues to improve and to provide even better outcomes for our patients.

REFERENCE


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Dr. Kraff is in private practice at Kraff Eye Institute in Chicago and serves as a clinical instructor at Northwestern University Medical School. He is a consultant to Johnson & Johnson Vision and serves on the International Advisory Board for Optical Express.

ORA SYSTEM® Technology - IMPORTANT PRODUCT INFORMATION

CAUTION: Federal (USA) law restricts this device to the sale by or on the order of a physician.

INDICATIONS: Federal (USA) law restricts this device to the sale by, or on the order of, a physician.

INTENDED USE: The ORA SYSTEM® technology utilizes wavefront aberrometry data to measure and analyze the refractive power of the eye (i.e. sphere, cylinder, and axis measurements) to support cataract surgical procedures.

WARNINGS AND PRECAUTIONS: The following conditions may make it difficult to obtain accurate readings using the ORA SYSTEM® technology:

- Patients having progressive retinal pathology such as diabetic retinopathy, macular degeneration, or any other pathology that the physician deems would interfere with patient fixation;
- Patients having corneal pathology such as Fuchs’ I, EBDK, keratoconus, central pterygium impairing the cornea, or any other pathology that the physician deems would interfere with the measurement process;
- Patients for which the preoperative regimen includes residual viscous substances left on the corneal surface such as lidocaine gel or viscoelastic;
- Visually significant media opacity, such as prominent floats or asteroid hyalosis, which will either limit or prohibit the measurement process;
- Patients having received retro or peribulbar block or any other treatment that impairs their ability to visualize the fixation light;
- Use of iris hooks during an ORA SYSTEM® technology image capture will yield inaccurate measurements. In addition:
- Significant central corneal irregularities resulting in higher order aberrations might yield inaccurate refractive measurements.
- Post refractive keratotomy eyes might yield inaccurate refractive measurements.
- The safety and effectiveness of using the data from the ORA SYSTEM® have not been established for determining treatments involving higher order aberrations of the eye such as coma and spherical aberrations.
- ORA SYSTEM® technology is intended for use by qualified health personnel only.
- Improper use of this device may result in exposure to dangerous voltage or hazardous laser-like radiation exposure. DO NOT OPERATE the ORA SYSTEM® in the presence of flammable anesthetics or volatile solvents such as alcohol or benzene, or in locations that present an explosion hazard.

ATTENTION: Refer to the ORA SYSTEM® Operator’s Manual for a complete description of proper use and maintenance, as well as a complete list of contraindications, warnings and precautions.
Experience confirmation you can see.
The management of diabetic retinopathy (DR) presents a formidable and growing challenge to the ophthalmic community. According to the U.S. Centers for Disease Control (CDC), more than 30 million Americans (9.4% of the U.S. population) are diabetic, a number that is predicted to rise by 54% to 54.9 million by 2030. As a result, DR and other diabetic eye diseases are projected to follow a similar trend.

DR is a silent disease that can manifest initially with few if any symptoms. While 40 to 45% of Americans diagnosed with diabetes are affected, only about half of these patients are aware they have diabetic eye disease. Consequently, many go untreated for far too long, losing vision and in some cases, going blind. Thus, early detection, particularly of those whose disease is most likely to progress, is critical for successful disease management.

In my experience, the addition of ultra-wide-field (UWF) imaging to screening and evaluation protocols offers advantages that improve our ability to diagnose earlier and treat more effectively.

In recent decades, the standard for evaluating DR disease severity has been Early Treatment Diabetic Retinopathy Study (ETDRS) photography. These 35-mm color images, comprised of 7 stereoscopic pairs of photographs per eye (ETDRS 7 standard fields), are assessed using the extended modified Airlie House classification system, which evaluates the location and degree of retinal lesions in the posterior pole. The ETDRS 7 standard fields includes the central posterior 90° of the retina, which equates to about 30% of the entire retina surface.

For years this has been the gold standard for identifying vascular pathology in DR. However, relying solely on this limited field of view means we risk missing a pathology present in the periphery that may contribute to the progression and outcome of the disease. DR studies have shown that pathology often exists outside the ETDRS 7 standard fields and in some cases, peripheral pathology is associated with greater disease severity and higher risk of disease progression.

This has long been suspected, but recent research has begun to illuminate the role of peripheral pathology in early disease detection and determination of the risk of progression. Ischemia, which is an important factor in DR progression, may appear in the periphery first and has been associated with the presence of peripheral lesions on color images.

One study found that predominantly peripheral lesions (PPLs) are present in up to 40% of patients with early nonproliferative diabetic retinopathy (NPDR) were linked to a nearly 5 fold DR progression over 4 years.

The body of research supporting the value of ultra-widefield (UWF) imaging is considerable and continuously growing. As a result, UWF is fast becoming the standard of care for retinal vascular disorders especially diabetic retinopathy.

UWF IMAGING CONTRIBUTES TO EARLIER DISEASE DETECTION

New research confirms agreement with 7 standard field imaging

By Rishi P. Singh, MD; Special to Ophthalmology Times

The management of diabetic retinopathy (DR) presents a formidable and growing challenge to the ophthalmic community. According to the U.S. Centers for Disease Control (CDC), more than 30 million Americans (9.4% of the U.S. population) are diabetic, a number that is predicted to rise by 54% to 54.9 million by 2030. As a result, DR and other diabetic eye diseases are projected to follow a similar trend.

DR is a silent disease that can manifest initially with few if any symptoms. While 40 to 45% of Americans diagnosed with diabetes are affected, only about half of these patients are aware they have
benefits, because these images can be captured in less than ½ a second and without dilation, routine use of the technology can contribute to practice efficiency by facilitating assessment and documentation and allowing more patients to be screened in less time.

The images are easily annotated, stored and shared, serving as a useful resource for making treatment decisions and referrals when necessary. Other systems on the market capture varying degrees of the periphery using montaging techniques but they have not yet been widely adopted or validated versus gold-standard technologies.

UWF images also create a valuable tool for patient engagement and education. The ability to show patients the areas of concern or changes since a previous visit makes both their condition and your recommendations easier to explain and easier for the patient to understand. Seeing the damage to their retina firsthand may even encourage compliance with treatment recommendations or inspire behavior modification, such as taking steps to improve blood glucose control.

**UWF Images = To ETDRS**

While UWF imaging should not be considered a replacement for a dilated fundus exam, several published clinical studies have demonstrated its equivalence to ETDRS in the evaluation of DR severity. Recently, a large, multicenter, cross-sectional observational study conducted by the Diabetic Retinopathy Clinical Research Network (DRCRN) found moderate to substantial agreement between ETDRS and Optos 200 degree UWF images. Masked readers graded more than 700 subjects for DR level. When evaluated, the images agreed exactly in 435 eyes (59%) and were within one level in 96.9% (714 eyes). Additionally, the results indicated that UWF images were better for assessing DR level in 27% of eyes than ETDRS. PPL were observed in 41% of these eyes and indicated increased DR severity by 2 steps or more in 11%. The authors concluded that these findings could support the use of UWF to evaluate DR severity in future clinical studies.12

**UWF for Telemedicine**

UWF has also begun to be evaluated for its use in telemedicine environments given the ease of use, seamless integration with EMR and value of additional information captured. When implemented in one large telemedicine system, UWF detected double the amount of DR, reduced ungradable rates by up to 81%, due to the ability to easily image through small pupils and media opacity.13

Another study in a diabetic screening program found in eyes without diabetic retinopathy, approximately 20% may have ocular findings identified on UWF imaging.14 In our own Cleveland Clinic Executive Health Clinic, UWF imaging detected peripheral pathology in 18.4% of eyes not visualized by traditional small field imaging in a population of health screening subjects.15

**Conclusion**

The body of research supporting the value of UWF imaging technology is considerable and continuously growing; as a result, UWF is fast becoming the standard of care for retinal vascular disorders especially DR. In my practice, we rely heavily on both the clinical and practical advantages that this technology provides.

Given the evidence and my experience, I believe that we have a responsibility to adopt technology that has the potential to detect disease earlier, treat it more effectively and ultimately, provide better care to more of our patients.

**References**


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HUMIRA is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients.

**INDICATION**

HUMIRA is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients.

**IMPORTANT SAFETY INFORMATION**

**SERIOUS INFECTIONS**

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Discontinue HUMIRA if a patient develops a serious infection or sepsis.

Reported infections include:

- Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Test patients for latent TB before HUMIRA use and during therapy. Initiate treatment for latent TB prior to HUMIRA use.
- Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.
- Bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria.

Carefully consider the risks and benefits of treatment with HUMIRA prior to initiating therapy in patients: 1. with chronic or recurrent infection, 2. who have been exposed to TB, 3. with a history of opportunistic infection, 4. who reside in or traveled in regions where mycoses are endemic, 5. with underlying conditions that may predispose them to infection. Monitor patients closely for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy.

- Do not start HUMIRA during an active infection, including localized infections.
- Patients older than 65 years, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressants may be at greater risk of infection.
- If an infection develops, monitor carefully and initiate appropriate therapy.
- Drug interactions with biologic products: A higher rate of serious infections has been observed in rheumatoid arthritis patients treated with rituximab who received subsequent treatment with a TNF blocker. Concurrent use of HUMIRA with biologic DMARDs (e.g., anakinra or abatacept) or other TNF blockers is not recommended based on the possible increased risk for infections and other potential pharmacological interactions.

**MALIGNANCY**

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including HUMIRA. Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers, including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn’s disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all of these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants.

- Consider the risks and benefits of HUMIRA treatment prior to initiating or continuing therapy in a patient with known malignancy.
- In clinical trials, more cases of malignancies were observed among HUMIRA-treated patients compared to control patients.

**HYPERSENSITIVITY**

- Anaphylaxis and angioneurotic edema have been reported following HUMIRA administration. If a serious allergic reaction occurs, stop HUMIRA and institute appropriate therapy.

**HEPATITIS B VIRUS REACTIVATION**

- Use of TNF blockers, including HUMIRA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers. Some cases have been fatal.
- Evaluate patients at risk for HBV infection for prior evidence of HBV infection before initiating TNF blocker therapy.
- Exercise caution in patients who are carriers of HBV and monitor them during and after HUMIRA treatment.
- Discontinue HUMIRA and begin antiviral therapy in patients who develop HBV reactivation. Exercise caution when resuming HUMIRA after HBV treatment.

**NEUROLOGIC REACTIONS**

- TNF blockers, including HUMIRA, have been associated with rare cases of new onset or exacerbation of central nervous system and peripheral demyelinating diseases, including multiple sclerosis, optic neuritis, and Guillain–Barré syndrome.
- Exercise caution when considering HUMIRA for patients with these disorders: discontinuation of HUMIRA should be considered if any of these disorders develop.
- There is a known association between intermediate uveitis and central demyelinating disorders.

**HEMATOLOGIC REACTIONS**

- Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF blockers. Medically significant cytopenia has been infrequently reported with HUMIRA.
- Consider stopping HUMIRA if significant hematologic abnormalities occur.

**CONGESTIVE HEART FAILURE**

- Worsening or new onset congestive heart failure (CHF) may occur; exercise caution and monitor carefully.

**AUTOIMMUNITY**

- Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in development of a lupus-like syndrome. Discontinue treatment if symptoms of a lupus-like syndrome develop.

**IMMUNIZATIONS**

- Patients on HUMIRA should not receive live vaccines.
- Pediatric patients, if possible, should be brought up to date with all immunizations before initiating HUMIRA therapy.
- The safety of administering live or live-attenuated vaccines in infants exposed to HUMIRA in utero is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants.

**ADVERSE REACTIONS**

- The most common adverse reactions in HUMIRA clinical trials (>10%) were: infections (e.g., upper respiratory, sinusitis), injection site reactions, headache, and rash.


Please see Brief Summary of full Prescribing Information on the following pages.
For adult patients with non-infectious (NI) intermediate, posterior, and panuveitis¹

**NON-INFECTIONOUS (NI) UVEITIS**

**CAN BE HARD TO CONTROL.**

**HUMIRA is proven to¹:**

- Provide steroid-sparing efficacy
- Prolong time to a combined measure of disease flare ‡ and decrease of visual acuity

Visit www.HumiraPro.com/uveitis to learn more.

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¹Intermediate, posterior, and panuveitis.

‡Disease flare is defined by an increase in 1 or more inflammatory markers: AC cells, vitreous haze, and/or development of new chorioretinal and/or retinal vascular lesions.
Clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease and in adult patients with moderately to severely active ankylosing spondylitis.

Further study is needed to establish the optimal duration of treatment for Crohn's disease or ankylosing spondylitis. This therapy should not be used in patients who are actively infected with hepatitis B or C. A negative hepatitis B surface antigen test is not indicative of immunity to hepatitis B virus and such patients may still develop post-treatment hepatitis B. Before initiating therapy with HUMIRA, a negative hepatitis B surface antigen test should be obtained. If a patient is reactive, hepatitis B vaccine should be administered, followed by a hepatitis B surface antigen test 1 month after completion of vaccination. If hepatitis B surface antigen test is positive, hepatitis B immune globulin (HBIG) should be administered to all patients as prophylaxis against hepatitis B. For treatment of active hepatitis B, consult a physician with expertise in the treatment of viral hepatitis.

In patients with tuberculosis, active or latent, the concurrent use of anti-TNF therapy and tuberculosis treatment should be avoided (see Warnings and Precautions and Drug Interactions).

The development of latent tuberculosis infection in patients treated with anti-TNF agents has been noted following both switching therapy from a non-TNF agent to HUMIRA and initiation of therapy with HUMIRA. Before initiating therapy with HUMIRA, a negative PPD skin test (or IGRA if patient is not PPD skin test-eligible) is recommended. If the result of the skin test is positive, treatment with appropriate anti-TB therapy is recommended. If the result of the skin test is negative, consider a chest radiograph, which may be negative in some patients with active infection. In all cases of active or latent tuberculosis, a negative PPD skin test or IGRA should be rechecked 1 month after initiating appropriate anti-TB therapy.

The concurrent use of HUMIRA and thiopurine drugs in patients with moderate to severe Crohn’s disease, rheumatoid arthritis, ankylosing spondylitis, or psoriatic arthritis has been reported. Cautious consideration is needed for the long-term use of these combinations because of increased risk of lymphoma (see Warnings and Precautions and Drug Interactions).

The concurrent use of HUMIRA in patients with a history of using methotrexate may be associated with increased risk of lymphoma. In controlled clinical trials, the incidence of lymphoma in the HUMIRA-treated patients was lower than the incidence in patients treated with methotrexate at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with methotrexate. The data do not support a direct causative relationship between the use of TNF blockers and the occurrence of HSTCL.

The development of lymphoma, including HSTCL, in patients treated with TNF blockers has been associated with concomitant use of other immunomodulatory therapies, such as thalidomide, cyclosporine, or methotrexate. The most common types of lymphomas reported were Hodgkin's disease, non-Hodgkin's lymphoma, and MALT lymphoma. The types of lymphoma that occur during TNF-blocker therapy are similar to those that occur in the general population. However, the malignancies in HUMIRA-treated patients in clinical trials occurred after a median of 30 months of therapy (range 1 to 65 months) among HUMIRA-treated patients and 0.2 (0.10, 0.59) per 100 patient-years among control-treated patients. Examine all patients, and in particular patients with a medical history or in remission for the development of lymphoma, even in the absence of TNF blockers. In patients with HUMIRA therapy, the rate (95% confidence interval) of all hematologic malignancies was 0.5 (0.2, 1.0) per 100 patient-years among 7973 HUMIRA-treated patients versus a rate of 0.7 (0.4, 1.1) per 100 patient-years among 4848 control-treated patients. The rate of HSTCL was 0.02 (0.00, 0.11) per 100 patient-years among HUMIRA-treated patients and 0.1 (0.0, 0.4) per 100 patient-years among control-treated patients.

Hematologic malignancies, including lymphoma, have been reported in patients on concomitant immunosuppressive therapy (see Warnings and Precautions). Consider the risks and benefits of TNF-blocker treatment including HUMIRA prior to initiating therapy for patients at increased risk for malignancy, such as patients with a medical history.

In adult patients receiving HUMIRA, the rate of all malignancies was 4.3 per 100 patient-years in 5299 HUMIRA-treated patients versus a rate of 2.2 per 100 patient-years in 7973 control-treated patients. In the controlled portions of the 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, Ps, UV and NS, the rate (95% confidence interval) of all malignancies was 0.3 (0.2, 0.5) per 100 patient-years among HUMIRA-treated patients versus a rate of 0.1 (0.0, 0.3) per 100 patient-years among control-treated patients. Examine all patients, and in particular patients with a medical history or in remission for the development of lymphoma, even in the absence of TNF blockers. In patients with HUMIRA therapy, the rate (95% confidence interval) of all hematologic malignancies was 0.5 (0.2, 1.0) per 100 patient-years among 7973 HUMIRA-treated patients versus a rate of 0.7 (0.4, 1.1) per 100 patient-years among 4848 control-treated patients. The rate of HSTCL was 0.02 (0.00, 0.11) per 100 patient-years among HUMIRA-treated patients and 0.1 (0.0, 0.4) per 100 patient-years among control-treated patients.

Hematologic malignancies, including lymphoma, have been reported in patients on concomitant immunosuppressive therapy (see Warnings and Precautions). Consider the risks and benefits of TNF-blocker treatment including HUMIRA prior to initiating therapy for patients at increased risk for malignancy, such as patients with a medical history.
In clinical Phase 3 trials of HUMIRA (initial doses of 10 mg and 80 mg, or 40 mg and 80 mg on Day 1 and 5, respectively, followed by 40 mg every other week in adults) in patients with ankylosing spondylitis, the incidence of serious infections was 2.9% among patients treated with HUMIRA compared to 0.3% among patients treated with placebo (5/111 vs 1/112). In controlled trials of HUMIRA (initial doses of 10 mg and 40 mg or 80 mg on Day 1 and 5, respectively, followed by 40 mg every other week in patients with UC, with or without concomitant 5-ASA therapy), the incidence of serious infections was 1.8% among patients treated with HUMIRA compared to 0.7% among patients treated with placebo (6/315 vs 2/297).

In adult patients with rheumatoid arthritis (RA), the incidence of serious infections was 2.1% among patients treated with HUMIRA compared to 1.6% among patients treated with placebo (89/4,089 vs 81/5,037). In controlled trials of HUMIRA (initial doses of 10 mg and 40 mg on Day 1 and 5, respectively, followed by 40 mg every other week in patients with UC treated with 5-ASA, or with UC and 5-ASA, or with placebo), the incidence of serious infections was 1.4% among patients treated with HUMIRA compared to 1.2% among patients treated with placebo (14/314 vs 14/263).

In pediatric patients with Crohn’s disease, the rate of antibody development in patients treated with HUMIRA, infliximab and placebo in a randomized, double-blind, controlled study was 10% compared to 1% and 3%, respectively. In patients treated with infliximab, the rate of antibody development was 3%. In patients with Crohn’s disease, the rate of antibody development in patients receiving HUMIRA, infliximab and placebo in a randomized, double-blind, controlled study was 10% compared to 1% and 1%, respectively. In patients treated with infliximab, the rate of antibody development was 3%.

In patients with AS, the rate of antibody development in patients receiving infliximab and placebo in a randomized, double-blind, controlled study was 1% compared to 1% and 2% respectively. In patients treated with infliximab, the rate of antibody development was 2%.

In pediatric patients with non-infectious uveitis, anti-adalimumab antibodies were identified in 4.8% of patients treated with HUMIRA compared to 1.3% and 2.3%, respectively, in patients treated with placebo and infliximab. Among the patients whose serum adalimumab levels were < 2 mcg/mL, anti-adalimumab antibodies were identified in 2.1% of patients treated with HUMIRA compared to 0.8% and 0.5%, respectively, in patients treated with placebo and infliximab. In patients treated with infliximab, the rate of antibody development was 3%.

In patients with AS, the rate of antibody development in patients receiving adalimumab and placebo in a randomized, double-blind, controlled study was 10% compared to 1% and 2%, respectively. In patients treated with adalimumab, the rate of antibody development was 3%.

In patients with AS who were 4 to 12 years of age, anti-adalimumab antibodies were identified in 14% of patients treated with HUMIRA. Patients in receiving concomitant MTX, the incidence was 6% compared to 20% with HUMIRA monotherapy. In patients weighing 15 kg or greater, anti-adalimumab antibodies were identified in 3% of patients treated with HUMIRA compared to 1% and 0% respectively, in patients treated with placebo and infliximab. In patients treated with infliximab, the rate of antibody development was 4%.

In patients with AS, the rate of antibody development in patients receiving infliximab and placebo in a randomized, double-blind, controlled study was 1% compared to 1% and 2%, respectively. In patients treated with infliximab, the rate of antibody development was 3%.

In general, the adverse reactions in the HUMIRA-treated patients in the polyarticular juvenile idiopathic arthritis (JIA) trials (Studies A1 and A2) were similar in frequency to those seen in patients with juvenile idiopathic arthritis treated with monotherapy, etanercept, methotrexate, and placebo. Important findings and differences from adults are discussed in the following paragraphs.

In Study A1, 44% of patients experienced an episode while receiving HUMIRA or etanercept during the 3 years of the trial. In patients receiving HUMIRA, 17% of patients discontinued treatment compared to 15% in the placebo group. In patients receiving etanercept, 15% discontinued treatment compared to 17% in the placebo group.

In the first 48 weeks of treatment in Study A1, non-serious hypersensitivity reactions were seen in approximately 3% of patients and included localized or generalized hypersensitivity reactions and allergic reactions.

In Study A1, 14% of patients treated with HUMIRA who had negative baseline anti-drug antibodies developed positive antibodies after 48 weeks of treatment with HUMIRA. No patients developed clinical signs of atopy during the clinical trial.

Approximately 15% of patients treated with HUMIRA developed mild to moderate reactions of creatinine phosphokinase (CPK) (≥ 5 x ULN) in Studies A1 and A2. Elevations exceeding 5 times the upper limit of normal were seen in 3% of patients treated with HUMIRA. None of these patients discontinued treatment due to these elevations.

In Study A1, 4% of patients experienced an episode while receiving HUMIRA or etanercept in the study. In patients receiving HUMIRA, 2% discontinued treatment compared to 3% in the placebo group. In patients receiving etanercept, 2% discontinued treatment compared to 4% in the placebo group.

In Study A1, 17% of patients treated with HUMIRA were on concomitant MTX. The rate of antibody development in patients on concomitant MTX was comparable to patients on HUMIRA monotherapy (10% vs 12%). However, in patients receiving HUMIRA and concomitant MTX, the rate of antibody development was 7% compared to 1% in RA.

In adults, patients with a history of anaphylaxis to adalimumab should be monitored closely for the development of anaphylaxis. In a clinical study involving 2,637 patients with anaphylaxis to adalimumab, 1 patient was receiving concomitant MTX.

In patients with AS, the rate of antibody development in patients receiving infliximab and placebo in a randomized, double-blind, controlled study was 1% compared to 1% and 2%, respectively. In patients treated with infliximab, the rate of antibody development was 3%.

In patients with UC, the rate of antibody development in patients receiving adalimumab and placebo in a randomized, double-blind, controlled study was 10% compared to 1% and 2%, respectively. In patients treated with adalimumab, the rate of antibody development was 3%.

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Other Medical Conditions
Advises patients to report any signs of new or worsening medical conditions such as congestive heart failure, neurological disease, autoimmune disorders, or cytopenias.

Advise patients to report any symptoms suggestive of a cytopenia such as bruising, bleeding, or persistent fever.

AbbVie Inc.
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A CONTACT LENS SENSOR (CLS)
(Triggerfish, Sensimed AG) may be able to identify which patients are at greatest risk of glaucoma progressing faster, according to Arthur J. Sit, SM, MD.

“There do seem to be specific patterns that are associated with glaucoma progression,” said Dr. Sit, professor of ophthalmology, Mayo Clinic, Rochester, MN.

However, Dr. Sit cautioned that the device cannot be used to measure an individual patient’s IOP, and more research is needed.

“To really understand where this fits into our clinical armamentarium, we’re probably going to need prospective data,” said Dr. Sit, who presented a research update on the device.

DIVING DEEPER
The most common methods of measuring IOP cannot effectively track changes over time, for example with circadian rhythms. IOP also spikes when patients lie down, Dr. Sit noted.

“When we think about how we measure IOP patterns it can vary a lot depending on our situation,” he said.

That leaves clinicians to rely on estimates.

“Most of us measure every few months, and we hope that what we’re measuring is the correct parameter for what we’re actually trying to treat,” Dr. Sit said.

The Triggerfish, by contrast, provides noninvasive, continuous, 24-hour monitoring. It consists of a silicone contact lens with an embedded strain gauge to measure changes in the corneal radius of curvature as it fluctuates with pressure within the eye. An antenna is embedded around the periphery of the lens. A matching adhesive antenna worn around the orbit transmits power and sends data to a portable recorder carried by the patient.

The device is sensitive enough to record changes in pressure with blinks and saccades, “so it pretty clearly picks up changes within the eye,” Dr. Sit said.

It also shows changes after treatment with selective laser trabeculoplasty, ab interno trabeculectomy, and ExPRESS shunt.

Rather than measuring IOP, however, the Triggerfish measures the distension of the eye with pressure, and produces output in millivolts. The device was approved by the FDA in 2016 “to detect the peak patterns of variation in intraocular pressure over a maximum period of 24 hours to identify the window of time to measure intraocular pressure by conventional clinical methods.”

So how well do the patterns it measures correlate to changes in IOP?

Dr. Sit cited a study from the University of California, San Diego (UCSD) that measured the patterns in one eye with the contact lens sensor and in the contralateral eye with pneumatonometry every 2 hours. These patterns correlated closely: R² = 0.956

 Peaks in pressure coincided between the Triggerfish and the pneumotonometer.

“However, when you look at the amplitudes that occur over 24 hour period with the [Triggerfish] and the IOP measurements with the pneumatonometer, there is in fact no correlation,” Dr. Sit said. “What that suggests is that they have similar patterns but they are not equivalent.”

In another study from UCSD, researchers measured the patterns over 24 hours and then repeated these measurements later. They found good correlation, but with significant individual variation, said Dr. Sit.

For example, in one 53-year-old male with a stable life, the two patterns overlapped. But in a 20-year-old male glaucoma suspect with variable sleep patterns, there was almost no correlation between the two measurements.

“Given these limitations, is there in fact clinical value that we can get out of the Triggerfish?” Dr. Sit asked. “There is emerging evidence that yes, there is.”

He cited a study from Hong Kong on primary angle-closure glaucoma. The researchers measured visual field progression by mean deviation slopes. They analyzed 55 variables in a multivariable model, including age, baseline disease and laser surgery.

They found that if they used a model with the Triggerfish parameters, it was more closely associated with fast visual field progression than if they used IOP measured by Goldman applanation tonometry in the office.

Another study, this one from Japan, looked at normal-tension glaucoma patients. The range of pressure fluctuation was larger in the eyes with normal tension glaucoma compared with patients without glaucoma. These researchers postulated that the larger fluctuation might be one of the reasons that patients developed glaucoma.

Another study, this one a multicenter, retrospective cohort study, conducted at 50 centers in 13 countries, included 445 eyes in 445 patients who were treated for manifest open-angle glaucoma.

The researchers measured visual field progression by mean deviation slopes. They analyzed 55 variables in a multivariable model, including age, baseline disease and laser surgery.

They found that if they used a model with the Triggerfish parameters, it was more closely associated with fast visual field progression than if they used IOP measured by Goldman applanation tonometry in the office.

A CONTACT LENS SENSOR (CLS)
(Triggerfish, Sensimed AG) consists of a silicone contact lens with an embedded strain gauge to measure changes in the corneal radius of curvature as it fluctuates with pressure within the eye. (Image courtesy of Sensimed AG)

**take-home**

➤ The contact lens sensor may be able to identify which patients are at greatest risk of glaucoma progressing faster, according to Arthur J. Sit, SM, MD.

**By Laird Harrison; Reviewed by Arthur J. Sit, SM, MD**
Exploring ins, outs of better imaging for LASIK, refractive surgery

Myriad tools can help surgeons better assess patients at consultation and postoperative

By Vanessa Caceres; Reviewed by Sonia H. Yoo, MD

IMAGING TOOLS — such as topography, tomography, ray-tracing, and anterior-segment optical coherence tomography (AS-OCT) — are helpful to both plan refractive surgeries and assess any potential complications, said Sonia H. Yoo, MD, professor, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine.

“It’s important to recognize pathological patterns to rule out candidates such as the patient with inferior steepening,” Dr. Yoo said. Keratorefractive surgery performed in such cases is associated with a higher risk of keratectasia and postoperative topographic instability.

A decentered myopic ablation and a central island are other complications that can be seen by topography and are associated with poor outcomes.

Tomography generates a 3-D recreation and can measure the anterior and posterior surfaces, which can be helpful with assessment of the cornea.

Wavefront maps and ray-tracing help surgeons to evaluate higher-order aberrations (HOAs), which can be responsible for reduced quality of vision, Dr. Yoo said. Ray-tracing is another tool to evaluate HOAs.

Anterior-segment OCT is a non-contact approach to evaluate the cornea and anterior segment, and it can penetrate through corneal opacities and scars. One way to use AS-OCT is to see if a patient is a candidate for a LASIK enhancement.

A CLOSER LOOK

Dr. Yoo presented some example patients evaluated with these imaging tools.

For instance, a 30-year-old male had LASIK and persistently blurry vision. By looking at topography and HOAs, Dr. Yoo could see significant amount of coma, consistent with his complaint of blurriness.

Another patient was a 28-year-old male wanting to have refractive surgery. Dr. Yoo also had treated the patient’s father, who had bilateral corneal transplants for keratoconus. The son had a spherical refraction, good best-corrected visual acuity (BCVA), and relatively normal tomography. Via wavefront, a high degree of coma was seen.

“Coma is an early finding with keratoconus and because of his strong family history, we decided to do surface ablation,” Dr. Yoo said. However, the patient ultimately had a good outcome.

Sonia H. Yoo, MD

This article was adapted from Dr. Yoo’s presentation at the 2018 meeting of the American Academy of Ophthalmology. Dr. Yoo is an equity partner in Resolve Ophthalmics and a consultant for Avedro.

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(FIGURE 1) Tomography generates a 3-D recreation and can measure the anterior and posterior surfaces, which can be helpful with assessment of the cornea. Top: Is this normal? Bottom: Forme fruste keratoconus (FFKCN).

(FIGURE 2) A 30-year-old male had LASIK and persistently blurry vision. By looking at topography and higher-order aberrations, Sonia H. Yoo, MD, could see significant amount of coma, consistent with his complaint of blurriness. (Figures courtesy of Sonia H. Yoo, MD)
Slit lamp biomicroscope workhorse tool for infectious keratitis diagnosis
Clinical evaluation is basis for deciding whether additional imaging is needed

By Cheryl Guttman Krader; Reviewed by Elmer Y. Tu, MD

ADVANCED imaging modalities can aid in the diagnosis of infectious keratitis, but slit lamp biomicroscopy is still the cornerstone for patient evaluation, said Elmer Y. Tu, MD.

“The slit lamp biomicroscope is our most powerful imaging tool for diagnosing infectious keratitis,” said Dr. Tu, professor of clinical ophthalmology and director, Cornea Service, Illinois Eye and Ear Infirmary, University of Illinois College of Medicine, Chicago. “The clinical evaluation begins with its use, and it is the basis for deciding whether additional imaging is needed.”

Confocal microscopy is the gold standard for diagnostic imaging in infectious keratitis, but optical coherence tomography (OCT) is usually turned to next because of its greater availability, Dr. Tu added.

CHARACTERISTIC CLINICAL PRESENTATIONS
Using the slit lamp, clinicians may determine the causative pathogen of infectious keratitis by determining the organism’s growth pattern within the cornea and other unique clinical signs.

“Based on slit lamp appearance alone, most clinicians can differentiate between bacterial and Acanthamoeba keratitis,” Dr. Tu said. “Identifying fungal keratitis based on clinical presentation alone can be a little more difficult, particularly if the patient has been put on a topical corticosteroid.”

Describing the different types of infectious keratitis, Dr. Tu said that bacterial keratitis typically presents with a small, superficial solitary lesion involving the epithelium.

“The appearance is similar to that of a bacterial culture on agar,” he noted, adding that there may also be inflammation with or without hypopyon.

With fungal keratitis, both inflammation and necrosis are minimal initially. Characteristic features include a central nidus of growth with branching filaments, a translucent, raised “frosted-glass appearance,” satellite lesions, and endothelial plaque. Also, IOP tends to be elevated.

“The branching filaments grow upward, creating punctate ‘on-end’ opacities and adding to corneal contour,” he said. “I teach residents that if the cornea looks thicker, think about fungal keratitis because it is the only infectious modality that adds to the corneal contour.”

The finding of pigment within a corneal ulcer suggests fungal etiology until proven otherwise—pigmented fungal species include Curvularia, Cladosporium, Acremonium, and Exserohilum. Absence of pigment, however, does not rule out pigmented fungus as the cause. Sudden onset or worsening of hypopyon may be a sign that the hyphae have grown through Descemet’s membrane. “The latter is a common finding in Fusarium keratitis, and it will lead to intracocular inflammation and possibly an endothelial plaque,” Dr. Tu said.

In cases of Acanthamoeba or herpetic keratitis, the corneal is fairly intact. The lesion presents with a smooth firm bed, there is mainly an infiltrative pattern of proliferation, and epithelial cysts, radial neuritis, ring infiltrates, and ulceration can develop.

Clues to the cause of infectious keratitis can also come from paying attention to tactile feedback while obtaining a sample for microbiological evaluation. Because of the necrotic bed with a bacterial ulcer, clinicians will perceive corneal pliability while performing corneal scraping, whereas with fungal keratitis and infections caused by atypical Mycobacteria, the rough corneal bed creates a gritty feel. When scraping the cornea in cases of Acanthamoeba disease, the instrument feels like it is skating over ice because of the smooth firm bed, Dr. Tu said.

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This article was adapted from Dr. Tu’s presentation during Cornea Subspecialty Day at the 2018 meeting of the American Academy of Ophthalmology. He has no relevant financial interests to disclose.

FIGURE 1
In cases of Acanthamoeba keratitis (shown here) or herpetic keratitis, the corneal is fairly intact. The lesion presents with a smooth firm bed, there is mainly an infiltrative pattern of proliferation, and epithelial cysts, radial neuritis, ring infiltrates, and ulceration can develop.

FIGURE 2
Confocal of Beauveria keratitis.
(Images courtesy of Elmer Y. Tu, MD)
Image-guided technologies enhance drive for cataract surgery perfection

Approach aids toric IOL alignment, IOL centration, wound/astigmatic keratotomy placement

By Lynda Charters; Reviewed by Zaina N. Al-Mohtaseb, MD

PATIENT expectations for cataract surgery are at an all-time high. As a result, to reach excellent refractive outcomes, great emphasis is placed on the preoperative steps taken in preparation for cataract surgery, such as keratometry, biometry, and IOL power calculations. With technologic advances, that list has lengthened to include intraoperative considerations.

Newer technologies that provide intraoperative imaging are continuously improving to aid surgeons with toric IOL alignment, IOL centration, and wound and astigmatic keratotomy placement to lessen errors as much as possible, according to Zaina Al-Mohtaseb, MD.

“Greater importance is being placed specifically on capsulorhexis and IOL centration, astigmatic keratotomy placement, and toric IOL alignment with the introduction of presbyopia-correcting IOLs that include both a multifocal and a toric component,” said Dr. Al-Mohtaseb, assistant professor of ophthalmology, Cullen Eye Institute, Baylor College of Medicine, Houston.

“Their optimization is definitely important to get excellent refractive outcomes.”

The impact of alignment errors is great and demonstrates the need for precision, and the degree of alignment errors increases exponentially in the more complex commercially available lenses. If the alignment is off-axis by about 10°, the result is a 34% error, and when an IOL is off-axis by 30°, this results in an error of 100% with almost no effective astigmatic correction but a resultant change in the axis, she said.

Errors can occur in a few key areas when placing a toric IOL, i.e., in determining the initial reference axis when the eye is marked for example at the 3, 6, and 12 o’clock positions, when marking the axis intraoperatively, and then aligning the lens to that axis.

Dr. Al-Mohtaseb provided a brief overview for some of the newer instrumentation technologies (including the Zeiss Callisto, Alcon Verion, and TrueVision) that aid in aligning toric IOLs with the goal of lessening potential errors.

ZEISS CALLISTO. A reference image is acquired during routine biometry with the IOLMaster 700. This reference image is then viewed intraoperatively to center the capsulorhexis and multifocal IOLs, place incisions, and align toric IOLs. She cited a study (Mayer et al. J Cataract Refract Surg. 2017;43:1281–1286) in which the accuracy and outcomes were compared between the Callisto (n = 28 eyes) and manual markings (n = 28 eyes). The study showed less degrees of postoperative IOL misalignment were in favor of Callisto digital marking, i.e., 2.0° for digital marking compared with 3.40° for manual marking, a difference that reached significance (p = 0.026).

Another finding was that the time required to perform IOL alignment was significantly shorter with the digital approach compared with manually, i.e., 37.2 seconds versus 59.4 seconds, respectively; p < 0.001.

Titiyal et al. (Clinical Ophthalmology. 2018;12:747-753) compared toric IOL alignment assisted by image-guided technology (Callisto) vs. manual marking methods and its impact on visual quality and reported a significant (p = 0.003) difference with lower refractive cylinder postoperatively, −0.89 D versus −0.64 D, respectively. The study also found less deviation from the target axis with the Callisto both on postoperative days 1 and 30 (p = 0.005 for both comparisons).

ALCON VERION. This system has a reference unit that obtains images preoperatively with a digital marker that captures the image. This image then is used intraoperative to aid in centration of the capsulorhexis and multifocal IOLs, incision placement, and IOL alignment. Elhohi and Helaly conducted a study (Medicine. 2015;94:1–4) in which they compared the Verion and manual marking capabilities for aligning toric IOLs. The results also pointed to the superiority of digital marking in the degrees of misalignment between the two methods (2.40° versus 4.33°, respectively).

Hura and Osher (J Refract Surg. 2017;33:482–7) compared the accuracy of the Callisto and the Verion for toric IOL alignment found that the two technologies, interestingly, were not interchangeable.

“Both did not necessarily have the same axis, but neither system was superior,” she said.

TRUEVISION. This system differs slightly from the previous two by offering toric IOL alignment with data integration with the preoperative data obtained from the Cassini, Pentacam, or Lenstar. The system obtains an image preoperatively that can then be used intraoperatively to account for cyclotorsion in real time using the overlay. When Dr. Al-Mohtaseb, Douglas D. Koch, MD, and colleagues at Baylor conducted a study in which they compared the manual markings with TrueVision, they found no significant difference between the two.

(The three-dimensional, TrueVision digital imaging technology/visualization system with heads-up display is partnership with Alcon Laboratories and is being used in both retina and cataract surgeries [NGENUITY]).

ORA SYSTEM. This platform differs from the other three systems in that it is an intraoperative wavefront aberrometer that can perform aphakic and pseudophakic refractions.

One situation in which this technology is helpful is in cataract patients who have had previous refractive surgery, she said. A study by Lanchelev et al. (Ophthalmology. 2014;121:56–60) found that ORA provided a significant improvement in predicting the lens power after a previous myopic refractive surgery. The technology also is helpful for toric IOL alignment. A study by Woodcock et al. (J Cataract Refract Surg. 2016;42:8107–825) found that more patients had less than 0.5 D of astigmatism when the ORA was used compared with standard preoperative biometry, she recounted.

take-home

The drive to perfection in cataract surgery is enhanced by intraoperative real-time appreciation of the status of individual patients.

ZEISS CALLISTO.

Dr. Al-Mohtaseb

By Lynda Charters

STATE-OF-THE-ART ADVANCES IN DIAGNOSTICS & IMAGING

This article was adapted from Dr. Al-Mohtaseb’s presentation during Cornea Subspecialty Day at the 2018 meeting of the American Academy of Ophthalmology. Dr. Al-Mohtaseb is a consultant to Alcon Laboratories, Bausch + Lomb, Carl Zeiss Meditec, and Johnson & Johnson.

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AI ANALYSIS

(Continued from page 1)

fore requires operator training, but training is minimal. Existing staff may be trained in a few hours, even if they have not done retinal imaging.

The algorithm uses a histogram to calculate the number of patients and to estimate the number of abnormal cases. The algorithm is trained on the ETDRS data set, and then it is used to test the accuracy of the algorithm. The results showed that for the AI system, the sensitivity, meaning the ability to capture the level of moderate or more DR and/or ME, was 87%, meaning 87% of cases were caught, compared to the much smaller area covered by the AI imaging.

The results showed that for the AI system, the sensitivity, meaning the ability to capture the level of moderate or more DR and/or ME, was 87%, meaning 87% of cases were caught, compared to the same ETDRS reference standard—but without OCT—have shown sensitivities of 34%, 33%, and 73% in the only available studies compared with full ETDRS. The reason for this is likely that while ophthalmologists are highly experienced in calling out no and severe DR, it is much harder to differentiate precisely between mild and moderate DR—which can depend on the presence of a single hemorrhage.

Another important item is imageability, which is the capacity of the AI system to be able to make a clinical decision, rather than report that there is insufficient quality to make a diagnosis. This happened in only 4% of cases, so in 96% of cases in the study, the system was able to make a clinical diagnosis.

**Practice Patterns**

The system output aligns very closely with the preferred Clinical Practice Patterns from the AAO. The “no or mild DR” results require no more than review at 12 months.

All other stages, including both center-involved and clinically significant DME as well as all more severe stages of DR, require closer follow up, and in some cases treatment.

**ETDRS**

The most commonly used standard for deciding the severity of DR is the Early Treatment Diabetic Retinopathy Study (ETDRS) severity scale. In the pivotal trial, the autonomous AI system was compared with this standard.

In Figure 2, the white outlines in the image on the left show the areas covered by the four widefield stereo images that are required for the ETDRS level grading to create the reference standard. Macular optical coherence tomography (OCT), shown in the lower left, was also obtained to determine center-involved DME for the reference standard.

In the image on the right, the two green circles show the much smaller area covered by the AI imaging. While these two non-stereo images are more patient-friendly to obtain, compared with eight flash widefield images required for ETDRS, the area covered is smaller, and so any hemorrhages or other lesions outside the green areas will be missed by the AI system, but will still contribute to the reference standard used to determine whether or not the AI system was correct.

**CLINICAL TRIAL**

A study was conducted on 900 subjects with diabetes from primary-care clinics around the United States, many of which did not have an ophthalmic clinic within close distance. The AI system was operated by minimally trained operators who had to confirm they had never imaged the retina before the start of the study, whereas the aforementioned ETDRS reference standard was obtained by highly experienced, certified retinal photographers, and then the ETDRS reference standard was compared to the output of the autonomous AI system.

The results showed that for the AI system, the sensitivity, meaning the ability to capture the level of moderate or more DR and/or ME was 87%, meaning 87% of cases were caught, and the specificity, meaning the ability to correctly identify those without disease, was 90.7%.

Board-certified ophthalmologists, compared to this same ETDRS reference standard—but without OCT—have shown sensitivities of 34%, 33%, and 73% in the only available studies compared with full ETDRS. The reason for this is likely that while ophthalmologists are highly experienced in calling out no and severe DR, it is much harder to differentiate precisely between mild and moderate DR—which can depend on the presence of a single hemorrhage.

Another important item is imageability, which is the capacity of the AI system to be able to make a clinical decision, rather than report that there is insufficient quality to make a diagnosis. This happened in only 4% of cases, so in 96% of cases in the study, the AI system was able to make a clinical diagnosis.

**Reference**


**Take-home**

- The approval last year for the first autonomous artificial intelligence (AI) to make a diagnosis without a physician has opened new doors for the first medical device to use AI to diagnose moderate or worse diabetic retinopathy or macular edema in adults who have diabetes.

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**Picture**

**Truth versus AI system**

<table>
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<tr>
<th>FPRC: 4 widefield stereo (Topcon Maestro)</th>
<th>AI system: two field mono</th>
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<tr>
<td>Highest quality imaging reference standard</td>
<td></td>
</tr>
<tr>
<td>Green: 2 fields covered by Topcon NW400</td>
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(FIGURE 2) Left: The white outlines show the areas covered by the four widefield stereo images that are required for the ETDRS level grading to create the reference standard. Right: The two green circles show the much smaller area covered by the AI imaging. (Images courtesy of Michael D. Abramoff, MD, PhD)
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Detecting vision-threatening conditions in early childhood

How one program uses instrument-based vision screening to achieve high-quality referrals

By Joannah Vaughan, MBA, Talitha Dale, and Daniel Karr, MD; Special to Ophthalmology Times

Regular vision-screening assessments in early childhood have been shown to reduce the risk of persistent amblyopia at 7 years of age by more than half.1,2

To better clarify the role of vision screening in primary-care offices, in 2016, the American Academy of Pediatrics (AAP) updated its guidance for ocular examinations and visual assessments on children. Key to the update is discussion and direction regarding instrument-based screening.

**OREGON ELKS EXPERIENCE**

The Oregon Elks Children’s Eye Clinic began using photoscreening exclusively in 2013 for its Preschool Vision Screening Program, which focuses on detecting amblyopia. The Oregon state legislature mandates that all children entering school show proof of a vision screening, and the Elks program provides free photoscreening using the plusoptiX S12.

Through the program, data on 7,551 children were collected from 2017 to 2018; 12.3% were referred for a complete eye examination. Of the children referred, 108 cases of amblyopia were diagnosed.

In 2017, in the Elks program, 87.8% of the children who were referred received treatment. A recent retrospective record review found that the most common reason for overreferral in the Elks program was astigmatism when using a 1.50 D referral criterion with the plusoptiX.12 When the setting was changed to 2.25 D, the false positives were reduced by 34%.

Overall, the program’s database contains more than 50,000 scans, and notes from follow-up eye examinations are analyzed to determine the accuracy of screenings. The Elks program’s well-developed follow-up component ensures that 62% of children identified for referral have a follow-up examination; a rate of 46% has been reported elsewhere.13

**CONCLUSION**

Photoscreeners like the plusoptiX estimate refractive error, media clarity, ocular alignment, and eyelid positions. Abnormalities in these characteristics are risk factors for the presence or development of amblyopia, which, when left untreated, is the most frequent cause of preventable vision loss in children. Although there appears to be broad awareness of the importance of childhood vision screening, only about 40% of pre-kindergarten children in the United States are screened.14–16

Photoscreening takes less than a minute, and it requires less attention and cooperation from the child compared with traditional visual acuity screening.

The Oregon Elks Preschool Vision Screening Program achieves high-quality, vision-screening referrals using photoscreening and well-validated criteria. Because not all school-age children will need a complete eye examination, photoscreening is a cost-effective method for identifying those who do.

**TAKE-HOME**

Instrument-based vision screening can identify high-quality referrals and is less time-consuming than using traditional optotypes.

**V A L I D A T E D  S C R E E N I N G S**

The report notes the availability and extensive validation of device-based screening in field studies and in the office.3–8 The AAP states that screening instruments detect amblyopia, high refractive error, and strabismus, the most common conditions that produce visual impairment in children.1,2,9

Although they can be used at any age, screening devices have better success when the child is older than 18 months of age, according to the AAP.4,10 Instrument-based screening can be repeated annually, through age 5, or until “visual acuity can be assessed reliably with optotypes.”

The AAP concludes: “Using these techniques in children younger than 6 years can enhance detection of conditions that may lead to amblyopia and/or strabismus compared with traditional methods of assessment.”11

On the heels of the AAP direction, the U.S. Preventive Services Task Force released a statement supporting device-based screening technologies for preschool vision screenings with a level B evidence rating.11

The Affordable Care Act requires that health plans fully cover preventive services that have an A or B rating (CPT code 99177 for an immediate result in office, CPT 99174 for remote interpretation).

**T A K E - H O M E**

- Instrument-based vision screening can identify high-quality referrals and is less time-consuming than using traditional optotypes.

**O T**

For the fully referenced article, go to OphthalmologyTimes.com/Screenings

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None of the authors has financial disclosures.
As a business coach, I walk a fine line. On one hand, I am paid to shine the harsh light of reality on practice performance; on the other, I reshape the things patients are afraid to say in a way that doesn’t make you cringe.

Delivering criticism can be uncomfortable, intimidating, and hard to share. Hardest is being the recipient and fighting past the emotion of rejection to get to understanding, acceptance, and change. Separating process improvement from the emotion of failure leads to long-term success.

Acknowledge and redress your shortcomings for a successful 2019. While it is true that patients can act just like disloyal consumers looking for a Black Friday deal, professional practices still find it helpful to ask themselves two important questions:

Have we made patients less loyal through our emphasis on our participation in vision plans and discounting goods and services?

Are we giving our patients enough value to keep them loyal?

**MOTIVATION WITHOUT TEARS**

The dynamic of disappointing patients is closely tied to understanding what the patient values. In a competitive environment, patients who do not feel they are being heard will take their business elsewhere. Do you, in fact, know how your patients define value?

Typically, patients value convenient exam times, a doctor who listens, and products that solve problems. Instead of waiting to see if the patient you saw today comes back, ask for feedback.

Complaints (or feedback from patients) are one of the most direct and effective ways for patients to tell practices that there is room for improvement.

What do you do if a new hire is struggling in their role, and dragging your team down? You offer feedback. As a practice, we cannot exceed expectations if we do not know exactly how we are failing. Only with feedback can we make the necessary changes.

**TAKE-HOME**

» Complaints are one of the most direct and effective ways for patients to provide feedback. Form a partnership with patients, and address negative feedback promptly, advises consultant Donna A. Suter.

**CLEAR PLAN TO IMPROVE**

Receiving feedback from patients is all about accepting their ratings (and comments) and fighting through strong emotions to the truth that will lead your practice into greater success.

The father of modern attribution theory, Fritz Heider, notes that most of us attribute blame to individuals, rather than the circumstances surrounding product or service failure. Because no one really likes to hear about his or her failures, we tend to dismiss the surface complaint and not listen to its deeper message.

Complaining patients are giving us an opportunity to find out what their problems are so we can help them. It is everyone’s job to encourage the upset patient to follow their plan of care and enjoy clear vision by purchasing premium optical products.

Unfortunately, I see more and more practices opting to “fire” the patient because they don’t care about their plan of care and enjoy clear vision by purchasing premium optical products. Unfortunately, I see more and more practices opting to “fire” the patient because they don’t care about their plan of care and enjoy clear vision by purchasing premium optical products.

Unfortunately, I see more and more practices opting to “fire” the patient because they don’t care about their plan of care and enjoy clear vision by purchasing premium optical products.

One solution that works with tech-savvy patients is making collecting customer satisfaction part of your digital outreach. The rare patient who complains is giving us a gift. We must develop the emotional discipline to look past how this gift is wrapped to its content. It is as if they are gifting us with a book entitled, “A Chance to Survive: Listen to Me and Stay in Private Practice.”

The more patients value what you do, the more loyal they will be. We all know that it is easier to take our business elsewhere than to go through the hassle of complaining. What this means is patients who complain to the practice are showing a greater degree of loyalty than patients who leave because of mediocre performance.

There are four things your patients want to tell you:

1. I expect you to have mastered the basics of what you say you will do. If you haven’t, I will switch to another source. Even if you have, that alone is not enough to keep me loyal.
2. I expect you to go beyond the basics and provide me with that which I value. If you do, you will have a loyal patient. If not, my business is ‘up for grabs.’
3. Some things you do irritate me, but are not important enough to drive me away. Besides, your competitors do the same things.
4. There are some things you do that I don’t care anything about.
I have discovered in helping more than 1,000 practices over the past 20 years that these four recurring themes circle the two things research confirms that the patient values.

Patients want to optimize two scarce resources—their time and money. Put simply, there are too many things to spend our time and money on today and, due to digital technology, the possibilities keep escalating.

This means that patients want a lot of things, but can only afford a few things; thus they have to prioritize. This explains why consumers say they are “interested in buying premium products” and then don’t. They weren’t kidding—they really were interested, but they didn’t see enough value to make it a priority.

In other words, people spend their time and money first on what they need and second on what they value. The same technology makes it easy to identify and work on performance issues or systems that are sticking points with your patients.

5 STEPS FOR IMPROVED SATISFACTION, REVIEWS
Punish your processes and not your people. Staff members will be more likely to pass along complaints to you if they know this is the practice’s approach to performance improvement.

In order for a complaint to truly be a gift, the root causes of that complaint must be identified. Once identified, it can be broken down into actionable steps that will help you retain existing patients and attract new ones.

STEP 1 FORM A PARTNERSHIP WITH THE UPSET PATIENT
Turn the hostility of upset patients into something positive. Offer a quick, painless way to complain. Each upset patient is identifying obstacles that are stopping other patients from being satisfied.

STEP 2 PREPARE FOR A DIRECT, AND UNCOMFORTABLE, CONVERSATION
The department or office needs to know exactly how they’re failing to meet expectations. Management’s job is to use feedback as a catalyst to make the necessary changes. Don’t point fingers. Factually share your concerns with employees and ask for their point of view about what’s been happening.

STEP 3 WORK ON A SOLUTION WITH AS MANY EMPLOYEES AS NECESSARY
Start off by saying something like, “Bob, I have a problem. I want to talk about opti-
Sometimes, it’s best to leave work at the office

"I’m glad you love your work, but from now on I’ll pick out artwork for our home decor."

Artwork by Jon Carter

in case you missed it

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Update in the treatment of dry eye and ocular allergy

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