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February 2020
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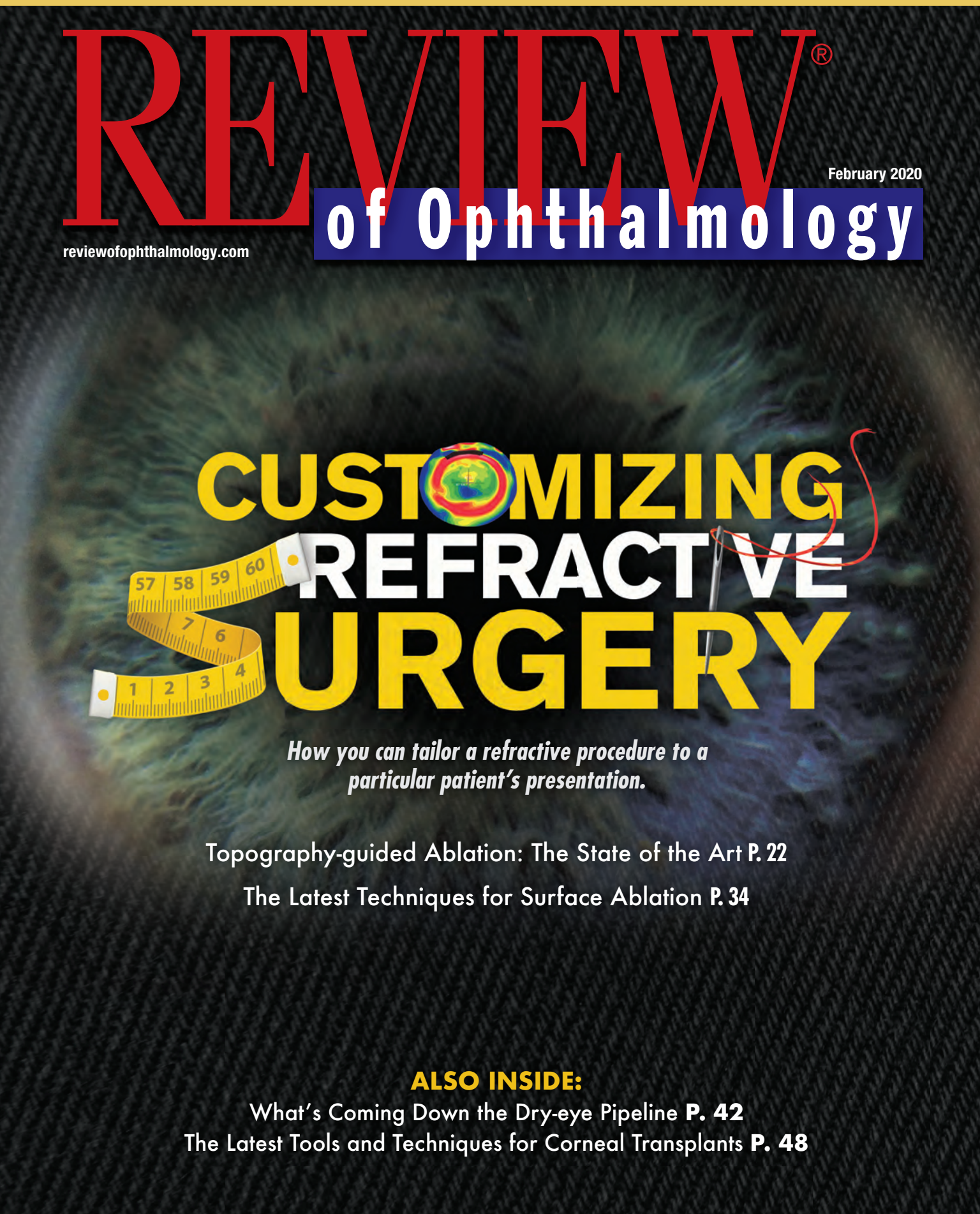

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You are encouraged to report Suspected Adverse Reactions to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

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REVIEW NEWS
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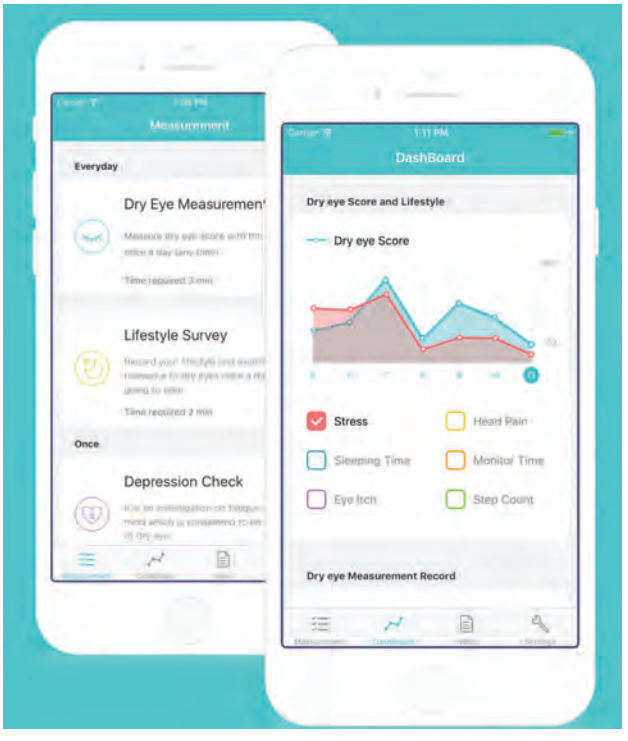
Researchers Use Big Data to Tackle Dry Eye

Taking advantage of big data and heavy smartphone use, a research team at Japan's Juntendo University designed the DryEyeRhythm free mobile app with Apple's ResearchKit to identify risk factors and characteristics of diagnosed and undiagnosed dry-eye disease. "This study is among the first to use a crowdsourced smartphone application to collect epidemiological data for dry-eye disease," says Michael T. M. Wang, MBChB, fellow in ophthalmology at the University of Auckland, New Zealand, School of Medicine. The app documents symptoms, medical history and lifestyle habits. "One of the advantages of using an app to conduct clinical research is the potential for unlimited participation and no geographical restrictions or participation cost," says Takenori Inomata, MD, PhD, MBA, of the Juntendo University Faculty of Medicine in the Department of Ophthalmology and one of the study authors.

The cross-sectional, crowdsourced research included an electronic informed consent step in the smartphone app. A total of 21,394 records were identified in the app's database; 11,485 were duplicate records, and after removing user records outside of Japan or with incomplete data, a cohort of 4,454 participants were enrolled in the study. Of the 4,454 users, 899 participants (27.3 percent) had diagnosed dry eye and 2,395 participants (72.7 percent) had undiagnosed symptomatic dry eye; 2,972 participants (66.7 percent) were women; mean age was 27.9 ±12.6 years.

Study participants reported daily subjective symptoms, such as ocular itching, stress levels and headache; and filled out disease-specific questionnaires, such as the Ocular Surface Disease Index (100-point scale; scores 0 to 12 indicate normal; 13 to 22 mild; 23 to 32 moderate; 33 to 100 severe dry-eye symptoms) and the Zung Self-Rating Depression Scale (total of 20 items; total score ranging from 20 to 80; ≥40 highly suggestive of depression).



Physicians used a smartphone app to track patients' symptoms each day to determine dry-eye risk factors and the characteristics of diagnosed and undiagnosed dry eye.

Study participants were classified as having no symptomatic dry eye (defined as an Ocular Surface Disease Index total score <13) or having symptomatic dry eye (OSDI ≥13). The symptomatic dry-eye group was further divided into diagnosed and undiagnosed symptomatic dry eye.

The researchers used multivariate-adjusted logistic regression analysis to identify risk factors for the disease. They found that risk factors for symptomatic dry eye included younger age, female sex, allergic rhinitis, mental health disorders, digital device screen exposure time and contact lens wear. For undiagnosed symptomatic dry eye, associated risk factors included younger age, male sex, absence of a collagen disease, mental health dis-

orders, ophthalmic surgery and contact lens wear.

"The identification of associated risk factors offers valuable information which might help to inform targeted health promotion strategies and/or opportunistic screening among those with a greater propensity of developing dry-eye disease, as well as risk factor reduction or modification strategies," says Dr. Wang.

"With the exception of younger age, the remaining risk factors identified in the current study are in agreement with those previously reported in the literature," Dr. Wang continues. "It's possible, however, that the potential selection bias associated with participant recruitment among those that use digital devices in the current study might have contributed to the association between younger age and symptomatic dry eye detected in the current study. Only a low proportion of survey respondents (8 percent) were 50 years or older. Furthermore, moderate-to-severe dry-eye symptoms might also limit the use of digital devices, which may potentially contribute to a risk of under-sampling."

"We were surprised to find a lot of symptomatic dry eye in younger males as undiagnosed dry eye," says Dr. Inomata. Dr. Wang agrees, pointing out that "the high proportion (72.7 percent) of the study's respondents with undiagnosed disease among those with symptomatic dry eye . . . represents a significant public health concern, particularly in the context of the high economic and societal burden of dry-eye disease."

Dr. Wang says the data on risk factors that the study uncovered might translate to the clinic in terms of timely intervention. "Recent research suggests that early detection and treatment can help delay the progression of dry-eye disease," Dr. Wang says. "Research surrounding risk factors of undiagnosed dry eye is particularly valuable and can contribute to the identification of barriers associated with disease detection and/or treatment, and might also prompt efforts of raising awareness among those who are less likely to contact health-care services."

The researchers believe that, without their mobile app, identifying undiagnosed symptomatic dry eye would be more difficult. Still, they say the sample size of the study may still be insufficient for identifying risk factors that are only weakly associated with diagnosed and undiagnosed symptomatic cases of dry-eye disease.

Some other limitations of the study include sources of bias, such as recall bias, volunteer bias and self-reporting bias, as well as bias for age and socioeconomic factors, since the app was released for only iOS and iPhone.

Additionally, only the OSDI questionnaire was used for identifying dry-eye disease. Dr. Wang notes that "mobile health technology does not yet allow for the clinical evaluation of ocular surface signs, which would limit the ability to formally diagnose dry-eye disease according the recent global consensus Tear Film and Ocular Surface Society Dry Eye Workshop II criteria, which would require the presence of both clinical signs and symptoms."

Clinical research is expected to improve through the use of artificial intelligence and big data, which make participant recruitment, communication and real-time data acquisition easier and more cost-effective.[1] Dr. Inomata believes that mobile health technology will lead to the development of better preventive medicines. REVIEW

1. Inomata T, Iwagami M, Kakamura M, et al. Characteristics and risk factors associated with diagnosed and undiagnosed symptomatic dry eye using a smartphone application. JAMA Ophth 2020;138:1:58-68.

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Ophthalmic Product Development Insights

Matthew Chapin *Andover, Mass.*

Pearls for Early Fundraising

It's that time of year: A sea of people scrambling around hotel lobbies and meeting rooms near San Francisco's Union Square for the annual JP Morgan Healthcare Conference. This conference sets the tone for the year in bio-tech and pharmaceuticals. It's where entrepreneurs, start-ups, investors and large multinational pharma companies all convene to discuss financing, licensing and co-development deals. By the time this issue of Review comes out, this conference will be behind us, and if you were part of it, you're likely working on related follow-up. This month's OPDI column will highlight a few key topics that have come up recently in our work with clients and partners, preparing plans and strategies for funding discussions—particularly for this event. Here, we'll gear our discussion toward the new entrepreneur.

In previous columns, we've talked about different case studies and deals at various stages in development and the nature of investment funds. With such a busy schedule of meetings, as is common at this conference, it's critical to ensure you're focusing on investors that fit the stage and profile of your project. Be sure to ask the right questions in order to understand this early on in discussions, and be able to adapt your presentation to focus on points that'll resonate the most with certain investment groups.

On one end of the spectrum, there are investors that focus on or are open to seed-stage financing. On the other end, some investors focus on late-stage financing, which may include already marketed products or services with established organizations that have revenue streams. That type of late-stage investor is generally a completely different type.

The early-stage label can cover many different expectations on a project's status, from projects at the ground floor-level or those coming out of academia or an institution, to projects that still need some key work (e.g., animal work, formulation, chemistry, etc.) before entering into the IND enabling stage. Other investors may consider projects already in that IND enabling stage as early stage, where your IND is slated for submission in the near term as a next step. Yet for other investors, early stage may mean you have some preliminary early clinical study proof-of-concept data.

(IND enabling is generally the time during which you're preparing your IND's key materials for submission to the FDA, which will allow you to move ahead with clinical trials. Key components of the IND enabling stage include the GLP toxicology studies that the FDA will view as pivotal support for safety, animal PK, the formulation optimization, stability, and scale-up of manufacturing for supplies, finalization of your planned clinical protocol, regulatory meetings, etc. A similar concept applies to devices for the relevant regulatory pathway for a given product.)

While a specific early-stage investor may focus preferentially on IND enabling stage-projects versus what they view as seed-stage, there's a fine line between seed stage and IND enabling. This line may be a single animal study or a single defined formulation step to confirm stability and/or other related activity. Proper positioning and labeling of your project as seed- or IND-enabling stage is key and can help orient investor discussions in the direction you want from the get-go. When it comes to positioning to investors—in terms of the work plan or how funds are being used—being able to message as an IND-enabling project could boost investor perception and help you gain traction at the beginning of your pitch.

Investors generally expect that by the more blocking-and-tackling IND-enabling stage, your overall concept has already been validated to proceed, and you've evolved from "seed" and gotten over the seed-specific humps. These humps—which are generally addressed in planned seed-stage rounds—might include confirmation of defined formulation work showing stability, selecting the lead drug, preliminary animal studies for determining the right amount of drug is delivered to the right tissue, confirmation of key efficacy data in animals or refining of drug delivery prototype manufacturing and planning for scale-up.

IND enabling may imply that a specific project is still within a one- to two-year window of IND submission, for example. You may encounter investors declaring your project to be "too early" for an investment. For some, "being too early" may not be that far off, but for others, "being too early" may mean they're looking for a project that's two or more years down the road and closer to IND filing. Focus your energy on discussions you can impact in the near term. Be careful about chasing investors and spending money trying to satisfy specific requests. And at the same time, make sure that any work being done satisfies a specific goal, informs decision making or closes a deal.

You need to understand what's really driving a particular investor's decision. Simply adding more animal work (or in vitro work) into an early-stage preclinical asset won't necessarily eliminate that label of "being early" or add value or get an investor over the hump. Will that investor be driven by confirmation of pharmacological effects in animals (a lower species such as a rodent) to confirm robustness of your existing data, or is it an issue, for example that PK in higher species (e.g. primates) is really the key gating item you need to raise money to evaluate (as is often the case with a biological or retinal drug delivery project)? In that case, conducting mouse models or PK in rats or rabbits may not move the needle for investors.

We're often asked, "Should I raise $2 million now for IND-enabling work (Series A) and go back to raise funds for a subsequent round for IND/Phase 2 (Series B); or should the round be a larger Series A to cover it all?" Ultimately, you should follow the money. You may receive different feedback from investors with different appetites. Don't always assume that simply moving along the IND-enabling stage process will significantly increase your valuation in the eyes of the investor. You may not have the step-up you hoped for between that Series A (IND enabling) and Series B (to fund the clinical study). But the investors you are targeting at that stage may have resources just to fund up to the IND. Regardless, you need to have your plan fleshed out so you know your timeline and budget. Your timeline and budget will get you through the key value inflection, which is your key activity that'll drive, for example, a license deal, exit to a pharmaceutical partner or IPO (i.e., "going public"). So even if you are focusing on IND-enabling activities, have your clinical plan and budget defined and ready.

Another important consideration is making sure you have the right investors for your plan. While there's no right or wrong answer, necessarily, the right investor should have the reserve funds appropriate for your project and risk to support any anticipated shifts in work streams that might require additional funding in a bridge round. Remember that you need to balance your hope and plan for a step-up between rounds, taking into account the risk of macro environmental changes during your program, such as in the stock market, political climate or changes in reimbursement/pricing—all of which may make it more advantageous to raise the larger round up front and avoid the need to go back to investors mid-stream.

Determining valuation is also not a matter of right or wrong either, but at a given time it's appropriate under certain circumstances. To get

an idea of a fair value, take a look at investment spent to date and comparables (where recently sold assets are compared to similar assets to determine value) that reflect, or are adjusted to, the current state of the project, risks, and the industry in general. Depending on the size of a particular venture capital fund, an investor may have different needs. A smaller fund investing in a larger round will need that lower valuation to drive a larger stake, taking into account potential for dilution later if they don't have the capital to follow-on throughout the program like a large fund, and to maintain their target ROI based on the expected future exit. And in some cases even if properly valued, it just may not fit the investment model for a given fund.

Another important pearl worth mentioning—since it's easy to get stuck—is to avoid treading water. It's critical to show progress. Investors can easily get turned off if they don't see progress since the last discussion. Progress doesn't always mean a huge step, considering you're also raising money to run key activities (and with any progress you may be able to go back to investors who said "no" six months ago), but you should be making your way forward. Is there a key FDA meeting that can be held? Maybe you can work on clinical protocol development with help from scientific advisors or key opinion leaders. Other examples of progress beyond the obvious significant activities, can include: recruiting new value-added members to the board (or scientific advisory board); additional pharmacology work showing application across other indications and use; refining patient population, endpoints or scales to help show de-risking of the clinical plan; formulation; ongoing stability testing; a natural history study without the drug that's defining disease progression; and recruiting and screening patients for ultimate enrollment in the study with the product at a later date. Just be sure your progression adds value and advances your project in an effort to answer key questions. Don't work for the sake of doing something.

This isn't intended to be a exhaustive list of all the elements of the fundraising stage. Other areas, such as addressing an unmet need, intellectual property and patentability, reimbursement, valuation planning/future revenue projections, have been addressed in past columns or will be addressed in future ones.

With the plan laid out for your financing rounds, it's helpful to model the expected returns for investors. Show what activities will drive a particular exit, expected over what time frame/investment and expected comps based on other industry deals. Paint the picture of the end game for investors, whether it's a license, acquisition or IPO and what the return on investment may look like, so the investor doesn't have to model and calculate it himself. REVIEW

Review and comments on this column were also supported by Aron Shapiro. Mr. Chapin and Mr. Shapiro are senior vice presidents of Corporate Development at Ora, which offers device and drug consulting, clinical research and development, and strategy and support to catalyze new client and partner initiatives. The authors welcome your comments or questions regarding product development. Please send correspondence to mchapin@oraclinical.com or visit oraclinical.com.

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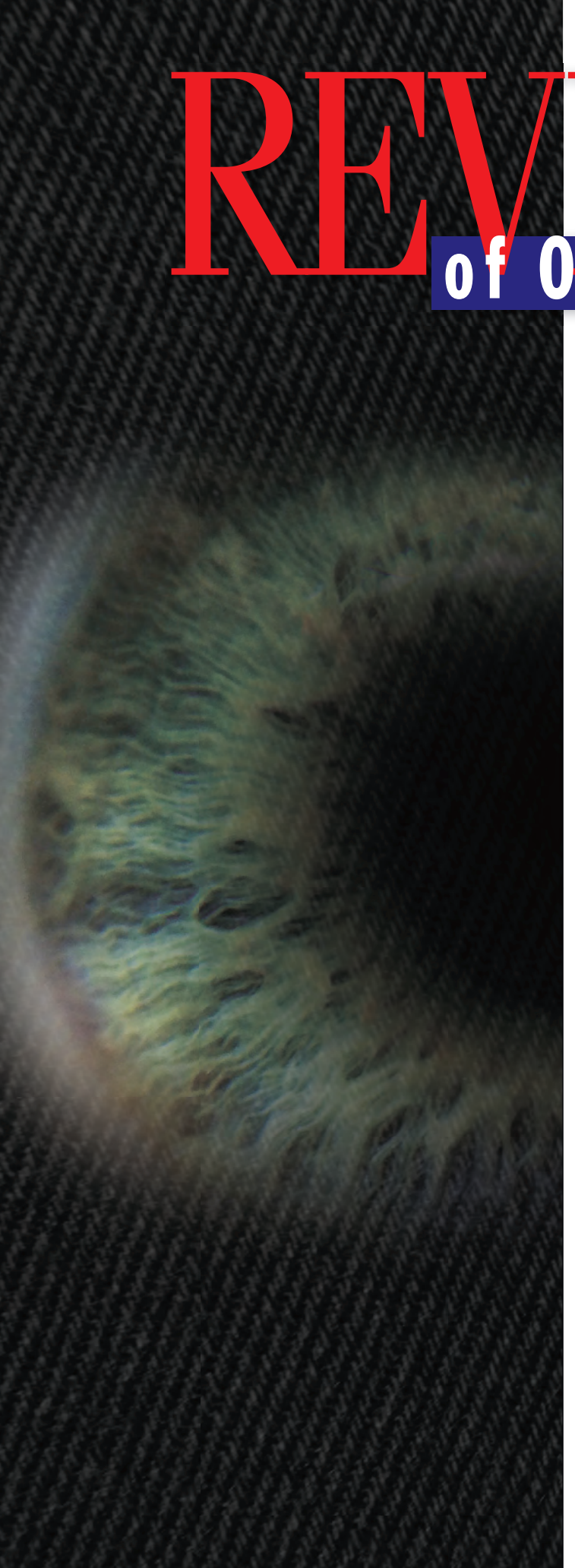
References: 1. McAlinden C. An overview of thyroid eye disease. *Eye Vis.* 2014;1:9. doi:10.1186/s40662-014-0009-8. **2.** Weiler DL. Thyroid eye disease: a review. *Clin Exp Optom.* 2017;100:20-25. **3.** Verity DH, Rose GE. Acute thyroid eye disease (TED): principles of medical and surgical management. *Eye (Lond).* 2013;27:308-319. doi:10.1038/eye.2012.284. **4.** Barrio-Barrio J, Sabater AL, Bonet-Farriol E, Velázquez-Villoria Á, Galofré JC. Graves' ophthalmopathy: VISA versus EUGOGO classification, assessment, and management. *J Ophthalmol.* 2015;2015:249125. doi:10.1155/2015/249125. **5.** Bartalena L, Baldeschi L, Boboridis K, et al. The 2016 European Thyroid Association/European Group on Graves' Orbitopathy Guidelines for the Management of Graves' Orbitopathy. *Eur Thyroid J.* 2016;5:9-26. doi:10.1159/000443828.

HORIZON



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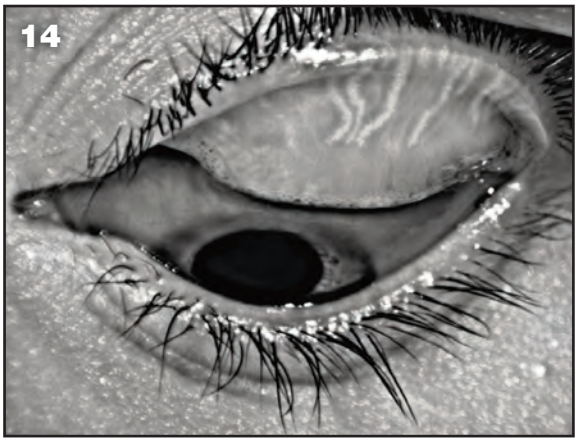

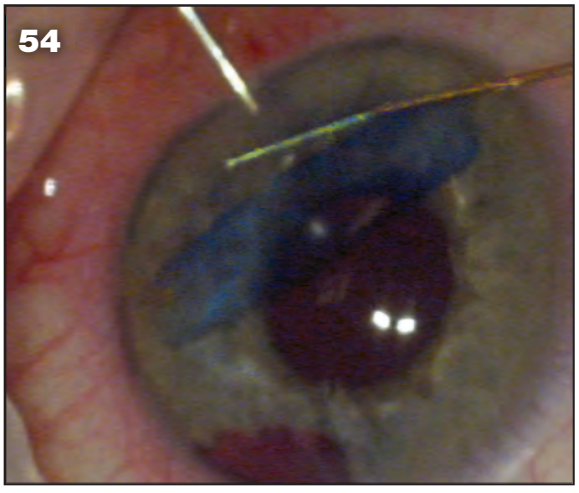

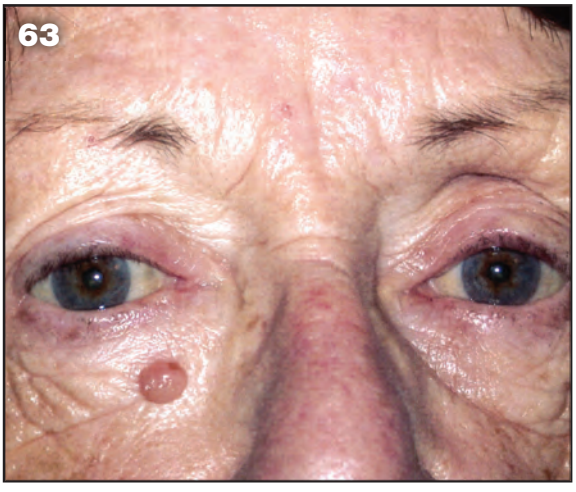

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ATTENTION: Reference the Directions for Use for a complete listing of Indications and Important Safety Information.

REFERENCE: 1. DOF2018CT4021. Johnson & Johnson Surgical Vision, Inc; 2018.

See the Passion in Each Patient

Johnson & Johnson VISION

Biomarkers of Surgical Happiness

How to find missed opportunities in the outcomes of dissatisfied refractive surgery patients.

Rohit Shetty, MD, MBBS, Bangalore, India, Nimrata Bajaj Dhami Sr., MD, Ludhiana, India
Neeraj Israni, MD, Mumbai, India

As you know, despite the many advances we've seen in refractive surgery, some postop patients with seemingly good or even perfect outcomes return to us in an unhappy state. Various factors—such as personalities, optics, ocular surface and not-so-obvious issues—can lead to these complaints. Using a retrospective case analysis of eight dissatisfied patients, we'd like to help you meet the high expectations of patients in your practice. By identifying what we call, "biomarkers of happiness" and responding to them properly before surgery, you can transform "20/20 unhappy" to 20/20 happy.

What Causes Unhappiness?

We've often wondered what drives unhappiness in some of our patients, even those who no longer need to wear glasses after surgery. The evidence of discontent can be found in the many lawsuits filed against surgeons. Although we usually prevail in court, settlements reached before sympathetic juries can be costly.[1]

How can we avoid this? One way is to look more closely during preop workups for those biomarkers of happiness, which requires us to understand the role of each aspect of refractive surgery, including the ocular surface and tears, meibomian glands, corneal surface, optics, epithelium, pupils, posterior segment, systemic factors and—the clinically unmeasurable biomarker—patient personality. Let's review each of the cases that we've selected.

Patient #1: A Case of Tears

A 25-year-old female post-femtosecond LASIK patient came to us complaining of glare. Her corneal topography revealed a central island around a relatively flat area in her right eye, an "irregular' finding reported by her previous physician. In collaboration with the physician, our plan was to fit her in scleral RGP lenses and, if they worked, replicate their effect with topography-guided surface enhancement.

However, the RGP lenses only made the patient's signs and symptoms worse. We determined that she had a normal pupil size and aberration profile. Then, after questioning her closely, we learned that she actually had a history of severe preop contact lens intolerance. During an ocular evaluation, we found that she had a low tear-film breakup time (three seconds OD, four seconds OS) and a high ocular disease index (24 points and 50 percent on the scale, indicating a severe degree of ocular surface symptoms). Findings from an Optical Quality Analysis System evaluation (Visiometrics, Costa Mesa, California) correlated with symptoms of dry eye.[2] Confocal laser scanning microscopy revealed dendritic corneal cells and aberrant, branching nerve loops, confirming disturbed ocular surface homeostasis.[3] (*See Figure 1.*) These results, combined with ocular surface fluorescein staining and her history, pointed to dysfunctional tear syndrome, leading to fluctuating vision and light scattering the patient had described as glare.[4]

We treated her with lubricants and meibomian gland massage, as well as steroids and cyclosporine drops for ocular surface inflammation. A week later, the patient responded favorably. She was relieved that she wouldn't need to wear contact lenses or undergo an enhancement. We provided regular follow-up care, including a repeat to-

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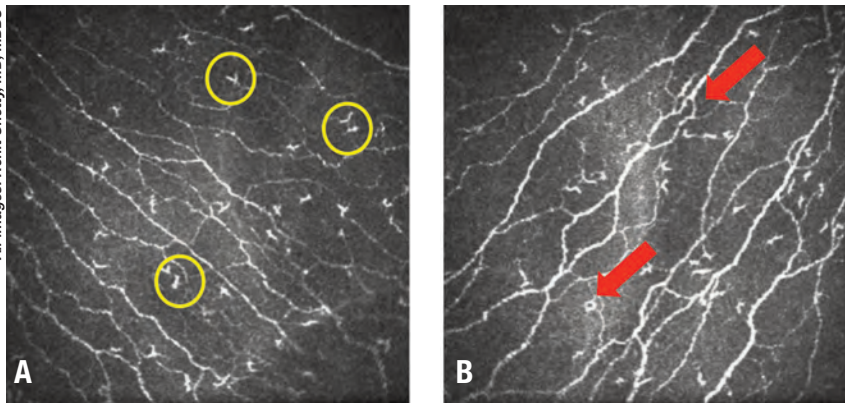

Figure 1. Confocal images show increased dendritic cells (A) and aberrant nerve loops and branching (B), which could indicate disturbed ocular surface homeostasis.

pography, and she maintained stability. OSDI scores decreased. She's now a much happier 20/20 patient.

The key to success was to listen more closely—specifically to her description of past contact lens intolerance. Of course, this should have occurred before her surgery. Ocular surface disease needs to be confirmed and treated both before and after surgery. We concluded that the patient would have fared better if she had undergone SMILE, a potentially nerve-sparing surgery, especially in view of her history of contact lens intolerance.

Biomarker of happiness: Listen to your patient more closely before choosing a mode of refractive surgery.

Patient #2: Microdistortions

A 27-year-old male SMILE patient, four weeks postop, OU, was unhappy with the quality of his vision despite a 20/20 outcome. We don't expect an acute visual recovery one day after SMILE, so we didn't evaluate the patient until he returned for his four-week postop visit with unclear vision, despite an expected full qualitative visual recovery.

The patient had normal topography findings and no signs or symptoms of dry eye. Microdistortions in his Bowman's layer, which would have been expected soon after surgery, were still evident. Althought difficult to visualize with a slit lamp, the microdistortions were clearly visible when we used anterior segment OCT.

We concluded that intraoperative recognition of striae and subsequent cap repositioning could have increased the chances of improving this patient's outcome significantly, likely avoiding his blurred vision.

Instead, he needed to wait longer for recovery to occur at the microstructural and cellular levels. We now recommend repositioning the cap and anterior surface of the cornea during SMILE surgery in cases when this approach is prudent.

Although refractive error before surgery determines the extent of microdistortions, intraoperative cap repositioning can reduce them, expediting acute visual recovery after SMILE.[5] The cap is repositioned by stroking the anterior surface of the cornea with a spatula in a superior to inferior direction with mild to moderate pressure over the cap area.

Biomarker of happiness: Consider the use of intraoperative cap repositioning to reduce microdistortions in SMILE surgery.

Patient #3: Mesopic Pupil

Two years after undergoing femtosecond LASIK, OU, a 23-year-old male presented with 20/20 vision (-025 -0.75 x 140 degrees), with normal topography maps. However, he was complaining of glare. Our examination revealed normal corneal optics and a normal ocular surface. We noticed, though, that he also had a mesopic pupil—measuring 6.58 mm—that appeared to be a possible cause of distortion and higher-order aberrations. These symptoms can increase proportionately with the increasing size of a pupil in a post-LASIK patient.[6,7]

This case reinforced a key objective we share. We strive to ensure that the effective optical zone is always greater than the peak scotopic pupil size in refractive surgery. Also, just as important, we need to consider that increasing the effective optical zone should be weighed against the risk of excessively increasing the ablation depth.

Biomarker of happiness: Assess your patient's pupil size and optical zone and plan accordingly to ensure an optimal outcome.

Patient #4: Blurriness and Glare

A 40-year-old female visited us after six months of blurred vision and glare. She had undergone femtosecond LASIK, OU, three years earlier and an enhancement, OS, one year earlier. Her refraction was -0.25 -0.25 x 40 and her vision was 20/20. We found dominant internal higher-order aberrations.

Biometry and a slit lamp exam didn't show significant findings, so we decided to monitor her symptoms. The patient was lost to follow-up but returned a year later, still complaining of blurred vision.

This time, we saw obvious crystalline lens changes. The take-home message: For patients in the pre-presbyopic and presbyopic age group, watch for lenticular aberrations and a concerning "dysfunctional lens index." (The index is a measure of the lens's health/opacity used on the Tracey iTrace system; some surgeons use it to decide whether to offer patients refractive-lens exchange before they develop a

textbook-definition cataract.) The DLI is an objective measure of the earliest, most appropriate time to consider RLE for the aging, dysfunctional lens.

This case highlights the importance of lens optics. Instead of an enhancement of previous refractive surgery, this patient needed cataract surgery, which we eventually provided.

Biomarker of happiness: Examine the crystalline lens of every refractive surgery candidate to precisely understand the origin of the refractive error.

Patient #5: Severe Dry Eye

A 37-year-old female was referred to us with severe dry eye. She had 20/20 vision three years after undergoing LASIK, but was extremely unhappy, noting that she was unable even to drive her car because of her symptoms. A dry-eye workup produced a TBUT of two seconds OD and three seconds OS. Her Schirmer's result showed 14 mm and 12 mm of moisture, OD and OS. Her optical profile was normal. After lubricants, hot fomentation (compress) and meibomian gland massage failed to improve her symptoms, we scanned the meibomian glands.

The scans showed significant gland drop-out (*See Figure 2*). This condition, missed preoperatively, had wreaked havoc in this patient's life. Merely prescribing continued hot fomentation would have been futile. We recommended thermal pulsation therapy, such as treatment with LipiFlow, followed by topical steroids, antibiotic ointment for meibomian gland dysfunction, frequent lubrication and oral omega-3 fatty acids. These treatments improved her overall status.

Biomarker of happiness: A preop dry-eye workup can safeguard against an avalanche of postop inflammation.

Patient #6: Low-Vision Issues

A 25-year-old female high hyperope (+10 D) was experiencing glare. She had undergone RLE with a multifocal lens because she wasn't a candidate for corneal refractive surgery.

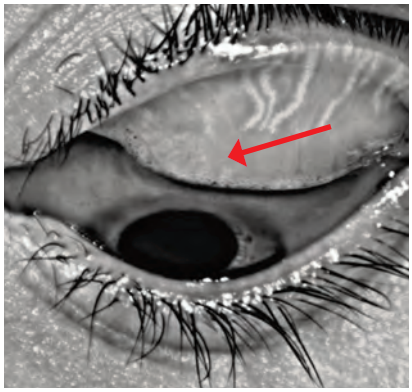

Figure 2. Meibomian gland dropout.

Vision measurements of the operated eye showed a low modulation transfer function. A multifocal electroretinogram (mfERG) revealed subclinical maculopathy. We also evaluated the retina using a fundus exam and OCT.

Biomarker of happiness: Conduct preop retinal exams in all patients, investigating any degree of low vision.

Patient #7: Systemic Disease

A 22-year-old female came to us to undergo LASIK surgery. During preop testing, we found that she had low contrast sensitivity. After seeing pristine results in her anterior and posterior segment exams, we noted that she had no signs or symptoms of systemic illness and, as a result, determined that a possible neurologic problem could not be ruled out. The patient was referred to an internist and, subsequently, to a neurologist, who ordered an MRI and later diagnosed her with multiple sclerosis.

With this experience in mind, we now maintain a low threshold for referral when encountering complaints such as low contrast sensitivity, sudden vision loss, weakness of any part of the body, headaches and related symptoms. We know that optic neuritis is the most common visual disorder associated with MS. Besides loss of contrast sensitivity, of course, other symptoms of optic neuritis include blurred vision, dimming of colors and pain. In this case, we obviously couldn't satisfy a patient intent on undergoing refractive surgery to improve her vision. However, we were able to take actions that led to her receiving the care she needed.

Biomarker of happiness: Always take time for a systemic evaluation, with the hope that your intervention can identify a disease process before it gets more serious.

Patient #8: Perfect—and Bitter

We saw a 25-year-old male one year after he had undergone SMILE, OU. He'd experienced no surgical complications and had achieved perfect visual results. However, this patient was bitter about his outcome, despite an emmetropic refraction. His topography, aberration profile and dry-eye workup were all markedly normal. So why was he bitter?

To find out, we reviewed his preop evaluation and expectations to discover that the patient had a history of anxiety. He also had been alternately compliant and noncompliant with his pharmaceutical regimen for obsessive compulsive disorder, and he was addicted to a number of drugs.

During our workup, we uncovered an interesting finding—a fluctuating pupil diameter, accompanied by a fluctuating refraction. Dynamic accommodation testing also revealed accommodation spasms. After testing, in collaboration with the patient's psychiatrist, we documented a psychiatric evaluation that produced the following findings:

- Agreeableness: very low
- Conscientiousness: very high
- Neuroticism: high

We noted that a psychologically disordered state can cause pupil

(Continued on page 20)


Manual LRIs: Tools of the Trade

Despite the availability of more high-tech options, manual LRIs can still be a useful way to address astigmatism.

Christopher Kent, Senior Editor

Today, minimizing postoperative astigmatism has become the standard of care for refractive surgery, especially when a patient is receiving a high-tech implant that requires vision with as few aberrations as possible. Hand-made limbal relaxing incisions have been a time-honored way to accomplish this. Today, surgeons' options for addressing astigmatism have grown. Nevertheless, LRIs haven't gone away.

R. Bruce Wallace III, MD, FACS, founder and medical director of Wallace Eye Surgery in Alexandria, Louisiana, and clinical professor of ophthalmology at Louisiana State University and Tulane Schools of Medicine in New Orleans, has been making limbal relaxing incisions for years. "Given all of today's new intraocular lens technology and new surgical options and techniques, patients expect to have extraordinary postoperative vision," he says. "Giving them that requires addressing corneal astigmatism.

"Using manual limbal relaxing incisions to reshape the corneal surface is a tried-and-true method for addressing astigmatism intraoperatively or postoperatively, especially when it's a small amount of astigmatism," he continues. "It's a great way to help patients achieve excellent postoperative vision, which is even more important when premium IOLs are involved. And today, the tools for creating manual LRIs continue to evolve, whether you prefer diamond knives or disposable blades."

Still Useful

Dr. Wallace notes that with so much other new technology available—e.g., femtosecond lasers and toric intraocular lenses—the relative importance of LRI knives depends on the individual surgeon's preferences and the patient's circumstances. "For example," he says, "making limbal relaxing incisions with a femtosecond laser generally isn't a good option for a postoperative touchup, unless the surgeon doesn't do manual LRIs at all. Typically, femtosecond laser LRIs are only made during cataract surgery.

"Usually this achieves the desired refractive result, but occasionally a touchup may be needed," he continues. "If that's the case, using the laser postoperatively would be relatively expensive, and I don't think it offers much more predictability than a manual LRI. Why take the patient back to the OR and pay the fees to use the laser when you can just correct the problem by creating an LRI manually in the office?"

Toric IOLs have also become an increasingly popular way to address astigmatism, but Dr. Wallace points out that manual LRIs have one significant advantage over toric IOLs. "An LRI can be quite effective for correcting low levels of astigmatism," he says. "If a patient only has 1 D or 1.5 D of cylinder, a toric IOL might be overkill. An LRI can easily correct that amount of astigmatism, and it's much less expensive. The only real requirement is that the surgeon be comfortable performing the incision."

Dr. Wallace has created three short instructional videos explaining how to create manual limbal relaxing incisions, which can be viewed on YouTube. Part one is available at youtube.com/watch?v=SgM-Ud_6lYI. (You can also find the videos by going to YouTube.com and searching for "Wallace LRI.")

This article has no commercial sponsorship.

An LRI Knife Sampler

Here's a brief list of some of the LRI knives and kits that are currently available:

ASICO

• ***Koch Double-footplate LRI Diamond Knife.*** This knife uses a trifacet blade for a controlled entry and a double-footplate for the creation of consistent wound architecture, according to the company. It has side-cutting edges for easy extension of the wound. It comes in three depth settings: 500; 550; and 600 µm. (Also available with 450-, 500-, and 550-µm depth settings for small pupils.)

The Koch Double-footplate Diamond Knife

• ***Zaldivar LRI Diamond Knife.*** This uses a tri-facet blade for controlled entry and side-cutting edges for extending the wound. ASICO says the single footplate allows for better visualization. It has a preset depth setting of 600 µm.

• ***Fukuyama LRI Diamond Knife.*** This lancet blade also has side-cutting edges for easy wound extension and a double footplate. Precise depth settings go up to 2,000 µm.

• ***Multi-incision Diamond Knife.*** This is a 10-facet blade with side-cutting edges and a single footplate for better visualization. Seven adjustable depth settings up to 6,000 µm for various procedures, with three depth settings specifically for performing LRIs: 500; 550; and 600 µm.

• ***Three-step LRI Diamond Knife.*** The three-step has a trifacet blade for controlled entry and a single footplate. It has side-cutting edges for easy wound extension, and three depth settings: 500; 550; and 600 µm. (Also available with 450-, 500-, and 550-µm depth settings for small pupils.)

• ***Dual Micrometer LRI Diamond Knife.*** This six-facet blade also has side-cutting edges for easy wound extension and a single-footplate. Its depth settings go up to 2,000 µm.

Katalyst Surgical

• ***Gemcision 550-µm Angled LRI Knife.*** This particular knife is also available in 300- and 600-µm depths.

The Gemcision 555-µm Angled LRI Knife

Storz (Bausch + Lomb)

• ***Wallace LRI Diamond Knife Kit.*** The kit includes an LRI diamond knife (600 µm preset blade depth). The knife has a straight, 120-mm retractable handle and a 0.2-mm front flat tip. The company says the single footplate allows easier visibility of the knife as it passes through corneal tissue. The knife's handle is designed for finger twirling as the blade follows the arcuate pattern of the limbus. It comes with a sterilizing tray. (Also available through Ambler Surgical.)

• ***Donnenfeld LRI Diamond Knife.*** This uses a single-footplate design, and has a fixed, 0.6-mm depth. The tri-facet 20-degree blade is for incisions to the left or right and is angulated 10 degrees for better alignment and approach. The shorter handle length promotes ease of use under the microscope or at the slit lamp, the company says. The blade assembly retracts into the handle for safe storage. (Also available from Duckworth & Kent and MSI Precision Specialty Instruments.)

The Donnenfeld LRI Diamond Knife

• ***Nichamin LRI Diamond Knife.*** This knife's small footplate is curved to conform to the fixation/degree gauge; it provides a guide for making the arcuate incision at the limbus. The company says that the fine 15-degree, 100-µm diamond blade with a microflat tip ensures blade stability and a "smooth glide" through corneal tissue. Step adjustment allows surgeons to dial in the desired incision depth, ranging from 0.5 mm to 0.8 mm in 0.05-mm increments. (Also available from MSI Precision Specialty Instruments.)

• ***Oyakawa LRI Diamond Knife.*** The company says this tri-facet, 20-degree blade offers a very thin profile for tracking through the cornea and a small square tip configured for accurate depth control. The footplate is designed to ease the movement of the blade through the LRI incisions and allow for visualization when aligning the blade to the desired incision width. The micrometer handle allows depth adjustments in 0.01-mm steps. The blade is retractable.

The Oyakawa LRI Diamond Knife

MicroSurgical Technology

• ***AccuSharp Guarded Ophthalmic LRI Knife.*** MST describes these knives as disposable, single-use metal blades with "superior sharpness." The knife's handle features smooth, single-handed blade retraction and ergonomic design. The blades are 1 mm wide, available in 500-, 550- and 600-µm preset incision depths. The knives come sterile, packaged individually, with six knives per box.

Katena

• ***LRI Step Knife.*** Katena says this is a gem-quality diamond knife with a titanium handle, a six-facet blade for bi-directional cutting and three precalibrated depth settings of 500, 550 and 600 µm. A single, highly polished footplate provides a smooth gliding

surface and serves as a depth guard while permitting full visualization of the blade. The company says it's available in single, double, triple and micrometer settings.

Katena's LRI Step Knife

Diamatrix

• Seven different LRI knife options are available: 20-degree Tri-facet; Brown Universal Cataract Knife; 45-degree double edge; lance; standard tri-facet; Stat III; and Woody Davis Triple 90.

Rumex

• Five LRI Knife options are available. All models feature 20-degree tri-facet blades and titanium handles. One features three preset depth settings of 500, 550, and 600 µm. Other models feature preset depths of 500 or 600 µm; some are designed for use at the slit lamp.

Beaver-Visitec International

• ***Limbal Relaxing Incision Kit***. This is a single-use kit with a disposable 600-µm knife. The knife creates precise-depth incisions with a pre-set guard, the company says, and the bidirectional blade cuts left or right. Multiple depth options are available. The LRI kit includes a surgical marking pen and 13-mm swivel fixation ring, with guide marks at 10-degree increments.

MSI Precision Instruments

• ***LRI Knife Micrometer.*** This is a single footplate, ultra-thin knife: 1 mm wide and 0.1 mm thick with a 60-degree truncated lance. The blade cuts in both directions. The micrometer is in 0.1-mm increments ranging from 0 to 1.5 mm.

• ***Precision Aluminum Silver and Blue Economy Trifacet Diamond Knife.*** This knife is 1 mm wide and 4 mm long.

• ***Precision CV Universal Diamond Knife.*** This knife has a titanium J-slot bayonet handle design with a single footplate. The knife is preset at 0.5 mm. The 20-degree, 0.4 truncated lance is 1 mm wide and 0.1 mm thick. It's also available with three settings: 0.5; 0.55; and 0.6 mm.

Ambler Surgical

• Multiple LRI knives are available. The company says these are affordable knives with different blade and tip characteristics; they offer diamond and sapphire knives. REVIEW

(Continued from page 17)

fluctuations.[8] The psychiatrist restarted the patient on treatment for his OCD.

This case shows the potential effect of any number of maladies on patient behavior. It also demonstrates the importance of patient behavior, one of the key factors for achieving refractive surgery success.

Biomarker of happiness: Always keep in mind that successful refractive outcomes depend on a combination of the eye's optics and the patient's mind.

From Tears to Brain

To solve a refractive surgery problem that defies explanation—which we must all try to do at times—we propose this type of systematic investigation, following a diagnostic trail that can lead from the tears to the brain.

By identifying any biomarkers of happiness that were missed in any of your patients, you can make sure you don't miss them in the future.

Each biomarker discussed here provides an approach to decode sources of patients' unhappiness before such unhappiness can occur in other patients, helping to advance our refractive surgery practices. The processes we've used can be replicated and expanded in your practice.

By understanding our patients, studying and perfecting optics, working up potential dry-eye cases, treating ocular surface disease, remaining mindful of lens profiles, utilizing retinal exams, relying on systemic evaluations, collaborating with other clinicians and harnessing research, we can achieve "20/20 happy" outcomes in the vast majority of cases. REVIEW

Dr. Shetty is a clinician, translational scientist and vice chairman of Narayana Nethralaya Eye Institute in Bangalore, Karnataka, India. He is also a professor at Sri Devaraj Urs Medical College in Kolar, Karnataka; an adjunct associate professor at MS Ramaiah Medical College in Bangalore; and BS affiliate associate professor and PhD guide at the Maastricht University in The Netherlands. Dr. Dhami is an ex-fellow of Narayana Nethralaya trained in cornea and refractive services and is currently heading the Cornea & Refractive department at Dhami Eye Care hospital, Ludhiana, Punjab, India. Dr. Israni is a consultant in cataract and refractive services at Infigo Eye Care, Mumbai, Maharashtra, India. Drs. Shetty, Dhami and Istrani report no financial relationships related to this topic.

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Topography-guided Ablation: State of the Art

Christopher Kent, Senior Editor

Addressing corneal surface aberrations is taking refractive results to a new level.

Today, 20/20 refractive surgery outcomes have become commonplace. Nevertheless, refractive surgeons continue to look for ways to improve their results, increasing the percentage of patients achieving 20/20—and better.

One of the technologies helping to make these increasingly excellent outcomes possible is topography-guided ablation. Here, surgeons with extensive experience using this technology—as well as refractive surgery systems that integrate topographic information in other ways—share their experience treating both virgin and so-called "20-unhappy" eyes.

The Argument for Topography

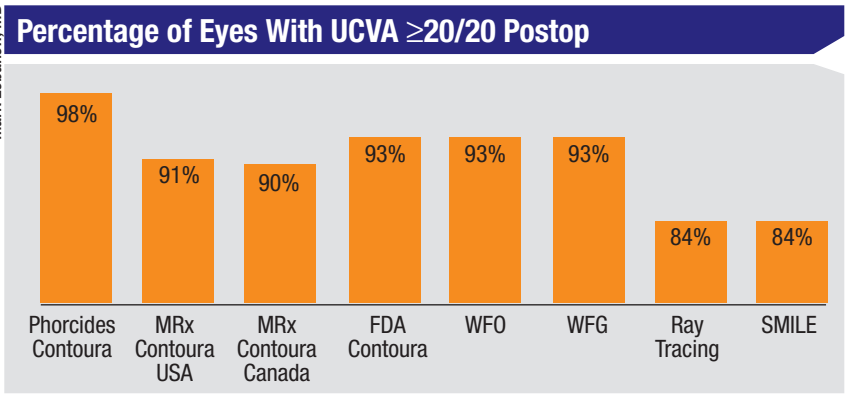
Ronald R. Krueger, MD, director of the Truhlsen Eye Institute and McGaw Professor and chairman of the department of ophthalmology at the University of Nebraska Medical Center in Omaha, who uses the WaveLight Allegretto Wave Eye-Q excimer laser platform to perform topography-guided ablations, notes that topography may not intuitively seem like the best data on which to base an ablation. "You'd think that using wavefront data would be the best way to get a great outcome, because you want to treat the optics of the entire eye," he says. "However, most of the refractive surface is on the cornea, and most of the aberrations are there as well. Furthermore, the resolution of a topography scan is much greater than what you get with a wavefront reading. Topography can give you something like 20,000 points of information about the corneal surface, as compared to 100 or 200 points of optical information from a wavefront reading.

"Topography-guided ablation isn't a perfect approach, because an eye can have lenticular astigmatism or posterior corneal astigmatism," he admits. "But the data suggests that topography-guided ablation is helping us give our patients better-quality vision. For example, in one study I published last year involving 256 eyes, the data showed that at three months, uncorrected distance visual acuity was 20/20 or better in 95.7 percent of the eyes and 20/15 or better in 81.4 percent, while 25.6 percent gained one or more lines of corrected distance visual acuity.[1] That last number indicates that we corrected some corneal aberrations, since patients gained lines of CDVA.

"I'm currently working on a retrospective study comparing physicians who were treated with wavefront-optimized technology to those treated with topography-guided ablation," he

This article has no commercial sponsorship.

Mark Lobanoff, MD



Use of sophisticated software such as Phorcides to analyze the data on which a topography-guided ablation is based is increasing the percentage of excellent outcomes. (Phorcides Contoura data is from a retrospective analysis of data from five U.S. clinics examining 725 eyes.[5] Data shown is three months postop for Phorcides Contoura, FDA Contoura,[6] WFO,[7] WFG,[7] and Ray Tracing.[8] Data shown for SMILE is six months postop.[9]

adds. "The data is showing statistically greater 20/10 and 20/15 results in the topography-guided group. I think this is why topography-guided is gaining some traction; it's that next increment of creating better vision."

Nancy Tanchel, MD, in private practice at Liberty Laser Eye Center in Vienna, Virginia, performs topography-guided ablations using the Nidek Advanced Vision Excimer Laser System (NAVEX) EC-5000 Quest, featuring Customized Aspheric Treatment Zone software (CATz). She explains that the Nidek system can do multiple types of corneal ablation, including topography-guided ablation for myopia and astigmatism. "[The topography-guided ablation] doesn't completely remove corneal irregularities, however," she notes. "Instead, it treats about 40 percent of the measured topographic irregularities.

"We use the OPD Scan instrument to measure the eye," she continues. "It captures both wavefront and topography data, which allows it to separate the internal aberrations from the surface aberrations. The topography-guided ablation then optimizes the light entering the eye using wavefront optimization, while correcting any topographic surface aberrations. In contrast to wavefront-guided ablations, CATz doesn't try to compensate for internal or lenticular aberrations on the cornea."

Dr. Tanchel says she's noted slightly better results using the topography-guided approach. "Patients have fewer night-vision issues," she says. "The original FDA study found that topography-guided treatment with the Nidek system caused a 23-percent improvement in subjective night-driving symptoms, and we definitely hear fewer complaints about that. As far as improving best-corrected visual acuity, most of our patients are fairly young and have excellent best-corrected visual acuity before the treatment, so it's hard to assess how much better it is afterwards."

Taking It To the Next Level

"Topography-guided customized ablation has been around for a long time," says Karl Stonecipher, MD, medical director for TLC Laser Eye Centers in Greensboro, North Carolina, and clinical associate professor of ophthalmology at the University of North Carolina. (Dr. Stonecipher uses the WaveLight Allegretto Wave Eye-Q excimer laser platform to perform topography-guided ablation.) He notes that topography-guided ablation in the United States has evolved through three formats to date. "At first we used a protocol designed for the FDA trial," he says. "We put the manifest refraction and the topography into the software and proceeded with the treatment. The biggest problem with the resulting data was that we chose patients for the trial who had 'normal' topographies. If the topography looked unusual, that patient wasn't included in the study. So we tested the software on the *crème de la crème* of normal corneas.

"Then, John Kanellopoulos and Manoj Motwani pursued the idea of using the amount of astigmatism and axis measured by the Vario Topographer, instead of using the astigmatism data from the manifest refraction," he continues. "They've reported very good outcomes with that approach. However, we've tried it and couldn't duplicate their results; we ended up with a lot of flipped axes. We got better results using the FDA trial protocol.[2,3]

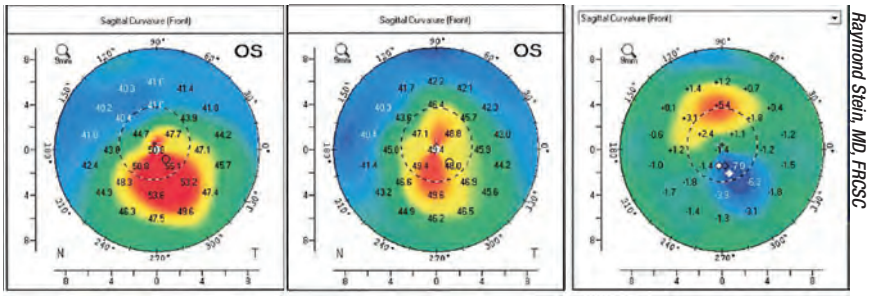
"The third version of topography-guided ablation has resulted from the advent of the Phorcides software," he says. "Phorcides is a new software package developed by Mark Lobanoff, MD. Mark looked at a lot of data from his practice and designed software to improve the diagnostics and the way that data is then used to ablate the cornea.

"Phorcides does weight-averaging of several datasets: the standard topographic data, the topography from the WaveLight Vario device, the topography from the Pentacam—for both the anterior and posterior corneal surfaces—and the manifest refraction," Dr. Stonecipher explains. "The result is a vectored analysis. In particular, Dr. Lobanoff figured out a way to analyze all of the factors relating to astigmatism, whether it's regular astigmatism, irregular astigmatism or astigmatism caused by a higher-order aberration."

Dr. Krueger agrees that predicting

the outcome is more difficult when astigmatism is an issue—especially if the manifest refraction and your topographic measurements report conflicting data about the amount and/or axis of the astigmatism. "For instance, if the manifest refraction shows a different astigmatism value than you get with topography, you're kind of at an impasse," he says. "Which should you treat? By and large, studies suggest that using the topography-based astigmatism will probably produce a better outcome than using the manifest data, but you have to look at each case carefully and understand it very well.

"That's where some of the latest software can help," Dr. Krueger notes. "The Phorcides analytical software package does vector analysis on all of the different components of astigmatism and gives you a calculated value to put into the instrument. That's probably been the most robust solution for getting the best outcome when there's some disparity in the measurements. In fact, it's been licensed by Alcon to use as a planning tool to help surgeons come up with the right numbers."



Raymond Stein, MD, FRCSC

Some surgeons outside the United States have been treating irregular astigmatism with topography-guided ablation for many years. Above: Following a topography-guided PRK, this patient's best-spectacle-corrected acuity improved from 20/100 to 20/30. (Preop, left; two years postop, middle; difference, right.) The difference map shows the superior cornea was steepened by 5.4 diopters and the inferior cornea flattened by 7.0 diopters. The reduction in irregular astigmatism was responsible for a significant improvement in BCVA.

Fine-tuning Phorcides

Dr. Stonecipher says that a group of surgeons with topography-guided experience decided to see how the Phorcides software did with patients whose measurements showed, for example, completely different axes on topography vs. manifest refraction. "We retrospectively looked at the data from more than 100 cases fitting that description, eyes that were treated with the different topography-guided options," he explains. "We found that the best outcomes resulted when Phorcides was used. These findings are currently submitted for publication.

"Right now we have more than 600 eyes involved in a prospective contralateral eye study comparing manifest TCAT to Phorcides," he says. "So far, both groups are doing well. [Dr. Stonecipher showed some preliminary data from this study at the annual meetings of the American Society of Cataract and Refractive Surgery and the European Society for Cataract and Refractive Surgery in 2019.] Next, we want to analyze how these patients did at three months, and find out which patients—if any—didn't do well with this approach. We're also putting our data into the cloud, and using 'deep learning' to improve the software even further."

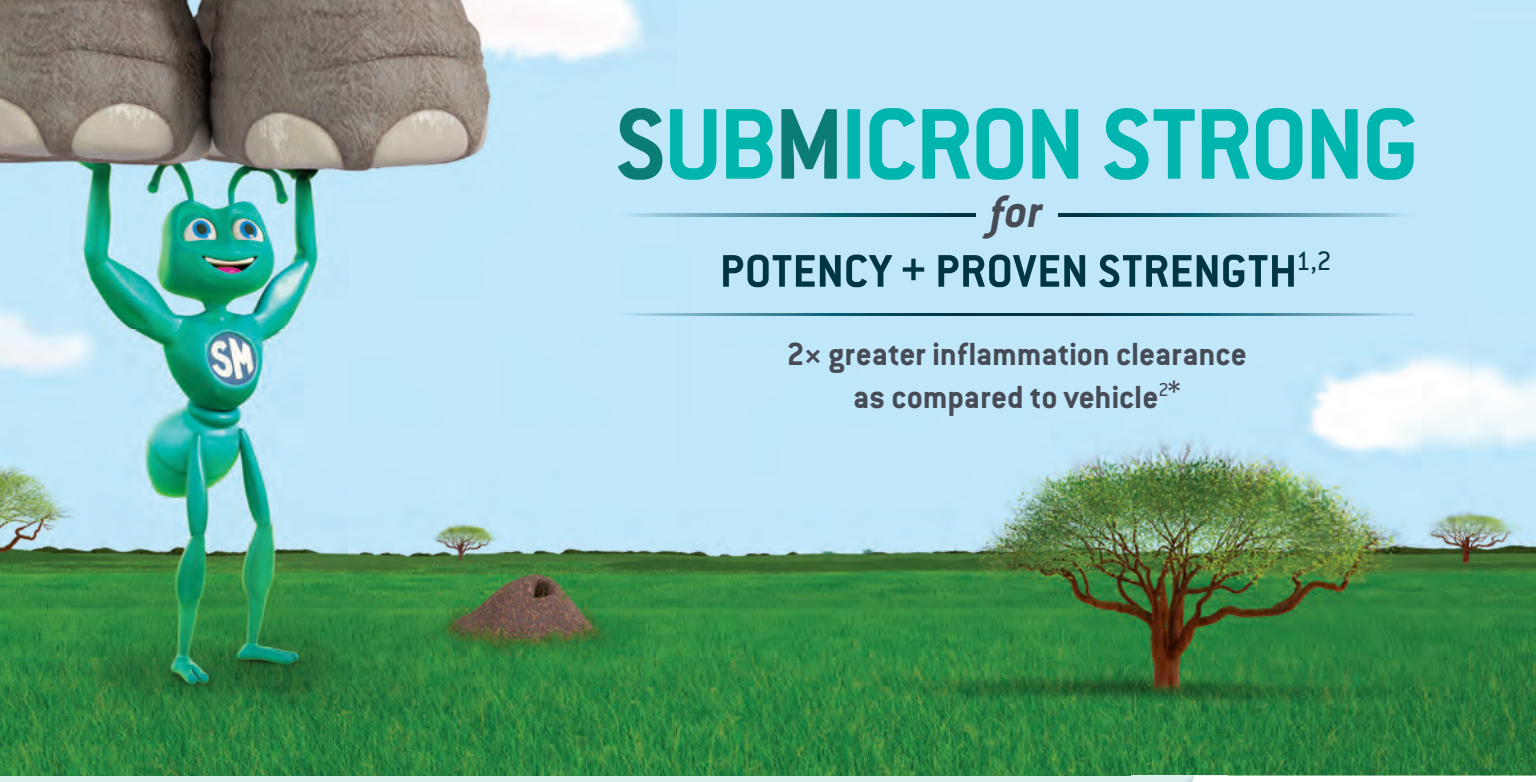
Dr. Stonecipher notes that, so far, Phorcides is not designed to analyze eyes with keratoconus or post-LASIK ectasia. "We're looking at those cases, but it's currently designed to make a virgin eye see better," he says. "Nevertheless, the current version of Phorcides is pretty robust. It's especially useful when dealing with eyes that produce conflicting measurements. To date, I've haven't had to enhance a single eye treated using this software.

"Right now, Dr. Lobanoff is trying to release Phorcides to everyone as a beta software," Dr. Stonecipher adds. "We're hoping to improve the outcomes with data from multiple surgeons on multiple platforms at multiple sites." (Dr. Lobanoff is currently building a module of Phorcides for complex/repair cases, such as off-centered ablations, small ablation zones, post-RK or keratoconus, that will also incorporate epithelial thickness maps into the analytics. That version should be available later this year.)

Treating Irregular Corneas

It's no secret that topography-guided ablation can be an effective way to address vision problems caused by corneal disease or previous refractive surgeries. Although the FDA approval didn't include this use, it did make the technology available in the United States. "The FDA tested this technology on primary eyes simply because it was too hard to measure the success of the results with 20-unhappy eyes, and the primary enrollment is reflected in the labeling," Dr. Krueger says. "But the technology is now accessible for American surgeons to use on these more complex eyes on an off-label basis. If we can fix patients who have an aberrated cornea because of a past correction, it will help reduce any fear of having laser vision correction."

Meanwhile, some surgeons outside the United States, not having to worry about FDA approval, have accumulated years of experience using this technology to correct more seriously aberrated corneas. One of those surgeons is Raymond Stein, MD, FRCSC, medical director of the Bochner Eye Institute in Toronto and an associ-



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†Pooled analysis of Phase 3 clinical studies. **Study 1:** 29% LOTEMAX® SM (N=171) vs 9% vehicle (N=172). **Study 2:** 31% LOTEMAX® SM (N=200) vs 20% vehicle (N=199); *P*<0.05 for all.

‡Pooled analysis of Phase 3 clinical studies. **Study 1:** 73% LOTEMAX® SM (N=171) vs 48% vehicle (N=172). **Study 2:** 76% LOTEMAX® SM (N=200) vs 50% vehicle (N=199); *P*<0.05 for all.

Indication

LOTEMAX® SM (loteprednol etabonate ophthalmic gel) 0.38% is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery.

Important Safety Information

- LOTEMAX® SM, as with other ophthalmic corticosteroids, is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.
- Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. If LOTEMAX® SM is used for 10 days or longer, IOP should be monitored.
- Use of corticosteroids may result in posterior subcapsular cataract formation.

Important Safety Information (cont.)

- The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those with diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.
- Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infections.
- Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).
- Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal cultures should be taken when appropriate.
- Contact lenses should not be worn when the eyes are inflamed.
- There were no treatment-emergent adverse drug reactions that occurred in more than 1% of subjects in the three times daily group compared to vehicle.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit **www.fda.gov/medwatch** or call **1-800-FDA-1088**.

Please see brief summary of Prescribing Information on adjacent page.

References: 1. LOTEMAX SM Prescribing Information. Bausch & Lomb Incorporated. **2.** Data on file. Bausch & Lomb Incorporated. **3.** Cavet ME, Glogowski S, Lowe ER, Phillips E. Rheological properties, dissolution kinetics, and ocular pharmacokinetics of loteprednol etabonate (submicron) ophthalmic gel 0.38%. *J Ocul Pharmacol Ther.* 2019. doi: 10.1089/jop.2019;35(5):291-300.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use LOTEMAX® SM safely and effectively. See full prescribing information for LOTEMAX® SM.

LOTEMAX® SM (loteprednol etabonate ophthalmic gel) 0.38%

For topical ophthalmic use
Initial U.S. Approval: 1998

INDICATIONS AND USAGE

LOTEMAX® SM is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery.

DOSAGE AND ADMINISTRATION

Invert closed bottle and shake once to fill tip before instilling drops. Apply one drop of LOTEMAX® SM into the conjunctival sac of the affected eye three times daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period.

CONTRAINDICATIONS

LOTEMAX® SM, as with other ophthalmic corticosteroids, is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, in mycobacterial infection of the eye and fungal diseases of ocular structures.

WARNINGS AND PRECAUTIONS

Intraocular Pressure (IOP) Increase: Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. If this product is used for 10 days or longer, intraocular pressure should be monitored.

Cataracts: Use of corticosteroids may result in posterior subcapsular cataract formation.

Delayed Healing: The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

Bacterial Infections: Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection.

Viral infections: Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).

Fungal Infections: Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal cultures should be taken when appropriate.

Contact Lens Wear: Contact lenses should not be worn when the eyes are inflamed.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Adverse reactions associated with ophthalmic steroids include elevated intraocular pressure, which may be associated with infrequent optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, delayed wound healing and secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera. There were no treatment-emergent adverse drug reactions that occurred in more than 1% of subjects in the three times daily group compared to vehicle.

USE IN SPECIAL POPULATIONS

Pregnancy: Risk Summary: There are no adequate and well controlled studies with loteprednol etabonate in pregnant women. Loteprednol etabonate produced teratogenicity at clinically relevant doses in the rabbit and rat when administered orally during pregnancy. Loteprednol etabonate produced malformations when administered orally to pregnant rabbits at doses 4.2 times the recommended human ophthalmic dose (RHOD) and to pregnant rats at doses 106 times the RHOD. In pregnant rats receiving oral doses of loteprednol etabonate during the period equivalent to the last trimester of pregnancy through lactation in humans, survival of offspring was reduced at doses 10.6 times the RHOD. Maternal toxicity was observed in rats at doses 1066 times the RHOD, and a maternal no observed adverse effect level (NOAEL) was established at 106 times the RHOD. The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies. Data: *Animal Data.* Embryofetal studies were conducted in pregnant rabbits administered loteprednol etabonate by oral gavage on gestation days 6 to 18, to target the period of organogenesis. Loteprednol etabonate produced fetal malformations at 0.1 mg/kg (4.2 times the recommended human ophthalmic dose (RHOD) based on body surface area, assuming 100% absorption). Spina bifida (including meningocele) was observed at 0.1 mg/kg, and exencephaly and craniofacial malformations were observed at 0.4 mg/kg (17 times the RHOD). At 3 mg/kg (128 times the RHOD), loteprednol etabonate was associated with increased incidences of abnormal left common carotid artery, limb flexures, umbilical hernia, scoliosis, and delayed ossification. Abortion and embryofetal lethality (resorption) occurred at 6 mg/kg (256 times the RHOD). A NOAEL for developmental toxicity was not established in this study. The NOAEL for maternal toxicity in rabbits was 3 mg/kg/day. Embryofetal studies were conducted in pregnant rats administered loteprednol etabonate by oral gavage on gestation days 6 to 15, to target the period of organogenesis. Loteprednol etabonate produced fetal malformations, including absent innominate artery at 5 mg/kg (106 times the RHOD); and cleft palate, agnathia, cardiovascular defects, umbilical hernia, decreased fetal body weight and decreased skeletal ossification at 50 mg/kg (1066 times the RHOD). Embryofetal lethality (resorption) was observed at 100 mg/kg (2133 times the RHOD). The NOAEL for developmental toxicity in rats was 0.5 mg/kg (10.6 times the RHOD). Loteprednol etabonate was maternally toxic (reduced body weight gain) at 50 mg/kg/day. The NOAEL for maternal toxicity was 5 mg/kg. A peri-/postnatal study was conducted in rats administered loteprednol etabonate by oral gavage from gestation day 15 (start of fetal period) to postnatal day 21 (the end of lactation period). At 0.5 mg/kg (10.6 times the clinical dose), reduced survival was observed in live-born offspring. Doses ≥ 5 mg/kg (106 times the RHOD) caused umbilical hernia/incomplete gastrointestinal tract. Doses ≥ 50 mg/kg (1066 times the RHOD) produced maternal toxicity (reduced body weight gain, death), decreased number of live-born offspring, decreased birth weight, and delays in postnatal development. A developmental NOAEL was not established in this study. The NOAEL for maternal toxicity was 5 mg/kg.

Lactation: There are no data on the presence of loteprednol etabonate in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for LOTEMAX® SM and any potential adverse effects on the breastfed infant from LOTEMAX® SM.

Pediatric Use: Safety and effectiveness of LOTEMAX® SM in pediatric patients have not been established.

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma tk assay, or in the chromosomal aberration test in human lymphocytes, or *in vivo* in the mouse micronucleus assay. Treatment of male and female rats with 25 mg/kg/day of loteprednol etabonate (533 times the RHOD based on body surface area, assuming 100% absorption) prior to and during mating caused preimplantation loss and decreased the number of live fetuses/live births. The NOAEL for fertility in rats was 5 mg/kg/day (106 times the RHOD).

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ate professor of ophthalmology at the University of Toronto. Dr. Stein has been involved with topography-guided treatments for the past 10 years.

"Probably the number one indication we treat using this technology is irregular corneas, such as those with keratoconus, pellucid marginal degeneration or ectasia following laser vision correction," he says. "Those constitute about 90 percent of the patients we treat. Other less-common indications include patients having post-refractive-surgery complications such as a decentered ablation. That's pretty rare today, thanks to the use of active tracking systems. The other problem we sometimes treat is a small optical zone, usually the result of surgery done a long time ago. That can cause significant haloes at night when the pupil dilates."

Dr. Stein says that topography-guided technology allows him to improve best corrected visual acuity. "That's a big advance," he says. "We can take an irregular cornea and flatten the steep areas and steepen the flat areas, thus making the cornea more regular and improving best corrected spectacle acuity. We generally use this technology when patients have a best-corrected spectacle acuity of at least 20/30 or worse."

Taking It Step-by-Step

Dr. Stein describes the steps involved in a typical treatment. "First, we take about eight topographic maps," he says. "The data is fed digitally into our Allegretto excimer laser, which we've used for a number of years. The computer averages the data; then the surgeon selects the depth of the ablation and the optical zone. The larger the optical zone, the more tissue the ablation will remove, and we want to minimize the depth of the ablation. My preference is to use a 6- or 6.5-mm optical zone, because I feel it's more stable; there's less chance of regression. However, if the patient has a very thin cornea or a significant difference between the steep and flat areas, we have to use a smaller 5.5- or 5-mm optical zone."

Dr. Stein notes that removing the epithelium before measuring the topography helps to ensure the best result. "Normally, when we measure corneal topography it's done with the epithelium intact," he says. "Many eyes with ectatic disease have a very irregular cornea, and the epithelial thickness can vary from one area to another. For example, in keratoconus, the epithelium tends to be thinner over the cone and thicker out in the periphery. Normally, surgeons rely on preoperative measurements made when the epithelium is intact. However, we've found that if we remove the epithelium and then do a topography measurement, the data is significantly different.

"For that reason, we do a phototherapeutic keratectomy first, followed by the topography-guided photorefractive keratectomy," he explains. "I think you can get reasonable outcomes taking the epithelium off manually, but the results are more accurate if you do a PTK. We remove 50 µm of tissue, usually at a 6.5-mm optical zone with a transition zone at the edge, and then perform the topography-guided PRK. Sometimes, if the cornea is thick enough, we can try to reduce some cylinder at the same time. But overall, we try to limit the total treatment after the PTK to another 50 µm."

Dr. Stein says that when treating ectatic corneas he applies mitomycin-C for 30 to 60 seconds, irrigates the surface and then proceeds with corneal cross-linking to lock the changes in place. "When treating ectatic disease, we're weakening the cornea, and there's a risk of further ectasia," he says. "That's why we need to combine this procedure with cross-linking. Also, using mitomycin-C is critical. I've been doing PRK for 28 years, and

Managing a Change in Spherical Refraction

Ronald R. Krueger, MD, McGaw Professor and chairman of the department of ophthalmology at the University of Nebraska Medical Center in Omaha, notes that one of the challenges when performing topography-guided ablations is that correcting significant ablations can alter the spherical refraction. Until technology is able to handle this for us, the surgeon must either learn to predict the amount of spherical change that will result (which some surgeons have become adept at doing), or plan to do a separate procedure later to correct any spherical change caused by correcting the aberrations.

"In a way, it's like treating a moving target," says Dr. Krueger. "You have a certain spherocylindrical refraction when you start, but as you treat the aberrations, that may change. Therefore, you have to try to predict the amount of change the aberration correction will cause and compensate for it. I've found it to be a manageable challenge, because there are certain clues and tricks you can use. There are metrics within the device that tell you about the level of spherical aberration and give a number to it. You can often correlate that with the amount of spherical change your treatment will cause. It's really about understanding the technology."

Nancy Tanchel, MD, in private practice at Liberty Laser Eye Center in Vienna, Virginia, uses the Nidek EC-5000 Quest system to perform topography-guided ablations. She says she hasn't encountered any cases in which the topography-guided ablation caused a measureable shift in the spherical refraction. "Compensating for that seems to be part of the internal nomogram in the Nidek system," she says. "Plus, the system isn't attempting to completely correct all surface aberrations; it corrects topographic abnormalities by about 40 percent. That may limit changes in the spherical refraction."

—CK

in the early days we had a very high incidence of corneal haze—especially when we did high-diopter treatments. The risk of corneal haze increases slightly when you combine topography-guided PRK with cross-linking; we've found that mitomycin-C decreases the incidence of corneal haze."

Knowing the Limits

Dr. Stein says that a critical factor in the success of these treatments is how much difference there is between the steepest and flattest parts of the cornea. "The results are much better when patients have less than a 10-D difference across the cornea," he explains. "Those are the eyes in which we get a significant improvement in best-corrected visual acuity. So, within the 6-mm optical zone we look at the steepest part and the flattest part. If the difference is large, such as 20 D, it will be very difficult to smooth that cornea with a topography-guided PRK. We'd have to flatten the steep area by 10 D and steepen the flat area by 10 D, which would be impossible to do. On the other hand, if the difference is less than 10 D, we only need to flatten one area by about 5 D, and steepen another area by 5 D. In fact, our research has revealed that the patients that do the best are those with less than 5 D of difference across the cornea. In those cases, we only have to flatten the steep area by 2.5 D and steepen the flat area by 2.5 D. It's very easy to smooth those corneas."

Dr. Stein says that once you're familiar with the technology, doing the treatment is relatively straightforward. "The most important thing is identifying the patients that are the best candidates," he notes. "For example, I wouldn't go out of my way to use this technology to correct irregular astigmatism in a patient with 20/20 acuity. Certainly it's critical to rule out false ectasia cases, whether it be epithelial basement membrane dystrophy, superficial punctate keratopathy, Salzmann's nodular degeneration or amiodarone keratopathy. And a map that's not created properly can produce an irregular topographic pattern where there really isn't one. You have to be conscientious about looking for those factors so you can rule out poor candidates.

"Beyond those concerns, you should limit the ablation to a certain number of microns," he continues. "Most of the patients we treat have a corneal thickness of 430 µm or more, because we want to limit our ablation to about 50 µm and have enough thickness left to do cross-linking. We also prefer to treat eyes in which we can create a large optical zone. And, as noted earlier, we have to consider the dioptric difference across the cornea. If the maximum difference is large, we won't be able to smooth the cornea. The ones with a difference less than 10 D—especially less than 5 D—are the best patients to treat with this technology."

Making the Transition

Dr. Stein notes that the learning curve for using this technology on irregular corneas can be steep. "It takes a number of years to get really comfortable with this," he says. "It's a matter of reading as much as you can about this type of procedure, and maybe observing some cases done by surgeons who do this on a regular basis. Of course, right now there aren't that many surgeons fitting that description. John Kanellopoulos in Greece, David Lin in Vancouver and myself are the ones doing the largest number of irregular cornea treatments."

Dr. Stein says that he does sometimes treat normal corneas with this technology. "There are some advantages to using this technology, even in that situation," he notes. "For example, the treatment is centered over the

line of sight instead of the center of the pupil. That can improve the quality of vision the treatment produces, especially in hyperopic eyes where the line of sight can be more nasal. Those patients often have a positive angle kappa."

Dr. Krueger notes that Alcon understands that surgeons hope to eventually use this technology to help those "20-unhappy" patients. "When Alcon released this technology, they said, 'This isn't approved for that purpose, so don't begin by treating those highly aberrated eyes with this technology—you don't understand it well enough. Do a large number of normal eyes first. Then, when you're really comfortable with the technology, maybe you can selectively use it on previously treated eyes.'

"That's what I did," Dr. Krueger says. "It's helped me to offer some visual improvement to those patients, and I've had some successes that were rather dramatic. Sometimes you get patients who have very specific symptoms such as double vision, and you may be able to resolve that by minimizing the irregularities. Sometimes you may have a disillusioned patient who's lost hope, and you're giving that person a whole new lease on life."

Topography-integrated Ablation

Several refractive surgery systems have found other ways to incorporate topographic data into their ablation planning, without using it as the primary basis for the ablation. One such system is the iDesign Refractive Studio (Johnson & Johnson Vision). Marc Odrich, MD, associate professor of ophthalmology at the University of Virginia, has consulted with Johnson & Johnson Vision on the development of the iDesign Refractive Studio. He explains how the current model—version 2.0—incorporates topographic data into its ablation plan.

"The iDesign instruments have always performed a customized treatment," he notes. "Prior to version 2.0, the system would capture wavefront aberrometry, wavefront refraction, corneal topography, keratometry and pupillometry. The ablation used the wavefront measurement data to create a treatment, also taking into account the keratometry to compensate for the cosine effect. That's important, because the shape of the cornea affects how the wavefront data propagates from the pupil plane to the corneal plane, and also affects how the laser and cornea interact.

"In the new version of the system, version 2.0, we're no longer just using keratometry data to adjust how the wavefront correction is delivered," he explains. "Instead, we're using the full-gradient topography data the instrument collects. Keratometry provides estimates of the corneal surface details, but only around the central 3 mm; topography provides detailed, specific data about the x and y slopes at 125 points on the corneal surface, allowing the system to compensate more precisely for laser-tissue interactions on that individual cornea."

Dr. Odrich says the company hasn't done a head-to-head comparison of the topography-integrated version to previous versions of the system. "However, surgeons using the new version are reporting getting many more 20/10 and 20/12 outcomes than they did before," he says. "To me, that means the treatments are based on more accurate information. In my own practice I've seen the number of 20/10s and 20/12s double. Before, about 40 percent of my patients treated with the system ended up 20/12; now about 80 percent achieve 20/12. That translates into a huge difference in patient satisfaction."

Dr. Odrich says the 2.0 iDesign Refractive Studio is even easier to use than the previous models, despite incorporating more sophisticated technology. "The acquisition cycle is short-

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M18-069-00

For Special Cases, or Standard of Care?

Perhaps because of its complexity, topography-guided ablation is still not the primary offering for many refractive surgeons that use the technology. However, others are making it their go-to procedure.

Ronald R. Krueger, MD, McGaw Professor and chairman of the department of ophthalmology at the University of Nebraska Medical Center in Omaha, says it's become his primary offering to patients needing refractive surgery. "Some surgeons may only use topography-guided ablation when it looks like the corneal surface is a little more aberrated. If the case looks routine, they use wavefront-optimized," he notes. "I'd rather offer this to every patient. That makes it cost-effective for my patients, and my more extensive experience will help me to continue refining my results. Today, 85 percent or more of my myopic patients are treated with topography-guided technology. That's my standard of care."

Nancy Tanchel, MD, in private practice at Liberty Laser Eye Center in Vienna, Virginia, says she offers the topography-guided treatment to pretty much every patient. "We get excellent outcomes," she says. "If a patient has excellent best-corrected visual acuity before the treatment, the topography-guided part of the correction may not produce a major benefit, but it certainly won't do any harm. We don't ask patients to pay extra to have the topography-guided treatment. Nidek doesn't charge a click fee, so it doesn't change my cost whether I treat with it or without it. We just try to pick the best treatment for each patient. I'd only avoid using it if the topography scans were less than excellent."

Karl Stonecipher, MD, medical director for TLC Laser Eye Centers in Greensboro, North Carolina, says topography-guided ablation has become his primary offering. "I try to do 100 percent topography-guided ablations now, because it's significantly better for me in terms of outcomes," he says. "I've had three patients with UCVA outcomes of 20/8 and better. For me, postoperative UCVA better than the patient's preoperative BCVA in glasses or contact lenses has become common. So I automatically assume you'll be a topography-guided patient, unless I can't get a good topography on you because of dry eyes or irregular corneas, or the Phorcides software says a topography-guided treatment isn't advisable, or you're outside the FDA guidelines. If you're outside the guidelines, the computer won't let me put you in the laser; in that case I can still treat you with wavefront-optimized and get a great result. Finally, I need to have enough corneal tissue to support a topography-guided treatment, because it removes more tissue than wavefront-optimized ablation.

"My goal for this year is to get all patients to the point at which they can see better than they did with glasses or contact lenses," he adds. "With this technology I think we can already accomplish that in most of our patients who have 'normal' eyes."

—CK

er and more accurate," he says. "All of the wavefront and topographic data is collected with a single click. The automated exam selection mode uses an algorithm to choose the treatment that's most appropriate for each individual patient, and the instrument uses iris registration technology to compensate for any eye rotation. I've been using this model for seven months now, and I have yet to find a patient whose data I can't capture, even when eye disease is present."

Strategies for Success

Surgeons offer the following advice to help you increase the likelihood of excellent outcomes when using topography-guided ablation:

• ***The quality of the topographic maps is crucial.*** Dr. Krueger says some patients may not be eligible for topography-guided treatment because they fall outside the approved parameters. "However, that's fairly rare," he notes. "A more important issue is the quality of the topographic maps. Garbage in, garbage out. So, make sure there are no dry eyes or other exceptions. If you can't get a high-quality map because of variability due to dry eye or some other problem, you may want to optimize the cornea as much as possible before proceeding. Or you may say, this is a case where it's better to just plug in the numbers we have and use wavefront-optimized, rather than trying to base an ablation on data that you can't be completely certain is accurate."

Dr. Tanchel agrees, noting that the physician needs to be involved in sorting out which scans are used. "This task shouldn't be delegated to a lower-level employee in the office," she says. "You need to look at the topography scans yourself."

• ***If the magnitude of astigmatism measured on topography differs from the amount in the manifest refraction, consider treating an amount between those two numbers***. Dr. Krueger notes that the magnitude of astigmatism measured on topography is often slightly greater than that measured in the manifest refraction. "At least in the cases in which topography measured a higher value than the manifest refraction, my outcomes suggest it's best to split the difference," he says. "Alcon agrees; the company recommends that when you find a disparity between the topographic magnitude of astigmatism and the manifest magnitude, it's better to treat an amount between the two measurements."

• ***If you're treating irregular corneas, be on the lookout for patients with "false ectasia."*** "There are conditions that look like keratoconus or

pellucid marginal degeneration," Dr. Stein explains. "For example, patients with epithelial basement membrane dystrophy may appear to have an irregular cornea on topographic maps, but slit lamp examination will reveal changes within the epithelium. That's a contraindication for doing a topography-guided treatment. These patients can be helped by just removing the epithelium—essentially, performing a keratectomy.

"There are a number of other conditions like that, such as Salzmann's nodular degeneration, that can produce an irregular corneal picture," he continues. "Also, patients on amiodarone for heart problems can have an irregular cornea as a result of drug deposition in the epithelium. These patients should not have a topography-guided treatment. A slit lamp exam, often with fluorescein and a blue light, will allow the clinician to make a diagnosis of these false ectasia cases, which some people call pseudo-keratoconus." [For more about conditions that mimic ectasia, see Dr. Stein's recent article in *The Canadian Journal of Ophthalmology*.[4]]

• ***Track your outcomes and note which approaches are producing the best results.*** Dr. Krueger says this is a key part of using this technology. "I look at the eyes that gained at least one line of best corrected visual acuity after the surgery and analyze how I treated the astigmatism," he explains. "In those eyes, about 75 percent of the time, I treated the axis of astigmatism measured by the topography, no matter how much the manifest refraction disagreed with it. However, about 25 percent of the time, inputting the manifest axis produced a better outcome. The Phorcides software is now helping to clarify which one should be followed."

Worth the Effort

Dr. Krueger admits that using this technology takes a little longer than simply plugging a number into your laser and doing a treatment. "You need multiple instruments to gather all the data you require," he notes. "The Phorcides software is very helpful, but you need a Topolyzer Vario and a Pentacam to use it.

"Nevertheless, in my experience, the payoff is worth it," he says. "Today I'm getting at least 10 percent more 20/15 outcomes with topography-guided treatments than with wavefront-optimized treatments. Getting more 20/15s and 20/10s is what I want. In a more recent analysis of just my physician patients—because I treated a lot of physicians when I worked at the Cleveland Clinic—I was getting even higher values. Plus, I was getting 100-percent satisfaction rankings from the physicians having topography-guided treatment."

Dr. Stein notes that no other technology can do what topography-guided ablation can do. "Being able to smooth the cornea and design the treatment specific to the patient's topography is a significant advance," he points out. "For any patient with a significant loss of best corrected visual acuity, this is one of the best technologies to use to enhance their vision."

Dr. Krueger notes that some surgeons believe that topography-guided ablation is just a fad that will eventually pass. "That's probably true, because something even better will eventually show up," he says. "In fact we're about to embark on an FDA study using topography, wavefront and biometry as part of an all-in-one device that collects all of the information. It may eliminate the need for planning software and make the process even easier. But with that in the pipeline, my philosophy is, I want to be as good as I can be right now. I'm offering the technology and its amazing results to patients now, because that's going to make me more qualified and comfortable with getting into the next level of customization when more advanced versions of this technology hit the market.

"My hope is that eventually we'll reach a place where the technology is so good that the outcomes are statistically better than glasses or contact lenses in every case. It won't be just for the person who wants freedom from glasses; it will be for the person who wants to have 'super vision'—the best he or she can have.

"If our patients consistently gain lines of vision, that's a game-changer," he says. "We'll be improving people's vision beyond what they could otherwise achieve. Hopefully that will also open up the refractive surgery market in a bigger way." REVIEW

Dr. Stonecipher has worked with Alcon, VISX, Bausch + Lomb and Nidek. Dr. Krueger is a consultant for Alcon, Johnson & Johnson Vision and Bausch+Lomb Health. Dr. Odrich is a consultant to Johnson & Johnson Vision. Drs. Stein and Tanchel report no relevant financial ties.

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Time to Revisit Surface Ablation?

Sean McKinney, Senior Editor

Mastering today's techniques and new technologies.

Surface ablation continues to maintain a strong foothold in an increasingly competitive refractive surgery field. Some surgeons use the procedure more than in the past or even exclusively, arguing that today's advanced technology can make visual recovery faster, postop pain more manageable and complications easier to prevent, positioning this pioneering form of laser vision correction for growth and enduring success. As with most procedures, this one requires the skilled hands and eyes of knowledgeable, experienced and committed surgeons.

Have you considered the latest advantages of surface ablation when you plan your procedures? In this article, your peers explain how they succeed while meeting the familiar challenges of surface ablation—selecting appropriate patients, effectively debriding the corneal epithelium, managing postop pain and minimizing unwanted outcomes.

One and Only

Leading surgeon Marguerite McDonald, MD, FACS, the first to perform a surface ablation procedure when she completed PRK with an excimer laser at Louisiana State University on March 25, 1988, has now returned to her roots, performing only surface ablation procedures.

"I've done PRK, EBK, LASEK, Epi-LASIK and—for many years—LASIK. Everything short of SMILE, for which I'm awaiting further refinements," says Dr. McDonald, clinical professor at NYU Langone Medical Center in New York City. "Today, with modern surface ablation, I get virtually the same result as with LASIK. I achieve exquisite outcomes, quick recovery and virtually no pain. Plus, I don't have to worry about flap complications."

To achieve these results, Dr. McDonald exclusively uses Epi-Bowman Keratectomy (EBK), performed with the Epi Clear device (Orca Surgical, Israel). Before ablating the cornea with a Visx laser, she relies on the first "blade" of the Epi Clear device to create a microepithelial elevated fold, while letting the second blade gently peel the epithelium and draw it into a receptacle for complete removal from the site without touching the epithelial basement membrane or Bowman's layer. "If you take your time, you can lift up the epithelium in sheets, which is much more effectively done with the EBK technique," she says.

Norfolk, Virginia, surgeon Elizabeth Yeu, MD, takes a different ap-

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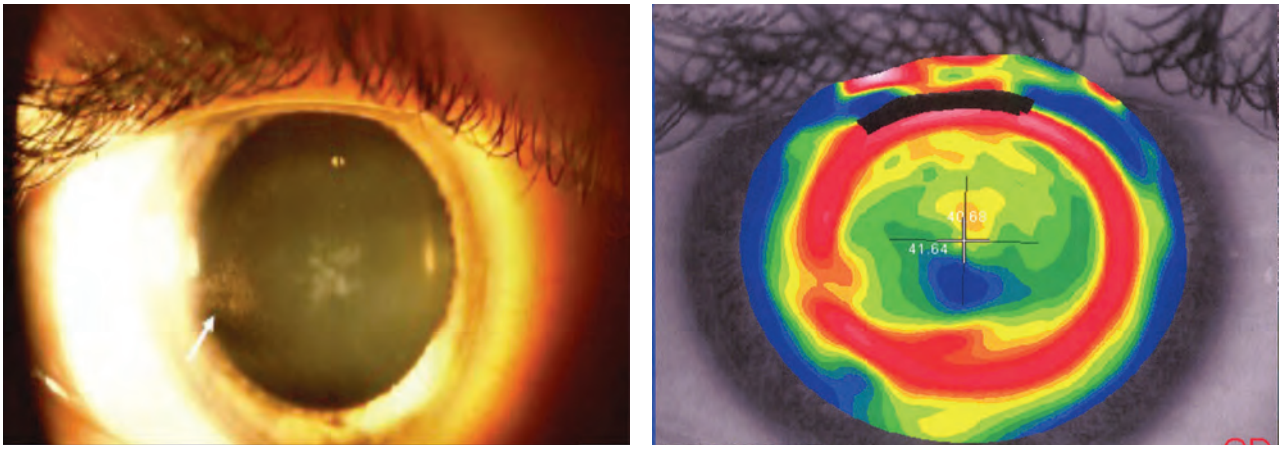


Figures 1-2. A corneal stromal divot and haze are shown (left) at 7 o'clock paracentrally after an Epi-LASIK blade inadvertantly cut into the stroma. The true curve topography of the same area is also shown (right). (*From Ou, JI, Manche, EE. Superficial keratectomy after epi-LASIK. J Cataract Refract Surg 2006; 32:2153-2154. Reprinted by permission from the Journal of Cataract & Refractive Surgery (jcrsjournal.org), the official journal of the American Society of Cataract and Refractive Surgery and the European Society of Cataract and Refractive Surgeons.*)

proach to surface ablation. "I would say 15 percent of my procedures are PRK and 85 percent, LASIK," she says. "I think advanced surface ablation provides us with a wonderful way to take care of our patients who may have marginal corneal thickness, a tendency toward more clinically significant dry-eye disease or who just shouldn't be getting flap surgery," she adds.

Rachel Epstein, MD, a refractive surgeon at Chicago Cornea Consultants, says she also offers PRK when surface ablation is indicated. "We probably perform a 50/50 split between LASIK and surface ablation," she says. "We're still exploring the possible implementation of SMILE into the practice. We have a very large referral base that includes patients with keratoconus and corneal ectasia. I think we're uniquely attuned to the prevention of post-LASIK ectasia. With the use of Pentacam scans or even clinical evaluation, I find far too often that PRK is a safer option. It's a procedure we were doing long before LASIK and a procedure we continue to do even with the availability of LASIK, so that speaks to its longevity."

Edward Manche, MD, division chief of the cornea and refractive surgical service at Stanford University School of Medicine at Byers Eye Institute, says 90 percent of his practice involves refractive surgery procedures, including 15 percent via surface ablation.

"I typically perform PRK in patients who may not be suitable for LASIK or SMILE surgery," he says, echoing the strategy of many of his colleagues. "The most common indication is for patients with thin corneas (i.e., less than 490 µ). I use the standard exclusion criteria for LASIK—ruling out patients with some autoimmune diseases, such as rheumatoid arthritis, Sjögren's syndrome, etc. I also exclude eyes with ectactic disorders, such as keratoconus and pellucid marginal degeneration, from undergoing LASIK."

Why Surface Ablation?

LASIK, producing minimal postop pain and rapid vision correction, emerged as the darling of laser refractive procedures at the turn of the century, when 1.4 million patients underwent the procedure in the United States in 2000. However, the number of procedures dropped to 749,000 in 2009, following the recession of 2008.[1,2] Besides the bad economy, a limited number of poignant complaints about LASIK complications and a well-publicized federal hearing held for distraught patients and their families on April 25, 2008 were blamed by some for the downturn in the number of LASIK procedures.[3,4,5]

The appearance of competing refractive surgery procedures—such as LASEK, Epi-LASIK, conductive keratoplasty, phakic IOLs, refractive lens exchange and SMILE—gave surgeons more options, and this has created opportunities for procedures that perform well.

"I've tried the newer surface ablation procedures, LASEK (ethyl alcohol [EtOH]-assisted laser-assisted subepithelial keratectomy)[6] and Epi-LASIK (epithelial laser in situ keratomileusis),[7] and I've found that PRK is superior," says Dr. Manche.

During LASEK, a trephine is used to cut and lift a flap of epithelial corneal tissue to treat low myopia. An EtOH-based solution is used to loosen the epithelial cells. Once the

epithelial flap is created and moved aside, the procedure is the same as PRK. "After the laser treatment, you're supposed to lay the flap of epithelium back in place," says Dr. Manche. "But that amounts to putting dead epithelial tissue back. The new epithelial cells need to reproduce under this dead tissue, which doesn't seem to make sense. Nobody is doing that procedure anymore."

Epi-LASIK, the other newer surface ablation method, involves the use of a special microkeratome called the Epi-keratome. "This technique was abandoned because every once in a while, even with the dullest of plastic blades, the blade would evulse a little chunk of stroma, which can create a significant decrease in vision if it happens over the visual axis," points out Dr. McDonald.

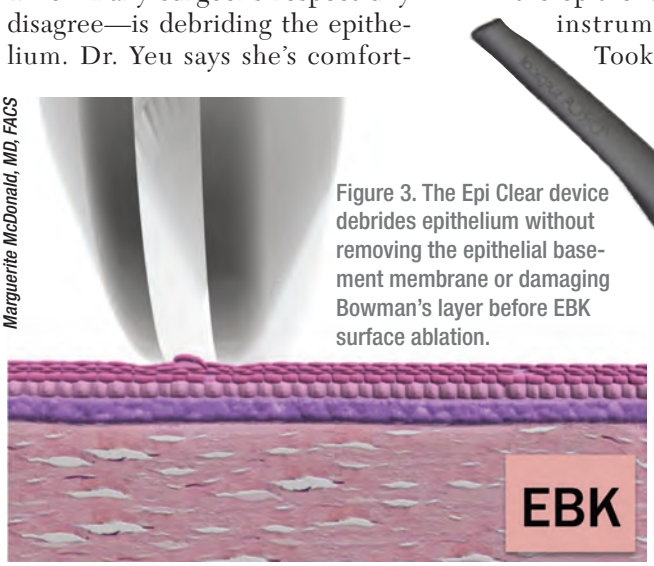
"We published a case report in which we had the Epi-LASIK blade cut into the stroma and the result was a really bad outcome,"[8] adds Dr. Manche. (*See Figures 1-2 on page 35.*) "This is another procedure that has never taken hold."

Division Over Debriding

One of the critical techniques involved in surface ablation—over which many surgeons respectfully disagree—is debriding the epithelium. Dr. Yeu says she's comfortable using an Amoils brush for naïve corneas and EtOH wells for enhancements. Dr. Epstein is also comfortable with EtOH. "One of my associates and I prefer to debride the epithelium with alcohol, while another associate prefers the Amoils brush," she says.

However, Dr. Manche, who debrides with a mechanical brush, only uses EtOH to debride when he needs to avoid disrupting the corneal surface of post-LASIK and post-radial keratectomy patients while preparing these patients for follow-up PRK. "I've seen cases where the alcohol affects areas differently than we'd hoped, and we've seen a little bit of an irregular ablation in some patients," he says.

Avoiding the use of EtOH to debride the cornea is one of several reasons Dr. McDonald uses EBK. "Published studies show that EBK's outcomes are superior, and the amount of discomfort is significantly less, than with standard PRK," she notes.[9,10] "Any time you have to remove epithelium, it will re-epithelialize faster and the patient will be more comfortable if you're using the EBK technique versus an alcohol-soaked/alcohol-containing device—which has been shown to be toxic to the epithelium[11,12]—or other instruments, such as a Tooke knife and the Amoils brush. (*See Figure 3, left, and Figure 4 on page 37.*)



Marguerite McDonald, MD, FACS

Figure 3. The Epi Clear device debrides epithelium without removing the epithelial basement membrane or damaging Bowman's layer before EBK surface ablation.

"Surgeons can also use the Epi Clear device to perform pterygium surgery or clean up the edges of an indolent non-healing corneal ulcer," Dr. McDonald continues. "With EBK, you never accidently damage the stromal tissue. In fact, you also spare the epithelial basement membrane and Bowman's layer."

She notes that the use of the Amoils brush, EtOH or transepithial PTK to debride the epithelium ruptures the epithelial cell walls, "causing pro-inflammatory cytokines to pour into the stroma and initiate an inflammatory cascade. Basement membrane is also removed."

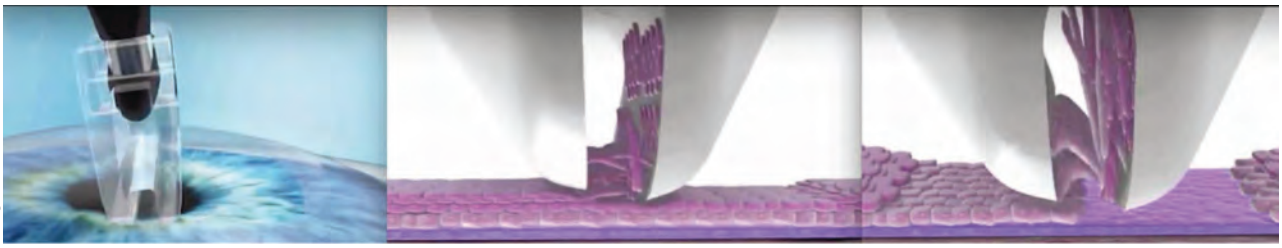
In the past, before improved laser technology enlarged ablation zones, Dr. Manche's preferred method of debriding the epithelium was to use transepithelial phototherapeutic keratectomy (T-PRK) before PRK.

"This is a feature on the Visx excimer laser," he says. "You could remove 6.5 mm of epithelium, allowing it to be perfectly centered, using autotracking and autocentration. In my opinion, it's best to remove exactly the right amount of epithelium, allowing the fastest rate of re-epithelialization. T-PRK uses a very sharp edge, so the cells grow back immediately, as opposed to when you use EtOH, a brush or mechanical scraping.

"We were once able to get eyes re-epithelizing in 24 to 36 hours. Unfortunately, with the development of larger treatment treatment zones, up to 8 or 9 mm, debriding with T-PRK isn't viable at this time."

Dr. Manche hopes an enlarged T-PRK target zone will be introduced in the United States with a new technology, such as the type used by Schwind Eye-Tech Solutions in Germany.

"That's something that would definitely be welcomed by surgeons in the U.S.," he says.



Marguerite McDonald, MD, FACS

Figure 4. After the EBK Epi Clear device makes contact with the eye (left), the first blade creates a micro-epithelial elevated fold (middle), while the second blade gently peels the epithelium and draws it into a receptacle for complete removal from the site (right).

Improved Technologies

No matter which debridement method you use, Dr. McDonald points to improved technologies as a primary motivation in her restored commitment to surface ablation.

"Before flying spot lasers, we had the wide beam lasers with the diaphragm opening or closing," she recalls. "As a result, more patients experienced haze and regression due to the rough surfaces created by the ablation. Now our laser treatments are so incredibly smooth that haze is really a non-issue, unless you attempt to remove too much tissue. Most surgeons stop at approximately 8 D of myopia.

"For virtually every patient, I use the Visx laser to do custom wavefront EBK," Dr. McDonald continues. "The only time I wouldn't consider this approach is if I were trying to touch up a multifocal or extended-depth-of-focus IOL, when you want to get patients closer to plano at distance. If you attempt to do a wavefront-guided procedure on these patients, you risk reversing the multifocality of the IOL."

Wavefront-guided treatment, which has improved the precision of LASIK, has benefited surface ablation equally, according to Dr. McDonald. "Higher-order aberrations and astigmatism are well-treated now with this technology," she says. "Topography-guided treatments also effectively treat highly-aberrated eyes, as you may find in a patient who's had a corneal transplant. The early results are good, although we're still refining those treatments."

Dr. Yeu uses the WaveLight Allegretto Wave Eye-Q excimer laser (Alcon) for patients who don't need significant cylinder correction. "I also use the Contoura Vision topography-guided system (Alcon) to individualize the treatment of patients who have higher amounts of astigmatism," she adds.

Dr. Manche says he has three excimer lasers, including a Star S4 IR Excimer Laser (Johnson & Johnson), Alcon's Allegretto system and a MEL 90 excimer laser (Carl Zeiss Meditec), awaiting FDA approval. "We also have an Intralase iFS Advanced Femtosecond Laser (Johnson & Johnson Vision) and a VisuMax femtosecond laser (Carl Zeiss Meditec)," he says. "I do all of my wavefront-guided treatments (both LASIK and PRK) on the Visx CustomVue system. My topography-guided treatments (both LASIK and PRK) are performed on the Allegretto Contoura system. I also use the Allegretto system for my wavefront-optimized treatments (both LASIK and PRK)."

And the breakdown of his cases? "I use wavefront-guided treatments in 95 percent of my PRK and LASIK cases," he says. "About 5 percent of the remaining cases are performed using topography-guided ablation, with only occasional use of wavefront-optimized ablations, which I most commonly provide when offering LASIK or PRK to pseudophakic multifocal IOL patients with residual refractive errors."

Dr. Manche says he achieves equal results with of all of his refractive surgery procedures. "The meta-analysis shows nearly identical outcomes," he notes. "We've done LASIK in one eye, PRK in the other eye. The outcomes are identical from the patient's perspective. We look at wavefront-guided in one eye and optimized in another, and we get the same results, as we do with PRK. You can find minor differences when looking at the results, such as higher-order aberrations. But when you ask patients which eye is better, they can't tell."

In Chicago, Dr. Epstein uses the Alcon/WaveLight EX500 laser for all of her refractive surgery patients and the Johnson & Johnson iFS femtosecond laser to create LASIK flaps. "We use this laser for LASIK and PRK," she says. "We've been implementing Dr. Mark Lobanoff's Phorcides planning software to both identify and treat astigmatism, utilizing some of the most advanced technology. This software allows for both Contoura and wavefront-optimized treatment planning."

Managing Pain

Of course, the least desirable aspect of surface ablation procedures is postop pain. But it's getting better.

Dr. Manche uses an AcuVue Oasys plano lens with a base curve of 8.4

postop. "It helps to have a relatively tight lens to reduce pain," he observes. "I use one drop of an NSAID at the conclusion of PRK surgery, and I treat patients with a fourth-generation fluoroquinolone antibiotic and topical steroids to control infection and pain. We also use oral NSAIDS (ibuprofen) and either hydrocodone bitartrate/acetaminophen (oral Vicodin) or acetaminophen/hydrocodone (Norco) for rescue relief."

Dr. Manche's PRK patients typically undergo the procedure on a Thursday because pain usually doesn't develop until inflammation peaks 48 to 60 hours after the procedure. "By Saturday, most of them have burning, tearing and light sensitivity," says Dr. Manche. "Some patients don't use any pills for rescue relief. Others go through the whole bottle. Because we're using the larger ablation zones of wavefront-guided and topography-guided lasers, we're exposing more corneal nerve endings, so it takes longer for the pain to diminish while these larger defects re-epithelialize. However, the contact lenses and nonsteroidal drops are better these days, so that helps a lot."

Based on research, Dr. McDonald has developed an effective postop pain control regimen for surface ablation. Below are the treatments she recommends:

• vitamin C 500 mg, twice a day by mouth, beginning the day surgery is scheduled, to help with corneal healing;[13]

• topical cyclosporine, b.i.d., begun immediately postop and continuing for three months, whether or not patients have dry eye;[14]

• rapidly-tapering oral steroids for healthy, nondiabetic patients, including eight 10-mg tablets taken under her supervision precisely 30 minutes before surgery, eight 10-mg tablets the first postop day, four the second postop day, two the third postop day,


Rachel Epstein, MD

Rachel Epstein, MD, uses the Alcon/WaveLight EX500 for LASIK and PRK and the iFS Advanced Femtosecond Laser (Johnson & Johnson Vision) to create her flaps.

one the fourth postop day and one-half of a tablet the fifth postop day. "I also put them on ranitidine (Zantac), p.o. 150 mg b.i.d for six days to protect against gastritis," she notes;

• loteprednol etabonate ophthalmic gel (Lotemax SM 0.38%) or prednisolone acetate (Pred Forte), four times a day for seven days, starting on the day of surgery;

• besifloxacin (Besivance, Bausch + Lomb) or ofloxacin (Ocuflox, Allergan), four times a day for seven days, starting on the day of surgery;

• ketorolac tromethamine ophthalmic solution (Acuvail, Allergan) up to four times a day for three days, as needed for pain;

• "comfort drops" from a specialty pharmacy that includes 0.1% tetracaine, one drop up to every hour for pain during the first three postop days;

• preservative-free tears, every two hours while awake;

• Refresh Celluvisc (Allergan), one drop at night until the patients' bandage contact lenses are removed at five to seven days, after they've worn them 24 hours a day for a week;

• over-the-counter Retain PM ointment (Ocusoft) when the contact lenses are removed, applied every night at bedtime until the one-month postop visit;

• over-the-counter, extra-strength acetaminophen tablets (Tylenol);

• Vicodin, 5 mg/300 mg, four to six tablets, for rescue relief;

• ice packs on the patient's eyes for 10 minutes after surgery, under Dr. McDonald's direction, then as much as possible at home during the first 24 hours postop.

Although Dr. McDonald thinks about cutting down her pain-control protocol because of EBK's pain-sparing benefits, she continues with the therapy. "When patients return to the office, their eyes are open, white and they're smiling," she says. "They've taken a shower. They're comfortable."

To ward off postop pain, Dr. Yeu prescribes ketorolac tromethamine (Toradol), 10 mg daily, for three days, and uses a compounded dilute topical lidocaine drop and oral tramadol, as needed, for rescue relief.

"For our PRK patients, if mitomycin-C is used, I rinse the surface thoroughly with two bottles of very chilled BSS and place an appropriately sized bandage contact lens made of appropriate material after treatment," says Dr. Epstein. "I also place a drop of homatropine, which we've found improves patient comfort. I generally give a very small amount of an oral painkiller, typically Vicodin, to use as needed, with the caveat that they first must try an over-the-counter NSAID. I also prescribe a topical NSAID, to be used during the first 48 hours postop. We also stress the importance of very frequent lubrication with preservative-free artificial tears, especially in the immediate postop period."

Preventing Ectasia

Surgeons also report progress in steering clear of thin corneas, a chal-

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For additional information or to schedule a demonstration, contact your Alcon sales representative.
For important safety information about this product, please refer to the adjacent page.

*Post hoc analysis of postoperative UCVA compared to preoperative BSCVA of 230 eyes contained in the FDA T-CAT pivotal trial at 12 months. The primary end point evaluated changes in BSCVA.
1. Results from FDA T-CAT-001 clinical study for Topography-Guided vision correction (with the 400 Hz ALLEGRETTO WAVE® Eye-Q Excimer Laser).

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WAVELIGHT® EXCIMER LASER SYSTEMS IMPORTANT PRODUCT INFORMATION

This information pertains to all WaveLight® Excimer Laser Systems, including the WaveLight® ALLEGRETTO WAVE®, the ALLEGRETTO WAVE® Eye-Q and the WaveLight® EX500.

Caution: Federal (U.S.) law restricts the WaveLight® Excimer Laser Systems to sale by or on the order of a physician. Only practitioners who are experienced in the medical mangement and surgical treatment of the cornea, who have been trained in laser refractive surgery (including laser calibration and operation) should use a WaveLight® Excimer Laser System.

Indications: FDA has approved the WaveLight® Excimer Laser systems for use in laser-assisted in situ keratomileusis (LASIK) treatments for: the reduction or elimination of myopia of up to - 12.00 D and up to 6.00 D of astigmatism at the spectacle plane; the reduction or elimination of hyperopia up to + 6.00 D with and without astigmatic refractive errors up to 5.00 D at the spectacle plane, with a maximum manifest refraction spherical equivalent of + 6.00 D; • the reduction or elimination of naturally occurring mixed astigmatism of up to 6.00 D at the spectacle plane; and the wavefront-guided reduction or elimination of myopia of up to -7.00 D and up to 3.00 D of astigmatism at the spectacle plane.

In addition, FDA has approved the WaveLight® ALLEGRETTO WAVE® Eye-Q Excimer Laser System, when used with the WaveLight® ALLEGRO Topolyzer® and topography-guided treatment planning software for topography-guided LASIK treatments for the reduction or elimination of up to -9.00 D of myopia, or for the reduction or elimination of myopia with astigmatism, with up to -8.00 D of myopia and up to 3.00 D of astigmatism.

The WaveLight® Excimer Laser Systems are only indicated for use in patients who are 18 years of age or older (21 years of age or older for mixed astigmatism) with documentation of a stable manifest refraction defined as ≤ 0.50 D of preoperative spherical equivalent shift over one year prior to surgery, exclusive of changes due to unmasking latent hyperopia.

Contraindications: The WaveLight® Excimer Laser Systems are contraindicated for use with patients who: are pregnant or nursing; have a diagnosed collagen vascular, autoimmune or immunodeficiency disease; have been diagnosed keratoconus or if there are any clinical pictures suggestive of keratoconus; are taking isotretinoin (Accutane*) and/or amiodarone hydrochloride (Cordarone*); have severe dry eye; have corneas too thin for LASIK; have recurrent corneal erosion; have advanced glaucoma; or have uncontrolled diabetes.

Warnings: The WaveLight® Excimer Laser Systems are not recommended for use with patients who have: systemic diseases likely to affect wound healing, such as connective tissue disease, insulin dependent diabetes, severe atopic disease or an immunocompromised status; a history of Herpes simplex or Herpes zoster keratitis; significant dry eye that is unresponsive to treatment; severe allergies; a history of glaucoma; an unreliable preoperative wavefront examination that precludes wavefront-guided treatment; or a poor quality preoperative topography map that precludes topography-guided LASIK treatment.

The wavefront-guided LASIK procedure requires accurate and reliable data from the wavefront examination. Every step of every wavefront measurement that may be used as the basis for a wavefront-guided LASIK procedure must be validated by the user. Inaccurate or unreliable data from the wavefront examination will lead to an inaccurate treatment.

Topography-guided LASIK requires preoperative topography maps of sufficient quality to use for planning a topography-guided LASIK treatment. Poor quality topography maps may affect the accuracy of the topography-guided LASIK treatment and may result in poor vision after topography-guided LASIK.

Precautions: The safety and effectiveness of the WaveLight® Excimer Laser Systems have not been established for patients with: progressive myopia, hyperopia, astigmatism and/or mixed astigmatism, ocular disease, previous corneal or intraocular surgery, or trauma in the ablation zone; corneal abnormalities including, but not limited to, scars, irregular astigmatism and corneal warpage; residual corneal thickness after ablation of less than 250 microns due to the increased risk for corneal ectasia; pupil size below 7.0 mm after mydriatics where applied for wavefront-guided ablation planning; history of glaucoma or ocular hypertension of > 23 mmHg; taking the medications sumatriptan succinate (Imitrex*); corneal, lens and/or vitreous opacities including, but not limited to cataract; iris problems including , but not limited to, coloboma and previous iris surgery compromising proper eye tracking; or taking medications likely to affect wound healing including (but not limited to) antimetabolites.

In addition, safety and effectiveness of the WaveLight® Excimer Laser Systems have not been established for: treatments with an optical zone < 6.0 mm or > 6.5 mm in diameter, or an ablation zone > 9.0 mm in diameter; or wavefront-guided treatment targets different from emmetropia (plano) in which the wavefront calculated defocus (spherical term) has been adjusted;

In the WaveLight® Excimer Laser System clinical studies, there were few subjects with cylinder amounts > 4 D and ≤ 6 D. Not all complications, adverse events, and levels of effectiveness may have been determined for this population.

Pupil sizes should be evaluated under mesopic illumination conditions. Effects of treatment on vision under poor illumination cannot be predicted prior to surgery.

Adverse Events and Complications

Myopia: In the myopia clinical study, 0.2% (2/876) of the eyes had a lost, misplaced, or misaligned flap reported at the 1 month examination.

The following complications were reported 6 months after LASIK: 0.9% (7/818) had ghosting or double images in the operative eye; 0.1% (1/818) of the eyes had a corneal epithelial defect.

Hyperopia: In the hyperopia clinical study, 0.4% (1/276) of the eyes had a retinal detachment or retinal vascular accident reported at the 3 month examination.

The following complications were reported 6 months after LASIK: 0.8% (2/262) of the eyes had a corneal epithelial defect and 0.8% (2/262) had any epithelium in the interface.

Mixed Astigmatism: In the mixed astigmatism clinical study, two adverse events were reported. The first event involved a patient who postoperatively was subject to blunt trauma to the treatment eye 6 days after surgery. The patient was found to have an intact globe with no rupture, inflammation or any dislodgement of the flap. UCVA was decreased due to this event. The second event involved the treatment of an incorrect axis of astigmatism. The axis was treated at 60 degrees instead of 160 degrees.

The following complications were reported 6 months after LASIK: 1.8% (2/111) of the eyes had ghosting or double images in the operative eye.

Wavefront-Guided Myopia: The wavefront-guided myopia clinical study included 374 eyes treated; 188 with wavefront-guided LASIK (Study Cohort) and 186 with Wavefront Optimized® LASIK (Control Cohort). No adverse events occurred during the post-operative period of the wavefront-guided LASIK procedures. In the Control Cohort, one subject undergoing traditional LASIK had the axis of astigmatism programmed as 115 degrees instead of the actual 155 degree axis. This led to cylinder in the left eye.

The following complications were reported 6 months after wavefront-guided LASIK in the Study Cohort: 1.2% (2/166) of the eyes had a corneal epithelial defect; 1.2% (2/166) had foreign body sensation; and 0.6% (1/166) had pain. No complications were reported in the Control Cohort.

Topography-Guided Myopia: There were six adverse events reported in the topography-guided myopia study. Four of the eyes experienced transient or temporary decreases in vision prior to the final 12 month follow-up visit, all of which were resolved by the final follow-up visit. One subject suffered from decreased vision in the treated eye, following blunt force trauma 4 days after surgery. One subject experienced retinal detachment, which was concluded to be unrelated to the surgical procedure.

Clinical Data

Myopia: The myopia clinical study included 901 eyes treated, of which 813 of 866 eligible eyes were followed for 12 months. Accountability at 3 months was 93.8%, at 6 months was 91.9%, and at 12 months was 93.9%. Of the 782 eyes that were eligible for the uncorrected visual acuity (UCVA) analysis of effectiveness at the 6-month stability time point, 98.3% were corrected to 20/40 or better, and 87.7% were corrected to 20/20 or better. Subjects who responded to a patient satisfaction questionnaire before and after LASIK reported the following visual symptoms at a "moderate" or "severe" level at least 1% higher at 3 months post-treatment than at baseline: visual fluctuations (28.6% vs. 12.8% at baseline).

Long term risks of LASIK for myopia with and without astigmatism have not been studied beyond 12 months.

Hyperopia: The hyperopia clinical study included 290 eyes treated, of which 100 of 290 eligible eyes were followed for 12 months. Accountability at 3 months was 95.2%, at 6 months was 93.9%, and at 12 months was 69.9%. Of the 212 eyes that were eligible for the UCVA analysis of effectiveness at the 6-month stability time point, 95.3% were corrected to 20/40 or better, and 69.4% were corrected to 20/20 or better. Subjects who responded to a patient satisfaction questionnaire before and after LASIK reported the following visual symptoms as "much worse" at 6 months post-treatment: halos (6.4%); visual fluctuations (6.1%); light sensitivity (4.9%); night driving glare (4.2%); and glare from bright lights (3.0%).

Long term risks of LASIK for hyperopia with and without astigmatism have not been studied beyond 12 months.

Mixed Astigmatism: The mixed astigmatism clinical study included 162 eyes treated, of which 111 were eligible to be followed for 6 months. Accountability at 1 month was 99.4%, at 3 months was 96.0%, and at 6 months was 100.0%. Of the 142 eyes that were eligible for the UCVA analysis of effectiveness at the 6-month stability time point, 97.3% achieved acuity of 20/40 or better, and 69.4% achieved acuity of 20/20 or better. Subjects who responded to a patient satisfaction questionnaire before and after LASIK reported the following visual symptoms at a "moderate" or "severe" level at least 1% higher at 3 months post-treatment than at baseline: sensitivity to light (52.9% vs. 43.3% at baseline); visual fluctuations (43.0% vs. 32.1% at baseline); and halos (42.3% vs. 37.0% at baseline).

Long term risks of LASIK for mixed astigmatism have not been studied beyond 6 months.

Wavefront-Guided Myopia: The wavefront-guided myopia clinical study included 374 eyes treated; 188 with wavefront-guided LASIK (Study Cohort) and 186 with Wavefront Optimized® LASIK (Control Cohort). 166 of the Study Cohort and 166 of the Control Cohort were eligible to be followed at 6 months. In the Study Cohort, accountability at 1 month was 96.8%, at 3 months was 96.8%, and at 6 months was 93.3%. In the Control Cohort, accountability at 1 month was 94.6%, at 3 months was 94.6%, and at 6 months was 92.2%.

Of the 166 eyes in the Study Cohort that were eligible for the UCVA analysis of effectiveness at the 6-month stability time point, 99.4% were corrected to 20/40 or better, and 93.4% were corrected to 20/20 or better. Of the 166 eyes in the Control Cohort eligible for the UCVA analysis of effectiveness at the 6-month stability time point, 99.4% were corrected to 20/40 or better, and 92.8% were corrected to 20/20.

In the Study Cohort, subjects who responded to a patient satisfaction questionnaire before and after LASIK reported the following visual symptoms at a "moderate" or "severe" level at least 1% higher at 3 months post-treatment than at baseline: light sensitivity (47.8% vs. 37.2% at baseline) and visual fluctuations (20.0% vs. 13.8% at baseline). In the Control Cohort, the following visual symptoms were reported at a "moderate" or "severe" level at least 1% higher at 3 months post-treatment than at baseline: halos (45.4% vs. 36.6% at baseline) and visual fluctuations (21.9% vs. 18.3% at baseline).

Long term risks of wavefront-guided LASIK for myopia with and without astigmatism have not been studied beyond 6 months.

Topography-Guided Myopia: The topography-guided myopia clinical study included 249 eyes treated, of which 230 eyes were followed for 12 months. Accountability at 3 months was 99.2%, at 6 months was 98.0%, and at 12 months was 92.4%. Of the 247 eyes that were eligible for the UCVA analysis at the 3-month stability time point, 99.2% were corrected to 20/40 or better, and 92.7% were corrected to 20/20 or better. Subjects who responded to a patient satisfaction questionnaire before and after LASIK reported the following visual symptoms as "marked" or "severe" at an incidence greater than 5% at 1 month after surgery: dryness (7% vs. 4% at baseline) and light sensitivity (7% vs. 5% at baseline). Visual symptoms continued to improve with time, and none of the visual symptoms were rated as being "marked" or "severe" with an incidence of at least 5% at 3 months or later after surgery.

Long term risks of topography-guided LASIK for myopia with and without astigmatism have not been studied beyond 12 months.

Information for Patients: Prior to undergoing LASIK surgery with a WaveLight® Excimer Laser System, prospective patients must receive a copy of the relevant Patient Information Booklet, and must be informed of the alternatives for correcting their vision, including (but not limited to) eyeglasses, contact lenses, photorefractive keratectomy, and other refractive surgeries.

Attention: Please refer to a current WaveLight® Excimer Laser System Procedure Manual for a complete listing of the indications, complications, warnings, precautions, and side effects.

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lenge in all refractive surgery procedures. Choosing the right patients for treatment is an obvious key to success.

"One of the areas where we have improved during the past decade or so is in our ability to properly screen and exclude patients who may be at higher risk for ectasia," says Dr. Manche. "The key is prevention. Sometimes, though, we don't find out about this problem until after surgery. In the rare cases where you do see ectasia postop, we now of course have the ability to offer corneal cross-linking."

Dr. McDonald says identifying ectactic conditions is critical when evaluating questionable preop patients. "Surgeons choose surface ablation when the cornea is too thin or the patient appears to possibly have keratoconus," she observes. "They're afraid to do LASIK in these cases, but they'll go ahead and do PRK. Well that, in my opinion, is a bad idea. In other words, if somebody looks like they have keratoconus, or a corneal thickness that's below 512 µm, I would not recommend laser vision correction.[15] I've had every possible complication you can have in refractive surgery, but I've never had ectasia because I'm conservative and I've always followed those few simple rules."

Because of the extensive preop evaluation performed in Dr. Epstein's practice, she says she has only seen ectasia in a handful of cases. "However, we do see a fair number of outside referrals for post-LASIK ectasia, generally in patients who underwent LASIK five-to-10-plus years ago," she says. "We typically recommend corneal collagen cross-linking and specialty contact lens fitting for these patients."

Dr. Epstein notes that her practice is investigating the potential for combined treatment of corneal collagen cross-linking and PRK for certain subsets of patients with keratoconus. "But generally, we avoid refractive procedures in patients with unstable refractions, abnormalities on Pentacam (posterior elevation, displaced apex), history of ocular herpetic disease, uncontrolled ocular surface disease and corneal endothelial dystrophy, as well as patients who are planning to become or are currently pregnant and breastfeeding."

Rachel Epstein, MD

Rachel Epstein, MD, uses Phorcides Analytic Engine, a planning software developed by Mark Lobanoff, MD, to identify and treat astigmatism by optimizing Alcon's Contoura Vision Topography. Phorcides uses imaging and mathematical models to analyze and plan topographic treatments.

Fewer Unwanted Outcomes

"With our modern technology, we have fewer induced higher-order aberrations," says Dr. Manche. "If you use wavefront- or topography-guided systems, you can improve those symptoms. Also, because of larger treatment zones, patients experience fewer night vision issues, such as glare and halos."

Dr. Manche notes that advanced technology allows you to effectively treat induced or residual astigmatism from a previous refractive procedure. "We were able to do it in the old days, but now we have lasers that are much more accurate. We've come a really long way because of iris registration, autocentration and tracking."

Dr. Epstein says she's found the Phorcides software to be a useful tool for both preventing and treating higher-order aberrations and astigmatism. "I employ that technology in both our primary and secondary treatments, where applicable," she notes.

Better strategies are also now available in the event of postop haze. When a postop patient develops haze, Dr. Epstein starts with a topical steroid—Durezol, if possible—to determine how much improvement she can achieve with medical management.

"I'm very careful to monitor IOP in these patients," she says. "If medical management doesn't provide us with a satisfactory degree of improvement, I'll recommend superficial keratectomy, followed by application of 0.02% mitomycin-C to the stromal bed for two minutes. This may have to be repeated. I typically wait to treat residual refractive error until we've adequately addressed the haze."

Dr. McDonald takes postop precautions to avoid haze and regression. "I tell surface ablation patients to wear UV-blocking sunglasses whenever they're outside, for at least the first year, though we really don't know how long the 'plastic period' lasts, during which UV light can cause haze and regression," she notes. "We do know that if you expose these eyes to significant amounts of direct sunlight during the early postop period, you can cause haze and regression."

If patients return to Dr. McDonald with postop haze, the prognosis is good. "Most of the time, if you just give steroid drops q.i.d. for a week or two and then wait, it'll go away," she says. "Even with a referral practice, however, it's been a long time since I've had to physically remove the hazy tissue with a Tooke knife or EBK. It's been years since I've seen a patient who needed the prior two-step procedure—haze removal followed three months later by a laser retreatment. It just doesn't happen anymore."

(Continued on page 61)

Dry Eye: What's in The Pipeline?

Michelle Stephenson, Contributing Editor

Several devices and drugs are expected to come to the marketplace in the next few years.

More than 16 million American adults have been diagnosed with dry-eye disease, and prevalence increases with age. To help these patients, researchers are looking at new ways to diagnose and treat the condition. Here's a look at some of the drugs and devices in the pipeline.

Reproxalap 0.25% (Aldeyra Pharmaceuticals)

One promising new product is a small-molecule reactive aldehyde species (RASP) inhibitor that covalently binds free aldehydes and diminishes excessive RASP levels. "Any blockage of RASP could potentially benefit dry-eye patients and allergic conjunctivitis patients," says Robert Latkany, MD, who is in practice in New York City. "This product is in Phase III trials for both dry eye and allergic conjunctivitis, and the Phase III trial for allergic conjunctivitis showed a reduction of ocular itching score. Additionally, the dry-eye study showed a reduction in symptoms as early as one week."

RGN-259 0.05% and 0.1% (RegeneRx)

This product is a Tβ4-based sterile and preservative-free eye drop that's designed to be a novel treatment for dry eye and neurotrophic keratitis. In a Phase II/III study for dry-eye syndrome that included 317 patients, RGN-259 0.05% and 0.1% demonstrated statistically significant improvements in both signs and symptoms of dry eye compared to placebo in a dose-dependent manner during a 28-day dosing period.[1]

Visomitin (Mitotech)

Visomitin is an eye-drop formulation of SkQ1 that's been developed to target ophthalmic disorders like dry eye, uveitis and macular degeneration. This drop is currently in Phase III trials in the United States.

VISTA-1 was a multicenter, randomized, double-blind, placebo-controlled clinical study involving three treatment arms: two concentrations of SkQ1 and vehicle, administered twice daily.[2] The study included approximately 450 patients, who received treatment over a two-month period. While nominal co-primary endpoints of the study (fluorescein staining in central corneal zone and grittiness) weren't met, multiple predetermined secondary endpoints demonstrated broad action of SkQ1 in the intent-to-treat population. Compared to the vehicle, which was an artificial tear, SkQ1 demonstrated a statistically significant reduction in ocular

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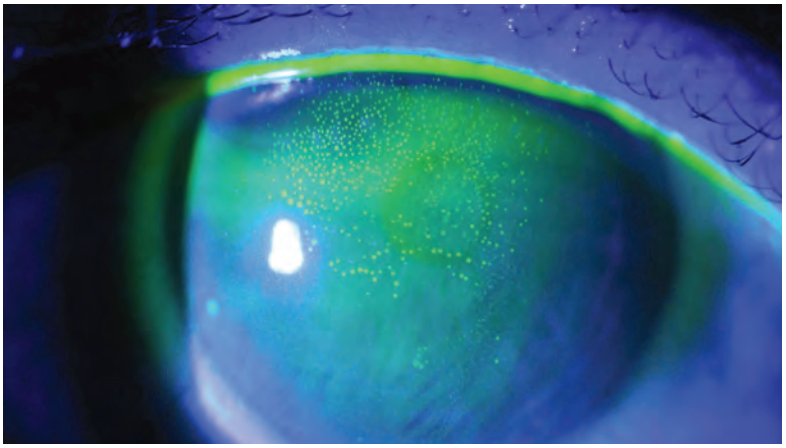
discomfort ($p<0.05$) as early as after four weeks of treatment. Additionally, there was a statistically significant improvement in conjunctival fluorescein staining as compared to the vehicle. The drop also had an excellent safety profile, with tolerability being statistically similar to that of an artificial tear.



New drugs such as Mitotech's SkQ1 and Oyster Point's OC-01 aim to treat symptoms of dry eye as well as signs like staining, shown here.

"The trials were pretty impressive at improving both staining and dry-eye symptoms. I love the approach of going at this from different angles," Dr. Latkany says.

VISTA-2 is a Phase III study that is similar in design to VISTA-1, but includes two treatment arms (SkQ1 solution and vehicle) with twice as many (300) patients per arm. Enrollment for this study began in December 2019.

OC-01 (Oyster Point Pharmaceuticals)

OC-01 is a nasal spray developed to treat the signs and symptoms of dry eye.

Francis Mah, MD, who is in practice in San Diego, is intrigued by the drug's mechanism of action. "I think it's really unique in that you're potentially stimulating all three sources or layers of the tear film," he says. "Data show that when mechanically stimulated, in addition to increasing the aqueous layer, the nasal stimulation is increasing the meibum being released from the meibomian glands. Additionally, mucin is being released from the goblet cells in the conjunctiva. I think that's very unique. If you can stimulate all three layers on demand, I think it's a very appealing drug for patients and doctors."

Dr. Latkany says the route of administration may help the drug achieve its effect in unique ways. "This is direct administration of varenicline, which is a nicotinic acetylcholine receptor agonist that might increase tear production," he says. "It's clear that you can do things to the nose to reflexively make tears, either through irritation or administering drugs into the nasal cavity. I'm definitely interested in this angle, just because I know reflexively it can make tears and also because some patients have a hard time putting eye drops in their eyes. Looking for alternative ways of administering therapy other than the eyes is always welcome."

In July 2019, Oyster Point Pharmaceuticals announced the enrollment of the first subject in the Phase III ONSET-2 trial, which is a multicenter, randomized, double-masked, placebo-controlled clinical trial to evaluate the safety and efficacy of OC-01 nasal spray for treating the signs and symptoms of dry eye.[3] The study will enroll approximately 750 subjects at approximately 20 centers in the United States and will evaluate two doses (0.6 mg/mL and 1.2 mg/mL) of the spray compared to a placebo nasal spray.

The company says its Phase IIb ONSET-1 study demonstrated statistically significant improvements in both the pre-specified primary sign endpoint and multiple pre-specified secondary symptom endpoints as compared to vehicle. OC-01 was well-tolerated with no significant ocular adverse events or serious drug-related adverse events.

New Cyclosporine Products

There are several new cyclosporine products in various stages of development. According to John Sheppard, MD, who is in practice in Norfolk, Virginia, Novaliq is investigating two products based on the company's semifluorinated alkane water-free vehicle. "They've come up with the first truly new vehicle [EyeSol] for topical eye medications in over a generation," Dr. Sheppard says. "This semifluorinated alkane permits really small drops. They are 20 µL instead of 50 µL, so there's no slop or spillover onto your cheek. These drops don't blur your vision as much either. Furthermore, the vehicle provides a sustained-release platform, homogeneous delivery with favorable first-order pharmacokinetics and distribution of any active pharmaceutical ingredient, including glaucoma medications, for example, as well as anti-inflammatories or immunomodulators. That's really cool, but what's cooler is that you can alter the molecular weight of the semifluorinated alkanes. They've developed a heavier molecular weight molecule that's advantageous to meibomian gland function. This product is in Phase III trials, so it should be the first approved in this family of semifluorinated alkanes."

Additionally, Novaliq has developed a product called CyclASol 0.1%, which is a low molecular weight semifluorinated alkane in a preparation containing cyclosporine. "It produces less stinging and irritation and better distri-

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1 McLaurin E, Cavet ME, Gomes PJ, Ciolino JB. Brimonidine ophthalmic solution 0.025% for reduction of ocular redness: A randomized clinical trial. Optom Vis Sci. 2018;95(3):264-271

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bution of the cyclosporine," Dr. Sheppard notes. "And, the concentration is 0.1%, so it's a higher concentration than either Restasis or Cequa. These products will complete their trials in the next year or so, and they should be on the market the year after that."

In late 2018, Novaliq announced positive topline results from ESSENCE, its first pivotal clinical trial of CyclASol 0.1% for the treatment of dry-eye disease.[4]

ESSENCE is a pivotal, randomized, double-masked, vehicle-controlled, multicenter Phase IIb clinical trial designed to evaluate the efficacy, safety, and tolerability of topical CyclASol 0.1% for the treatment of patients with aqueous-deficient dry-eye disease. The researchers evaluated the primary efficacy endpoint at four weeks, with continued dosing for efficacy and safety evaluations over a period of three months.

The trial met its primary efficacy endpoint (improvement of total corneal fluorescein staining over vehicle) at Day 29, with high statistical significance (p=0.0002). The effect started as early as two weeks after the initiation of treatment and was maintained for the duration of the study. The central area of the cornea benefited most. The clinical significance of these outcomes is further shown by a high responder rate (>50 percent) on both corneal staining (at four weeks) and conjunctival staining (at three months).

Novaliq's ESSENCE study also confirmed the excellent safety and tolerability profile of CyclASol. Only 2.5 percent of the CyclASol-treated group ofpatients experienced an instillation site reaction adverse event, the company says.

NOV03 (Bausch Health)

In late December 2019, Bausch Health acquired an exclusive license for the commercialization and development of the investigational treatment NOV03 (perfluorohexyloctane), a first-in-class investigational drug with a novel mechanism of action to treat dry eye associated with meibomian gland dysfunction.[5]

NOV03 is a proprietary, water-free, preservative-free solution based on Novaliq's EyeSol technology. In a Phase II study, NOV03 met its primary sign endpoint of improving total corneal fluorescein staining over control at eight weeks, with high statistical significance (p<0.001). It also demonstrated significant and clinically meaningful improvement in a variety of symptoms over the duration of the trial. A Phase III study is already

under way, and Bausch Health anticipates starting an additional Phase III study in 2020.

Lacripep (TearSolutions)

Lacripep is a first-in-class topical synthetic peptide treatment for dry eye. It's a synthetic tear protein fragment of Lacritin, which is a nanomolar concentration constituent of normal human tears, but is lacking in the tears of dry-eye patients. The enrollment for a Phase II trial of Lacripep is complete, and results are expected in the spring of 2020.[6] The study, which was conducted at 35 private and academic sites in 17 states, lasted eight weeks and included five visits to an ophthalmologist. Patients were provided with ophthalmic drops of Lacripep or placebo.

"Preclinical studies[7] in our laboratory found that both full molecular weight Lacritin and the Lacripep fragment restored tearing and ocular surface integrity," Dr. Sheppard notes. "It's an interesting approach. It's applying a protein that might be deficient and might be needed on the ocular surface."

Discovery (TearLab)

TearLab is finishing studies for a second-generation machine called Discovery. "Their first machine measures tear osmolarity—Discovery does that and also measures MMP-9," Dr. Mah explains. "This machine provides increased sensitivity for diagnosing and managing ocular surface disease. Hopes are that it will be approved soon."

Dr. Sheppard says that the beauty of looking at both osmolarity and MMP-9 is that the osmolarity acts as a normalizing comparator to further refine the accuracy of the MMP-9 test. "So, now you have a screening test for dry eye, and then you can look for the inflammatory component, all in the same tear specimen," he says. "We've used it successfully in our office, and we're looking forward to approval and distribution in 2020."

ECF843 by Novartis

Novartis is studying a biologic lubricant found in synovial fluid. ECF843 is a recombinant human lubricin (boundary lubricant) and an investigational compound. Efficacy and safety of ECF843 haven't been established.[8]

"The currently available clinical data are impressive. It really seems to be an impressive lubricant and could be a huge game-changer in the way we manage patient complaints of ocular surface disease," Dr. Mah says. "Having said that, it'll be interesting to see how the FDA handles this asset. I don't really know how this is going to be considered—whether the FDA will consider this a drug or a biologic. Novartis hopes to have approval within a year or two."

LacriPen (LacriScience)

According to Dr. Sheppard, LacriScience has developed a unique technology, the LacriPen, a handheld, portable diagnostic tool that you can carry in your shirt pocket. When touched to a patient's eye, it allows a specially processed surface plasmon resonance apparatus to come into direct contact with the tear film. The gold tip activator calculates minute changes in the refractive index on an extremely thin gold film. The company says that the device can analyze virtually any component of the tear film based upon its specific resonance profile. The resonance pattern is unique to any number of likely tens of thousands of molecules, LacriScience says. "So, this particular technology can be adapted to osmolarity, to issues with inflammation, to allergy, to infection, and is applicable not only to ophthalmology, but to other bodily fluids and disease states, as well," Dr. Sheppard explains.

The device currently detects tear osmolarity in the range of 260 to 400 mOsml with a resolution of about 2 mOsml.[9] The MMP-9 sensor detects a dynamic range from 1 to 100 ng/mL.

As the preceding list of cutting-edge approaches shows, our understanding of dry eye and its mechanisms is evolving, and so are our ways of treating the condition. REVIEW

Dr. Sheppard has a financial interest in LacriScience and serves as a consultant to Allergan, Sun Pharma, Novaliq, Aldeyra, Tear Science, Oyster Point, Novartis, Bausch & Lomb and TearLab. Dr. Mah has a financial interest in Allergan, Bausch & Lomb, Novartis, Senju, Sun and TearLab. Dr. Latkany has no financial interest in any of the products or companies mentioned in this article.

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Innovations in Corneal Transplants

Christine Leonard, Associate Editor

Surgeons discuss advances in corneal transplant techniques and the future direction of treatment.

Remember when a full-thickness transplant was the only option for corneal disease? Not so today. Over the past decade, we've seen a shift toward disease-focused surgeries, and there are now several options to choose from when matching a procedure to a patient. The challenge is to pick the right one.

"We customize treatments now," says Marjan Farid, MD, clinical professor of ophthalmology and director of both the cornea, cataract and refractive surgery; and the ocular surface disease programs at the UC Irvine School of Medicine. "If the disease is endothelial, then we move to endothelial keratoplasty. If it's in the mid-layers of the cornea or stroma or anterior, we do more anterior lamellar keratoplasty. This shift toward disease-focused treatment has been a big advance in and of itself."

Procedures such as DALK, DSAEK and DMEK have significantly advanced corneal surgery. In fact, Massimo Busin, MD, clinical director of the department of ophthalmology at Ospedali Privati Forlì, Italy, notes that "Lamellar procedures have largely replaced penetrating keratoplasty. In my practice, of the 564 transplantations performed last year, 55 percent were endothelial, 40 percent were anterior lamellar and less than 5 percent were penetrating keratoplasty." In this article, we'll cover the latest advances in corneal transplants and attempt to predict what the future has in store for these important, sight-saving procedures.

Disease-focused Approaches

Selecting a procedure goes beyond determining which corneal layers are affected. While standard-of-care routes are standard for a reason, you don't have to follow these guidelines to the letter, say surgeons such as Kathryn Colby, MD, PhD, chair of the department of ophthalmology and visual science at the University of Chicago Medicine and Biological Sciences. "You want to ask yourself where the pathology is and what the pathology is," Dr. Colby says. "Your standard of care for Fuchs' is DMEK, and sometimes DSO, but this is a general recommendation. Certain Fuchs' patients may be better served with a DSAEK or even a full-thickness transplant. It comes down to surgical experience and judgment."

Dr. Farid explains how she decides, in general, which corneal procedure is best-suited for a patient. "If a patient comes in with a corneal disease, you first isolate where the disease is," she explains. "Is this an endothelial disease

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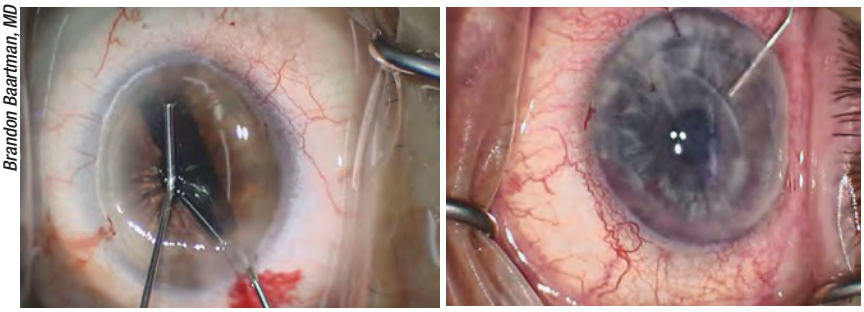
Brandon Baartman, MD



Working outside the eye, a bimanual DMEK technique is used to simultaneously hold the tissue in place while allowing fluid egress from the main wound (left). Working within the eye (right), a DSAEK tissue is manipulated into proper position, prior to gas bubble insertion).

like Fuchs' dystrophy or is this like keratoconus, where it involves the entire stroma and a misshapen cornea? If it's endothelial disease, I go down the road of endothelial keratoplasty. If it's a simple Fuchs' dystrophy and they have good visibility into the eye then the gold standard has become DMEK. However, if there's a lot of complexity in the eye or if the patient's visibility through their cornea and edema is significant, I may choose a DSAEK procedure over DMEK because it's a little more predictable and easier to do through a hazy cornea. If it's a keratoconus eye then I lean more toward a DALK and I always use a femtosecond laser to do cuts to get the best refractive outcomes."

The range of DMEK's applications has also broadened. "When DMEK was first being popularized, it was suggested that it was best for otherwise healthy eyes with FECD," says Brandon Baartman, MD, in practice at the Vance Thompson Vision in Omaha, Nebraska. Many surgeons, seeing the benefits to the patient, have since pushed these initial, arbitrary boundaries to bring DMEK to more complex scenarios, such as in patients with significant PBK, prior failed EK or in the setting of prior glaucoma filtering or shunting procedures. Many of the cornea talks at national meetings are now shifting from a focus on how to perform the routine DMEK to focusing on some of the ways it can be used successfully in unique scenarios. Certain techniques such as a DMEK 'pull-through' using insertion devices have helped navigate challenging cases."

The Pull-Through Technique

To perform the pull-through technique, a surgeon places a graft by pulling it through a clear corneal incision on a substrate, such a soft contact lens, corneal lenticule or an insertion device. The contact lens-assisted pull-through technique is one new approach for inserting tri-folded DMEK grafts.[1] According to a 2016 prospective, non-comparative, interventional case series, including 42 eyes with Fuchs' with or without cataract, this pull-through technique reduced surgical trauma to donor cells and facilitated spontaneous unfolding, which minimized surgical time.[1] Dr. Busin, the lead author on the study, explains his current technique for DMEK graft preparation and insertion. He uses pre-marked, pre-stripped donor tissue stained with Trypan blue and punched with a Barron Donor Cornea Punch. "Using a dedicated anatomic microincision forceps (Moria SA, Antony, France), the graft is tri-folded endothelium-in, transferred via a sterile soft contact lens into the groove of an IOL cartridge that is filled with BSS and sealed with a silicone plug," he says. "Then, using the same microincision forceps, the tri-folded graft is delivered bimanually into the anterior chamber under continuous irrigation from a dedicated AC maintainer with a lateral 0.5-mm port. The tri-folded graft spontaneously unfolds endothelium-out and air is injected for graft tamponade."

Dr. Busin says he's currently developing a dedicated system for the pull-through delivery of tri-folded DMEK grafts that includes "a fixed-depth corneal donor punch, a sliding glide (which replaces the sterile soft contact lens) and a glass cartridge (which replaces the IOL cartridge)." He hopes that "This new system will streamline our process from graft preparation to insertion and perhaps allow more beginning surgeons to be more comfortable with adopting DMEK."

Thinner Tissue

Another innovation in corneal transplant procedures, particularly endothelial keratoplasty, is the shift toward thinner and thinner tissue grafts. "Ultra-thin and nano-thin grafts result in better visual acuity and have a lower risk of rejection, leading to better graft survival," says Dr. Baartman. "DMEK is one of the latest iterations of tissue transplantation, representing a 1:1 tissue replacement," he says.

"Ten or 11 years ago when we started doing endothelial transplants, the tissue we were implanting was quite thick," adds Dr. Farid. "We were doing deep lamellar endothelial keratoplasty, or DLEK, which involves a very thick piece of posterior stroma and endothelium. This treated the disease, but the visual outcomes weren't great because we were adding significant tissue to the eye. Now we've moved toward Descemet's stripping endothelial keratoplasty and then ultra-thin and even nano-thin DSEK, which use thinner and thinner tissue. We're seeing that the thinner the tissue, the better and faster the visual recovery is. This also means intraoperative manipulation is more challenging," she adds. "However, with newer insertion instruments

such as the Endoserter (CorneaGen), it's getting easier and more predictable to do thinner DSEK."

The Role of Eye Banks

Dr. Colby and her research team members were among the early adopters of preloaded DSAEK tissue from eye banks. "The eye banks have made tremendous advances for us," says Dr. Colby. When the Lions Eye Institute for Transplant and Research in Tampa began preloading DSAEK tissue to ship as a test run, Dr. Colby ordered some and conducted a trial that found donor graft tissue preloaded by an eye bank could be successfully used for endothelial keratoplasty.[2] She and her research partner noted that the eye bank's pre-processing and preloading of tissue reduced intraoperative tissue manipulation.

"Back in 2006 when eye banks began precutting tissue, we went from doing about 5,000 EKs a year to about 15,000," says Dr. Colby. "I think eye banks may be a tipping point for endothelial keratoplasty in the United States."

Dr. Colby explains that there was more risk involved when surgeons had to take full responsibility for cutting tissue. "If you messed up, you couldn't transplant it, and your hospital had to assume the cost of the tissue—which is not inexpensive," she says. "Eye banks take that risk away from surgeons. Most surgeons might do four or six DMEKs in a month as opposed to someone whose job it is to prepare tissue every day."

"In the setting of endothelial transplantation, any amount of tissue preparation which the eye bank can perform for the surgeon speeds us up," Dr. Baartman notes. "We saw this with DSEK automation and we're seeing the same thing in DMEK, with pre-loaded tissue. When I trained in DMEK, the tissue staining, punching, preparation and loading all happened in an OR prior to the patient's arriving. With preloaded DMEK, the tissue and patient arrive in the OR at the same time, and minimal surgeon time is required for in-OR preparation. I believe the shifting of this work to those who provide tissue to surgeons lends itself to optimization of techniques and processes."

Dr. Baartman says two critical metrics for corneal transplant success have improved with the use of thinner donor tissue—postoperative BCVA and rejection rate. "With DMEK, it's not uncommon for us to see BCVA of 20/20 in patients as early as one to two weeks after transplant. In regard to rejection, I typically cite a 1-to 2-percent chance of tissue rejection for DMEK versus DSAEK, the latter of which I cite to be around 5 percent. It's important to remember that this can also be impacted by the indication for transplantation," he adds. "Fuchs' patients typically fare better than those patients with BK, regardless of technique used."

Dr. Busin says using pre-stripped, pre-marked tissue for DMEK allows him to "evaluate the graft and ensure proper orientation of the tri-fold during implantation. Tissue is S-stamped or F-stamped on the stromal side to help the surgeon orient the tissue correctly. Incorrectly-positioned grafts can lead to graft failure. For DSAEK and DALK, I prepare the grafts with the microkeratome based on pachymetry."

New EK, New Challenges

Experts agree that DMEK is the gold standard for endothelial keratoplasty. "Recent studies have suggested that DMEK is better than DSAEK in terms of final visual outcomes,[3,4] but there's still room for DSAEK because not every case that needs an endothelial keratoplasty would be appropriate for DMEK," says Dr. Colby.

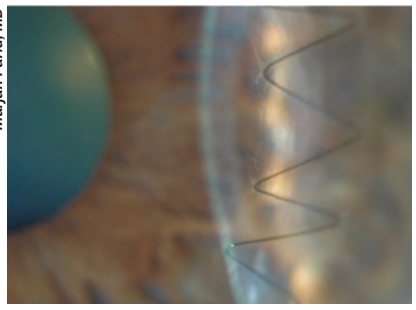
Dr. Baartman says one of DMEK's strengths is its minimization of tissue usage. "We've known for many years that the less corneal tissue you transplant, the less risk of rejection (e.g., EK versus PKP)," Dr. Baartman says. "Data is suggesting the same thing when looking at DMEK versus DSAEK. Overall graft survival is better with DMEK as compared to DSAEK, as are visual acuity outcomes. Even within the subcategory of DSAEK, ultra-thin and nano-thin techniques are being used to transplant the least amount of stromal tissue to capitalize on this knowledge."

With thinner tissue and no stroma to lend form, however, wispy DMEK grafts can be a challenge to manipulate. "Tissue curls endothelial-side out without the stroma to give it form," explains Dr. Colby. "That means the manipulation has to be done taking into account that any time you touch the tissue, you're touching endothelium. In contrast, DSAEK unfolds much more easily because it's got substance—maybe 40 to 120 µm of stroma. It's easiest to get DMEK tissue to unroll in a shallow chamber. In DSAEK, chamber depth isn't as much of an issue, and in fact, you may want a slightly deeper chamber because the tissue takes up more space."

"Another challenge with thinner grafts is the higher rebubbling rate [to facilitate attachment and avoid postop detachment]," Dr. Baartman says. Factors influencing rebubble rates in DMEK still need more study, but one group found that higher endothelial densities and well-centered Descemet's grafts may lead to fewer complications, and that a surgeon's decision to remove or leave a gas bubble doesn't affect whether or not a patient will need a rebubble.[5]

Femtosecond Lasers

"In the realm of deep anterior lamellar keratoplasty and full-thickness transplants, a big area of advancement is the use of the femtosecond laser for creating customized trephination



Marjan Farid, MD

Postoperative appearance after zig-zag femtosecond laser keratoplasty.

wounds for full-thickness keratoplasty and DALK," says Dr. Farid. "We've seen that with these customized femtosecond laser-enabled wounds, eyes have faster wound healing because with more surface area, they have more regular sealing with less irregular astigmatism. Sutures also come out faster and visual recovery takes less time.

"The original laser used was the Intralase (now iFS by Johnson & Johnson Vision)," she continues. "However, newer, faster lasers such as the VisuMax (Carl Zeiss) are also showing promise in creating smooth and predictable cuts." Other femtosecond lasers for keratoplasty include the Victus (Bausch + Lomb), Femto LDV Z8 (Ziemer), WaveLight FS200 (Alcon) and FEMTEC (Bausch + Lomb and 20/10 Perfect Vision).

Dr. Farid describes her trephination wound patterns as zig-zags or mushroom-shapes. These patterns increase the surface area of the graft and facilitate better wound alignment.[6] Her current research in femtosecond lasers aims at improving surgeons' ability to make deep corneal cuts for a more predictable DALK.[7]

"Manual trephination of the cornea is usually a straight up-and-down wound, like a butt joint in carpentry where it's just two straight incisions coming together," she explains. "But with a butt joint, you can have vertical and torsional misalignment of the tissue. That's how current conventional full-thickness transplants are done. The femtosecond laser creates more of a tongue and groove joint-type incision. This zig-zag incision creates a nice anterior alignment of the host and donor tissue. Better fit and less irregularity of the tissue mean faster healing."[8]

Though PK has been supplanted as the go-to procedure, there's still a place for it, argues Dr. Farid. "In the university setting, we see a lot of infections of the cornea that are full-thickness," she continues. "Full-thickness corneal transplants aren't going away—there are still a lot of scars that go through all the layers of the cornea and require full-thickness transplants. We're able to use femtosecond laser technology for full-thickness transplants in noninfected cases as well to optimize visual outcomes."

Descemet's Stripping Only

A newer technique that doesn't involve transplant of donor tissue has been on the rise. "Descemetorhexis Without Endothelial Keratoplasty, or Descemet's Stripping Only, involves the removal of central, visually-significant guttae without inserting new tissue," says Dr. Baartman. "I consider these techniques more like 'endothelial rejuvenation.' "

DSO requires some healthy peripheral endothelial cells to migrate across the posterior cornea to the center, so it's suitable only for mild to moderate cases of Fuchs' where the diseased endothelial cells are right in the central 5 mm of the cornea. "Oftentimes, a rho kinase inhibitor, or ROCK inhibitor, is used to help the peripheral cells of the endothelium migrate into the center to clear the central corneal edema," says Dr. Farid.

Beginning in early 2020, a large, multicenter clinical trial is taking place to study DSO for Fuchs'. Dr. Colby is the principal investigator, and has been a major leader in DSO research. "In the days of full-thickness transplantation, we used to counsel patients that about maybe one out of three or one out of four would have a rejection episode at some point during the life of the transplant," Dr. Colby explains. "With DSAEK, it's much less—less than 10 percent—and with DMEK, if you stay on topical steroids, it's less than 1 percent. With DSO, however, there's no risk of rejection.

"There's no transplant, unlike with traditional EK," Dr. Colby continues. "You remove the bad cells, like the first step of endothelial keratoplasty, but then you're relying on the patient's own endothelium to repopulate the central cornea. You first mark the central guttae and make an incision in the cornea. Then you go in and remove the Descemet's membrane with the guttae on it using a variety of techniques. Most recently, there's a special forceps designed for this."

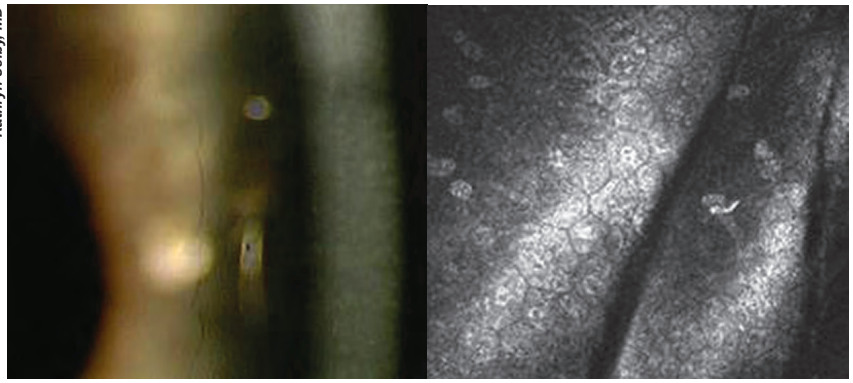
Dr. Baartman uses blunt-tip DSO Gorovoy forceps from Moria Surgical. He describes them as similar to capsulorhexis forceps, except the tips are pointed upwards like an inverted Utrata. "This allows a rhexis-like removal of the membrane, and it's actually easier and faster to remove," he says. "The forceps were designed for more precise removal of the Descemet's membrane in the setting of DSO procedures."

DSO is indicated for Fuchs' dystrophy only. If a patient presents with guttae over the entire cornea, DSO will not work for her, and she'll need an endothelial keratoplasty.

"DSO is growing in popularity," explains Dr. Colby. "In 2015 or 2016, people weren't sure of the position it might hold within our transplant armamentarium. But now there are many more people doing DSO."

Other Non-graft Options

"In terms of advances in medication, I think the ROCK inhibitor is very exciting," says Dr. Farid. "We're looking forward to testing that out in this 2020 trial to see if it really makes a difference in terms of helping endo-



Kathryn Colby, MD

A slit lamp photo (left) and its corresponding endothelial image from a DSO patient (right).

thelial migration and stability, so that we can do more DSO instead of having to transplant tissue."

"The recent literature suggests that the use of ROCK inhibitors after DSO and DMEK may increase final cell count," adds Dr. Colby.

Dr. Colby and Dr. Farid say that researchers in Japan are paving the way for ROCK inhibitor research. "Maybe at this point four dozen patients have been injected with cultured endothelial cells, supplemented with a ROCK inhibitor," says Dr. Colby. "The theoretical advantage of cells is that you can take one donor cornea and potentially make enough cells to transplant to 40 or 60 or even 100 patients. That kind of cell replenishment surgery can be done for all forms of endothelial dysfunction, whereas Descemet's stripping works for only Fuchs' where there's healthy endothelium in the periphery. Further advances are also under way with potential *ex vivo* expanded endothelial cells that can be injected into the eye."

Surgeons agree that injectable endothelial cells may be the next big wave in approaching endothelial disease. The goal would be for patients to receive an injection of endothelial cells, and then be positioned face-down for a few hours. "The next step is bringing the technology to the United States," says Dr. Colby.

Noriko Koizumi, MD, PhD, professor of biomedical engineering at Doshisha University, Kyoto, Japan, and her team worked on developing cultivated corneal endothelial cell sheets for transplantation. "Human corneal endothelial cells are very difficult to culture," she says. "We tried various compounds, and finally found the Y-27632 ROCK inhibitor stimulates the proliferation of human CECs. We also found that Y-27632 promotes the cell adhesion to the substrate. This finding led us to develop cell-injection therapy. We're working on cell-injection therapy with ROCK inhibitors for advanced-stage FECD and pseudophakic bullous keratopathy."[9,10,11]

In 2013, her team initiated a clinical trial to test to the effectiveness of cultured human CECs injected into the anterior chamber of patients with corneal endothelial decompensation. "The results were surprising and very impressive to me," says Dr. Koizumi. "Most of our patients had clear corneas and recovered good vision, almost to 20/20."

One exciting finding came with hope provided by ROCK inhibitors. "Human CECs had been considered nonregenerative, but the ROCK inhibitor results told us we could somehow proliferate corneal endothelial cells *in vitro* and *in vivo*," says Dr. Koizumi. At the time of their 2017 review of ROCK inhibitors for treating corneal endothelial dysfunction,[10] Dr. Koizumi and her team had treated 31 patients with cell-injection therapy. "This may be a paradigm shift in the treatment for corneal endothelial diseases," she says.

Compared to tissue-engineered corneal endothelial cell sheets, Dr. Koizumi says cell-injection is far easier to deliver. The next step for her team is development of a cell-therapy product in collaboration with a startup company. "It's for early-stage Fuchs' patients," she explains. "We're developing an eyedrop (not a ROCK inhibitor) to prevent the apoptosis of corneal endothelial cells."

Outside Challenges

Aside from the challenges of manipulating thinner tissue, one of the biggest challenges surgeons face with corneal procedures comes from outside the eye—their patients. Today, patient demands concerning refractive outcomes have increased. "Patients don't want to wear glasses and really want improved refractive outcomes," says Dr. Farid. "It's not enough to have a clear graft and put patients into hard contact lenses. They want to be free of rigid contact lenses for the rest of their lives or they want to get low-prescription glasses or have complete spectacle independence. So, we really need to deliver not only clear grafts, but better quality of vision."

All this patient demand has challenged surgeons to be more innovative. Dr. Farid points out that now, "as a result, patients have fewer HOAs, less irregularity and are better able to get low—or no—spectacle correction."

Pearls

With so many procedures to choose from and some new advances to be on the lookout for, here are some tips to keep in mind.

• ***Counsel patients carefully.*** "Procedural success is predicated on the health and proper functioning of the new tissue," Dr. Baartman says. "Sometimes this tissue needs a little extra care, like additional air bubbles or steroids. It's important that patients understand the process so they don't feel

as if their procedure is going wrong or that the extra work is a complication."

• ***Choose the right procedure for each patient.*** Matching the appropriate technique to the appropriate patient is key, says Dr. Colby. "You have to know all the benefits and disadvantages of the entire armamentarium. There's no one-size-fits-all."

• ***Master the different surgical techniques and use them wisely.*** "A well-executed DSAEK will yield better outcomes than a poorly-performed DMEK," says Dr. Busin.

• ***Choose straightforward cases if you're just starting out.*** Dr. Farid says that when she's teaching new surgeons how to do DMEK, she advises them to select eyes that are clear, straightforward and have good visibility. "You don't want to be doing your first 20 DMEKs on eyes with poor visibility, tube shunts or other glaucoma-related hardware," she says. "DSAEK or ultra-thin DSAEK is better for those complicated eyes. DSAEK is a more predictable procedure than DMEK, and the tissue is a little thicker, so it's easier to handle."

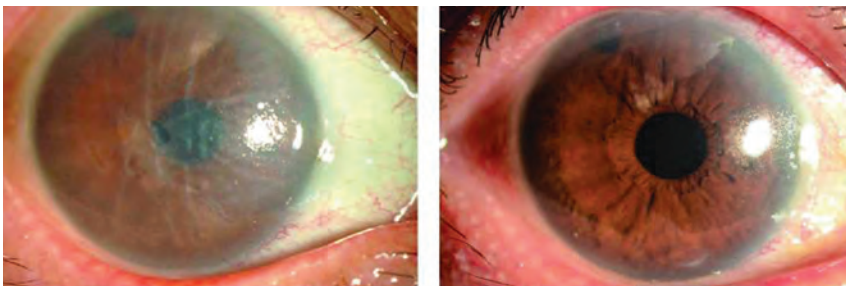
The Corneal Crystal Ball

"I predict that with techniques like cell culture, stem cell engineering, and other tissue rejuvenating advances, we'll likely see Descemet's membrane left alone in many eyes with endothelial cell loss, and we'll replace or enhance only diseased cells," says Dr. Baartman. "Less invasive techniques may lead to earlier intervention, with replacement occurring at early guttata development. I also believe we'll continue to see less bullous keratopathy with improved phacoemulsification efficiency and techniques."

Dr. Colby predicts that "we'll figure out early which patients will do well with DSO and ROCK inhibitors so that we'll be able to offer something to Fuchs' patients before they would need a transplant. Many doctors tell their patients to wait until their diseases are 'bad enough' for a transplant. If a patient's not having symptoms, I wouldn't recommend surgery, but I could see offering DSO to someone just beginning to have morning blurring symptoms or vision problems if we develop a solid way of predicting successful outcomes for DSO.

"I also think we'll see progress in cultured cell therapy," she says. "I'm imagining a future where you can have packaged endothelial cells available for order." Dr. Farid shares this hope. "If we could inject endothelial cells into the cornea and have the patient lie face-down for a few hours, we could cure them," she says.

The changes in corneal transplantation over the past 20 years have been remarkable, says Dr. Colby. "Back in the 90s, we basically waited for patients to be blind before we did full-thickness transplants on Fuchs' patients because of the long visual recovery and the many problems associated with full-thickness transplants," she says. "Fast forward 20 years, and we can strip off the endothelium and they do fine. My first patient is six years out; he's still 20/20 and very happy." REVIEW



Pre-treatment (A) and post-treatment (B) images of an eye that received cultured corneal endothelial cell injection therapy in clinical research. The patient, a Japanese female, had corneal endothelial decompensation induced by argon laser iridotomy (A). She underwent mechanical removal of an 8-mm diameter section of corneal endothelium followed by injection of cultured human CECs and a ROCK inhibitor into the anterior chamber. Her preop visual acuity was 1.0 logMAR (20/200) due to edema in the corneal epithelium and stroma. Her postop visual acuity was 0.04 logMAR (20/22), and she recovered corneal transparency.[4]

Drs. Colby and Busin have no relevant financial relationships to disclose. Dr. Koizumi has financial relationships with Senju Pharmaceutical and ActualEyes. Dr. Farid reports no relevant financial relationships, but notes that she's a consultant for Johnson & Johnson Vision and uses the company's femtosecond lasers in her research.

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Managing Corneal Disease and Glaucoma

These two conditions often exist side-by-side, and treating one often makes the other worse. MIGS may provide a solution.

John Berdahl, MD, Sioux Falls, South Dakota

When we're managing a patient, it's easy to focus solely on the main problem we're trying to treat. However, patients often have more than one problem. For example, both glaucoma and corneal disease are common conditions; about 3.5 percent of people in the United States have glaucoma. At the same time, according to the Department of Health and Human Services and the National Keratoconus Foundation, 1 percent have keratoconus, 20 percent have dry-eye disease and 4 percent of patients over age 40 have Fuchs' dystrophy. With these numbers, it's inevitable that some patients will have both glaucoma and corneal disease.

Furthermore, some of the treatments we provide to address either problem can create or exacerbate the other. It's no secret that treatments for glaucoma, whether pharmaceutical or surgical, can have implications for the cornea. For example, about half of glaucoma patients using eye drops develop dry-eye disease. Similarly, treatments for corneal disease (e.g., long-term steroids after full-thickness corneal transplant) can increase the risk of glaucoma. So even if patients don't have both problems upon presentation, they may have them after our treatment.

This is where MIGS comes into the picture. These minimally invasive procedures give us a way to address (or prevent) elevated intraocular pressure, without using drops that can negatively affect the cornea. At the very least, MIGS can reduce the number of drops patients need to use. For that reason, I believe it behooves us to 1) be aware of the possible negative cycle we may be creating when we treat either glaucoma or corneal problems; and 2) consider the use of MIGS procedures to break up that cycle.

Eye Drops & Corneal Disease

In terms of glaucoma treatment leading to corneal disease, there's no question that a primary culprit is the use of eye drops to lower IOP. That gives MIGS an advantage. Even if MIGS surgeries don't result in a complete resolution of elevated IOP in some patients, they almost always reduce the number of eye drops the patient needs to stay in the target pressure zone. This reduction in medication use has been confirmed via a number of studies:

- One recent study involving the iStent Inject found that the mean number of medications needed dropped from 1.6 to 0.4 at 23 months, a 75-percent reduction.[1]
- Another study found that implanting a Hydrus microstent reduced the mean number of medications from 1.7 to 0.3, an 82.4-percent reduction.[2]
- A study involving trabeculotomy using the TRAB 360 device found that medication use was reduced from 1.7 to 1.1 at 12 months, a 35-percent reduction.[3]
- A study combining phaco with a Kahook Dual Blade procedure caused a 70-percent drop in medication use at one year.[4]

We also conducted a prospective, controlled study in our own practice, evaluating the data from 30 of our patients that had received an iStent. In addition to a mean IOP reduction of 17 percent, medication use dropped by 60 percent, from 1.5 to 0.6 medications. This was accompanied by significant improvements in the

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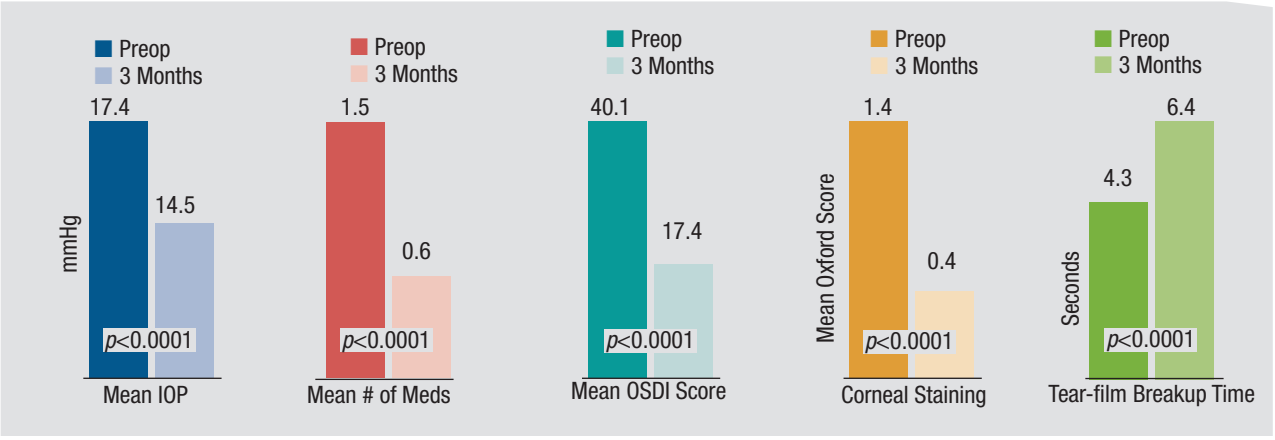
Impact of an Implanted iStent at Three Months Postop



To evaluate the impact of an implanted iStent, we conducted a prospective, controlled study involving data from 30 of our patients. At three months postop, the data showed a 17-percent reduction in IOP; a nearly three-fold reduction in medication burden; a significant improvement in ocular surface disease index score, with mean disease severity reduced from severe to mild; more than a three-fold decrease in corneal staining; and a significantly longer tear-film breakup time—eyes remained lubricated nearly 35 percent longer postop.

corneal surface:

- Ocular surface disease index score in these patients dropped from 40.1 to 17.4 at three months, a 57-percent drop ($p<0.0001$); average disease severity was reduced from severe to mild.
- The mean Oxford corneal staining score dropped from 1.4 to 0.4 at three months, a reduction of 71 percent ($p<0.0001$).
- Tear-film breakup time improved from 4.3 seconds to 6.4 seconds at three months ($p<0.0001$).

The correlation between number of eye drops being used and risk of ocular surface disease has also been confirmed by numerous studies. For example:

- A 2018 study found that amount of meibomian gland loss was significantly correlated with number of medications being used.[5] Patients using a greater number of eye drops had significantly shorter tear breakup time ($p=0.047$), lower meibomian gland density ($p=0.032$), higher meibomian gland loss ratio ($p=0.011$) and higher meiboscale ($p=0.036$).
- A 2017 study found that patients using eye drops had significantly higher OSDI scores (10.24 vs. 2.5; $p<0.001$) and corneal staining scores (64.93 percent vs. 32.61 percent; $p<0.001$).[6]

Given that reality, it should be no surprise that if you can safely decrease the number of medications by performing MIGS, you'll improve the condition of the ocular surface.

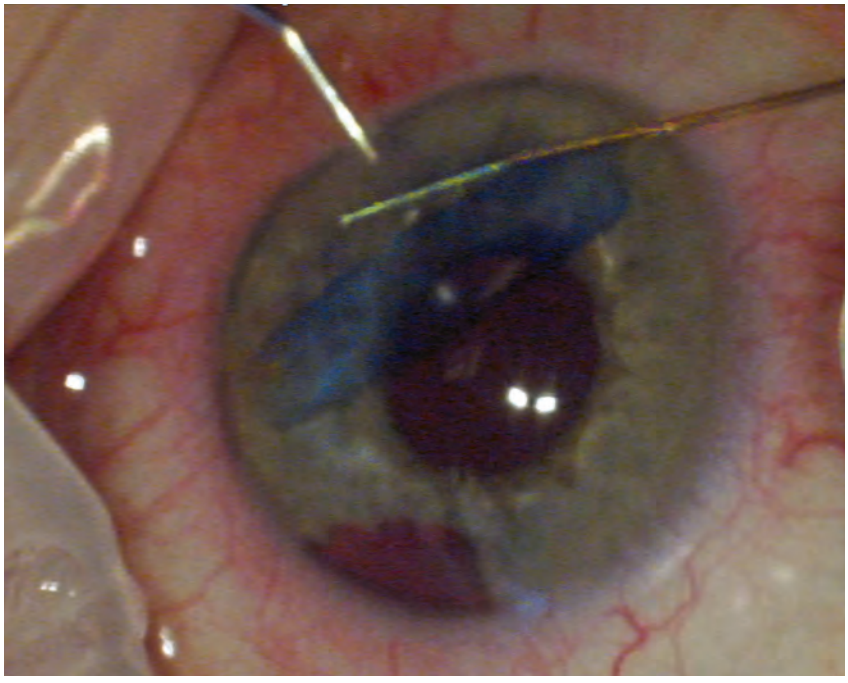
There's another aspect to the interaction between glaucoma and the cornea: Treating one condition can lead to worsening of the other, and vice versa. If our glaucoma treatment causes the patient to develop corneal disease, the temptation may be to address the corneal issues with steroid drops (or a steroid insert). As we all know, steroids can cause elevated IOP, possibly leading to glaucoma. If that occurs, the temptation will be to increase the number of glaucoma drops to lower the pressure, increasing the risk of corneal disease. The result can be an escalating, vicious cycle.

This is another reason to consider making MIGS a part of your armamentarium. MIGS gives us a way to lower both the IOP and the number of medications the patient is using, thus avoiding the vicious cycle that can be triggered by the use of eye drops to lower pressure.

MIGS with Corneal Surgery

Of course, steroids are generally prescribed following corneal surgeries such as penetrating keratoplasty and DMEK, which have also been associated with post-treatment glaucoma. After DMEK, IOP goes up in about 12 percent of patients,[7] and we know that about 20 percent of patients develop glaucoma following PK.[8] We think that this is primarily a result of the postoperative steroids. DMEK patients have to use steroid drops for a year following the surgery, and patients undergoing a PK sometimes have to use steroids for the rest of their lives. Then, if the steroids trigger elevated IOP, the problem may be compounded by the temptation to treat that with glaucoma drops, potentially injuring an already susceptible cornea. You can end up with the same vicious cycle, with each treatment making the other problem worse.

For this reason, we've been investigating the idea of combining MIGS with corneal procedures such as DMEK and PK. Today, this isn't a common approach. Part of the reason it's not common may be that many



When combining a DMEK procedure with implantation of an iStent, blood reflux through the iStent can occur, interfering with visualization and making the surgery more challenging.

glaucoma surgeons don't perform corneal surgery, and vice versa. (I'm an exception, having been trained in both cornea and glaucoma.) However, adding MIGS to these procedures can prevent the vicious cycle from starting, leading to better outcomes and happier patients.

We conducted a small study in our practice involving 16 patients with Fuchs' dystrophy. (We presented some of this data at the 2019 meeting of the American Society of Cataract and Refractive Surgery.) The patients underwent DMEK and a simultaneous trabecular bypass using an iStent. Results included:

- Vision improved; preoperative vision was 20/50, vision at six months postop was 20/25.
- The number of medications remained the same pre- and postop.
- The re-bubble rate was a little higher than normal at 26 percent. This was probably because of blood reflux, which can be a problem when doing an endothelial cell transplant like DMEK at the same time as a MIGS procedure. When we lower pressure in the anterior chamber, blood reflux can occur, making endothelial cell transplantation more challenging and riskier.
- One of the patients went on to need a tube shunt.
- Most notably, none of the patients' IOPs increased despite using the postoperative steroid.

I made a video of one such surgery, in which I combined cataract surgery plus DMEK, and also placed an iStent. *(See image, above.)* In this case, the lowered IOP that's part of the DMEK procedure caused blood to reflux through the stent, which might have made it more difficult to unfold the DMEK graft; however, the surgery was successful.

Whether to do the DMEK and iStent procedures separately or concomitantly is an important consideration. I often do them at the same time, but I have mixed feelings about recommending this approach to other surgeons because doing them together can make it very hard to unscroll the DMEK graft.

There's also the practical issue that in many cases a different surgeon would have to perform each procedure, making it more difficult to combine them in the OR. We've occasionally had two surgeons come in for one surgery, but the logistics of that can be challenging. For that reason, if you wish to try combining these surgeries to minimize the patient's need to use postoperative glaucoma drops, a prudent approach might be to perform the DMEK first and then come back later to do a procedure combining cataract surgery and MIGS, or a standalone MIGS procedure.

I also believe it makes sense to add a MIGS procedure when performing a PK, for the same reason—avoiding the postoperative need for drops that will harm an already fragile cornea. (Corneal surgeons know that many of these patients will develop glaucoma postop.) This is a very controversial topic, because intraoperative surgical complications can occur when MIGS and a PK are performed together. In addition, going back into the eye later, after the patient has a corneal transplant, is not without risk. Nevertheless, if I had my way, I'd do a MIGS procedure with every corneal transplant to help prevent that vicious postop cycle of cornea and glaucoma treatments from occurring.

Other Alternatives

What about other options for addressing postop pressure elevation when it occurs in corneal surgery patients? Options such as tube shunts can cause corneal decompensation, which would be totally unacceptable in these patients.

Selective laser trabeculoplasty is another option that could prevent postop IOP elevation; the question is whether it would be effective enough to prevent the vicious cycle from

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starting. In my experience, MIGS procedures—especially a trabecular meshwork bypass procedure like the iStent—are more effective. At a theoretical level, this makes sense: SLT appears to loosen the junctions in the trabecular meshwork, letting more aqueous pass through, but a stent allows fluid to bypass the meshwork and exit through the stent. So it seems less likely to me that a steroid-induced IOP increase would occur following a stent implantation than following SLT.

Finally, it might soon be possible to address steroid-induced glaucoma by delivering glaucoma drugs intraocularly, via an implant, for example, rather than by placing potentially damaging drops on the cornea. This would prevent the cycle of complications from starting, and is an option that should certainly be worth considering.

A New Perspective

I believe it's important to consider the interaction of corneal and glaucomatous disease whenever we treat glaucoma or corneal issues. Many of our patients present with problems in both areas, and our treatments can trigger—or worsen—either type of problem. Knowing that, we should go out of our way to avoid starting the vicious cycle in which treating one makes the other worse, and vice versa. MIGS procedures give us a way to prevent that from happening, leading to better outcomes, fewer additional drugs and surgeries, and happier patients. REVIEW

Dr. Berdahl is a corneal, refractive and glaucoma surgeon at Vance Thompson Vision in Sioux Falls, South Dakota, and associate clinical professor at the University of South Dakota. He's consulted for Allergan, Avedro, Bausch + Lomb, Equinox, Glaukos, Imprimis and Neuromedical.

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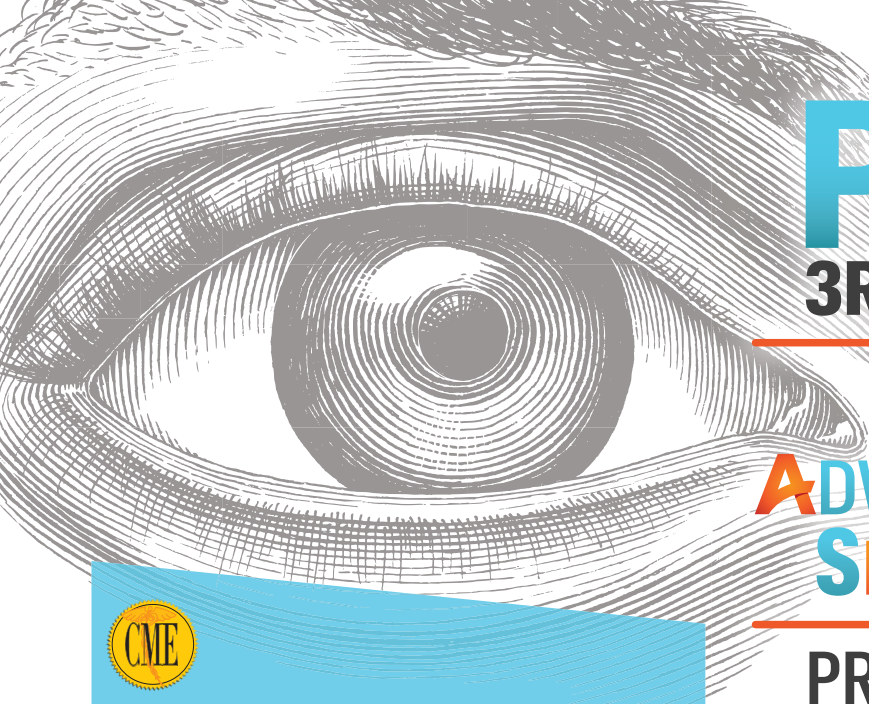

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This event will include one day of didactic, plus one day of hands-on wet lab experience to increase levels of resident preparedness and surgical competence. It is our hope that you will select and encourage your Third-Year Residents to attend this program, which is CME accredited to ensure fair balance.

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Yousuf M. Khalifa, MD, FACS

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Virtual Reality's Effects on Children

Though children under 13 are banned from using most products involving virtual reality headsets, researchers at St. Louis Children's Hospital say that might not be necessary.

In the prospective, interventional, before-and-after study, the investigators studied 50 children (29 boys) as they played a VR flying game on the Sony Playstation 4. The children used their head movements to control their flight in the game. Baseline testing preceded VR exposure, and each VR session was followed by testing of binocular corrected distance visual acuity, refractive error, binocular eye alignment, stereoacuity and postural stability. Visually induced motion sickness was probed using the Simulator Sickness Questionnaire modified for pediatric use (Peds SSQ). Visual-vestibulo-ocular reflex (V-VOR) adaptation was also tested pre- vs. post-trial in five of the children.

Surprisingly, the researchers found that VR discomfort in kids may be even less than that reported in adults. Forty-six of the 50 children (94 percent) completed both VR play sessions with no significant change from baseline in measures of binocular CDVA (p=0.89), refractive error (p=0.36), binocular eye alignment (p=0.90), or stereoacuity (p=0.45). Postural stability degraded an average of 9 percent from baseline after 60 minutes of VR exposure (p=0.06). Pre- versus post-trial, the Peds SSQ scores increased a mean 4.7 percent for each of four symptom categories: eye discomfort (p=0.02); head/neck discomfort (p=0.03); fatigue (p=0.03); and motion sickness (p=0.01). None of the children who finished both trial sessions (94 percent) asked to end the play time. V-VOR gain remained unaltered in the five children tested. Three children (6 percent)—two girls (ages 5 and 6 years) and one boy (age 7 years)—discontinued the trial during the first 10 minutes of the first session. The girls reported discomfort consistent with mild motion sickness, while the boy said he was bored and the headset was uncomfortable. No child manifested aftereffects in the days following the VR exposure.

Am J Ophthalmol 2020; 209:151-159
Tychsen L, Foeller P.

Leakage on FA After Intravitreal Aflibercept Injections

Researchers aimed to characterize leakage indices on ultra-widefield fluorescein angiography in proliferative diabetic retinopathy treated with intravitreal aflibercept. The prospective study enrolled subjects for treatment of proliferative diabetic retinopathy randomized 1:1 to receive 2-mg of intravitreal aflibercept every four weeks (2q4) or every 12 weeks (2q12).

Researchers analyzed ultra-widefield FA images obtained at baseline, 24 and 48 weeks using a semiautomated leakage segmentation platform. Forty eyes of 40 subjects were included, and mean age was 48 ±12.1 years. Mean number of injections was 11 ±1.7 in the 2q4 arm and 4 ±0.4 in the 2q12 arm. Median baseline leakage index in the 2q4 arm was 5.1 percent, and median baseline leakage index in the 2q12 group was 4.3 percent (p=0.28). Researchers found:

- At 24 and 48 weeks, the 2q4 group significantly improved to 1.1 percent (-79 percent, p<0.0001).
- At week 24, the 2q12 group demonstrated non-significant improvement (3.4 percent; -21 percent, p=0.47); by week 48, improvement was significant (1.4 percent; -68 percent, p=0.02).
- The 2q4 group had a lower leakage index (1.1 percent) compared with the 2q12 group at 24 weeks (3.4 percent) (p=0.008); but by 48 weeks, the leakage index was similar between both groups (1.1 percent [2q4 group] vs. 1.4 percent [2q12 group]; p=0.34).

Researchers found that PDR treated with intravitreal aflibercept demonstrated significant leakage index reductions at one year. Monthly dosing provided more rapid reductions in leakage index than quarterly dosing.

Retina 2020; Jan 8. [Epub ahead of print].

Babiuch AS, Wykoff CC, Srivastava SK, et al.

(Continued from page 41)

Dr. Yeu encounters other postop issues. "Besides excessive sun exposure, I also see haze from poor adherence to topical steroids," she notes. "Higher-diopter treatments (more than 5 D) can also have the tendency to raise potential issues. I turn to mitomycin-C 0.02% for six to 12 seconds—and for longer periods for higher-power treatments and retreatments (such as after I am performing PRK over LASIK)."

In Search of Perfection

Despite the progress surgeons have made in surface ablation procedures, they're quick to say there's room for improvement. "If you customize care for each patient and respond to their needs with the latest information in mind, you should do well with surface ablation," says Dr. McDonald. "Our surface ablation outcomes are much better now, in every way, and they'll only continue to improve." REVIEW

Dr. McDonald is a consultant to Orca, the makers of the Epi-Clear device. Dr. Yeu consults with Alcon, Allergan, Bausch+Lomb/Valeant, J & J Vision, Merck, Novartis, Ocular Science, Ocular Therapeutix, OcuSoft, Shire, Sight Sciences, Sun Pharma, Topcon, and Zeiss. Dr. Manche is a consultant for Allergan, Avedro, Zeiss and J&J Vision. He provides sponsored research for Allergan, Alcon, Avedro, Zeiss, J&J Vision and Presbia. He owns equity in RxSight and Vacu-Site. Dr. Epstein reports no relationships.

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FDA Makes New Stain Option Available

The Dutch Ophthalmic Research Center received FDA approval of its New Drug Application for TissueBlue (Brilliant Blue G Ophthalmic Solution) 0.025%. TissueBlue is the first FDA-approved dye for use as an aid in ophthalmic surgery by selectively staining the internal limiting membrane. The stain is injected onto the inner retinal surface for clear staining of the ILM as a way to distinguish it from unstained retina during its removal. Additional highlights include:

- its use with more than 350,000 surgical procedures since launch;
- a unique U.S. formulation featuring pharmaceutical-grade dye material to ensure a higher level of purity than lower-grade (compounded) dyes;
- the inclusion of polyethylene glycol to provide the density required by surgeons to ensure targeted application to the retina; and
- availability in a terminally sterilized, prefilled syringe.

DORC says it expects to start shipping TissueBlue to customers in early April. Visit https://www.dorc.eu/products for more information.

B+L Expands Parameters for Biotrue Oneday for Astigmatism

Bausch + Lomb recently announced the U.S. launch of expanded parameters for Biotrue OneDay for Astigmatism daily disposable contact lenses. The expansion will increase the toric parameter range by more than 60 percent, the company says. Similar to the other products in the Biotrue OneDay brand family, Biotrue OneDay for Astigmatism lenses are formulated with a patented dehydration barrier, which B+ L says helps the lens maintain nearly 100 percent of its moisture for a full 16 hours. An evolved periballast design features a tapered edge to limit lid interaction, and spherical aberration control to help reduce halos and glare, particularly in low-light conditions. Visit https://www.bausch.com.

Meet Theia, An Alexa for Your Eyes

MacuLogix announced its next generation of dark adaptation functional testing with the introduction of AdaptDx Pro, guided by "Theia." A new headset, custom-designed and tested for patient comfort, includes all of the functionality and accuracy of the company's table-top dark adaptometer, the company says. As a self-contained wearable headset, the AdaptDx Pro requires no darkroom or external computer, and features an artificial intelligence-driven onboard technician named Theia. After the in-office technician selects the testing protocol and places the device on the patient's head, Theia takes over to facilitate the testing experience by using automated instructions and adaptive feedback spoken directly to the patient. Theia's A.I. helps ensure consistent, reliable testing results, and frees up the technician to focus on other tasks, MacuLogix says. Visit https://www.maculogix.com/adaptdx/. REVIEW

The new AdaptDx Pro, guided by "Theia," helps patients test their dark adaptation.

This article has no commercial sponsorship.

Double vision and unilateral ptosis bring a 72-year-old woman to Wills Eye's Neuro-ophthalmology Service.

Rakhi Melvani, MD, and Mark Moster, MD

Presentation

A 72-year-old Caucasian female was referred to the neuro-ophthalmology clinic for gradual development of diplopia and a drooping right upper eyelid. Six months prior to presentation, she struck her head against her car trunk door and developed a mild headache that resolved on its own. She didn't pursue medical attention at that time. Two weeks after the incident, she noticed drooping of her right upper lid. Over a period of months, she developed binocular diplopia.

Medical History

Her past ocular history included dry-eye syndrome. Her medical history included diabetes, hypertension, hyperlipidemia, hyperthyroidism and remote history of breast cancer, for which she underwent mastectomy. She was on several medications including citalopram, ferrous sulfate, metformin, levothyroxine, losartan-hydrochlorothiazide, simvastatin and tamoxifen. She had no allergies to medications. Social history was significant for smoking one-half pack per day and occasional alcohol use. Her family history was noncontributory.

Examination

Ocular examination at her local ophthalmologist demonstrated visual acuity of 20/50, pinholing to 20/40 in the right eye and 20/20 in the left. Pupils were equal, round and reactive. Intraocular pressures and confrontational visual fields were within normal limits. Extraocular motility was notable for limited supraduction, infraduction and adduction in the right eye, but was full in the left eye. Her external exam was significant for ptosis of the right upper eyelid. Anterior exam and dilated fundus exam were otherwise noncontributory. The patient was referred to neuro-ophthalmology but was then lost to follow-up for several weeks.

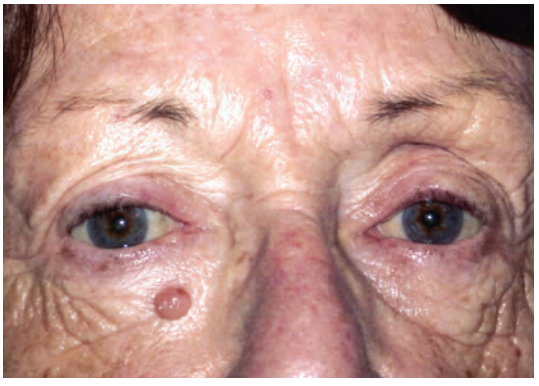

Figure 1. The external exam was significant for ptosis of the upper right eyelid.

Six weeks later, on presentation to neuro-ophthalmology, her examination was significant for anisocoria, a 3-mm pupil in the right eye and a 4-mm pupil in the left, with a greater difference in the dark. No afferent pupillary defect was noted. She was found to have 20 percent normal elevation and adduction, 60 percent normal depression and 80 percent normal abduction in the right eye. Left eye demonstrated full motility. On external exam, 3 mm of ptosis of the right upper lid was noted. She was orthophoric in primary gaze, with an exotropia in left gaze measuring 30 prism diopters and an esotropia in right gaze measuring 4 prism diopters. She also demonstrated downward displacement of her right globe and resistance to retropulsion of the right eye. Hertel measurement was significant for a 3.5-mm difference, right greater than left.

What is your diagnosis? What further workup would you pursue? The diagnosis appears on p. 64.

Workup, Diagnosis and Treatment

Given the patient's clinical findings, a differential diagnosis included etiologies that could cause signs and symptoms of deficits in multiple cranial nerves or extraocular muscles, Horner's syndrome, proptosis, resistance to retropulsion and downward displacement. This included inflammatory etiologies such as idiopathic orbital inflammatory syndrome, thyroid eye disease and orbital vasculitis, neoplastic causes such as benign or malignant intraorbital masses and vascular etiologies such as orbital varix, carotid-cavernous fistula, orbital arteriovenous malformations and veno-lymphatic malformations.

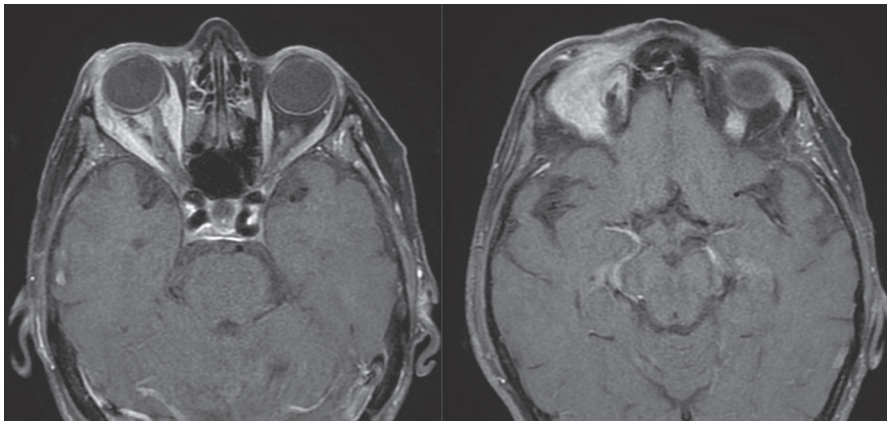

Figure 2. Left, MRI brain with contrast, axial T1 image with fat suppression depicting extraocular muscle enlargement. Right, MRI brain with contrast, axial T1 image of lacrimal gland, and extraocular muscle encased with infiltrative process.

An MRI of the brain with and without contrast was indicative of a multispacial, infiltrative and continuous process involving the extraocular muscles, lacrimal gland and orbital fat. Given the patient's history of remote breast cancer, these findings were thought to be consistent with metastatic breast cancer to the right orbit. The patient was then referred to an oculoplastic surgeon for biopsy. Biopsy of the lacrimal gland was significant for evidence of chronic inflammation and fibrosis on H&E staining. It was positive for cytokeratin AE1 and AE3 immunohistochemical stain, significant for carcinoma. Further specialized immunohistochemical staining was positive for CK7+, GATA3+ and ER+, narrowing the diagnosis of metastatic breast carcinoma, lobular type. Predictive and prognostic markers were also obtained on histology; biopsy was positive for ER and negative for Her2/neu. The patient was subsequently referred back to her primary medical oncologist for further systemic evaluation and consideration for additional treatment of metastatic disease.

Discussion

Though any cancer in the body can metastasize to the orbit, most orbital metastases are derived from lung, breast or prostate tumors. Presenting symptoms often include pain, proptosis and early ophthalmoplegia, though orbital metastases can present in a myriad of ways. Extraocular muscles are frequently involved, due to their abundant blood supply. Of those patients who present with metastatic tumors to the orbit, 75 percent have a history of known primary tumor. This leaves 25 percent of patients presenting with metastatic tumors to the orbit without a known primary.[1] These patients require immediate referral to a medical oncologist for systemic imaging and laboratory evaluation.

A survey from the Wills Eye Hospital Ocular Oncology department of 1,264 patients with orbital tumors and simulating lesions found that the three most common types were lymphoid tumors, idiopathic orbital inflammatory syndrome and cavernous hemangioma. Of these lesions, 64 percent were found to be benign, while 34 percent were malignant. Notably, the percentage of malignant lesions compared to benign lesions increased with age, comprising 58 percent of lesions in older patients age 60 to 92. Of those subclassified as having metastatic tumors to the orbit, 48 percent were due to breast carcinoma, making breast carcinoma the most common orbital metastasis.[2]

Breast cancer is the most common primary source of orbital metastases in women. It has a propensity to invade the extraocular muscles and orbital fat, theorized to be due to the increased relative estrogen concentration in these regions. Metastasis can occur many years after the initial breast cancer has been removed, as in this case, therefore a history should always include inquiries about previous cancer surgery.[3] Breast metastasis to the orbit can rarely also elicit a fibrous response

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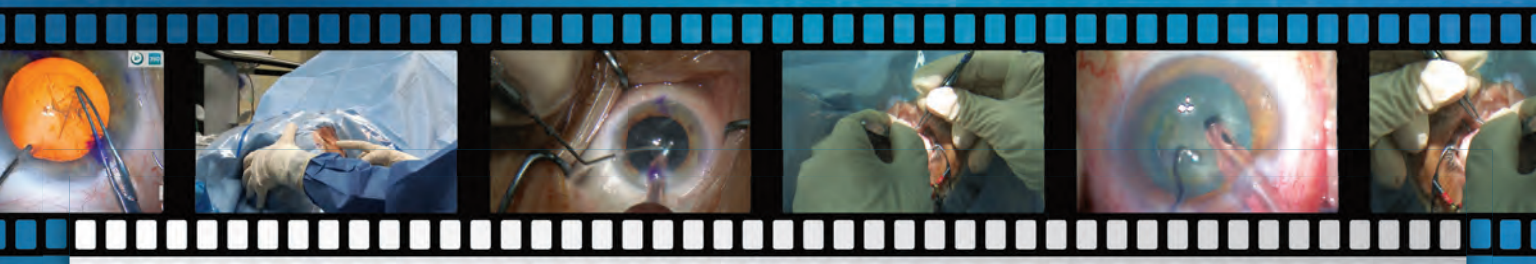

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Surgical Video by:
Richard J. Mackool, MD

Video Overview:
In this patient with severe claustrophobia and a moderately shallow AC, I discuss several maneuvers/ techniques that can reduce patient anxiety and increase the safety of nucleus removal.

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Richard J. Mackool, MD

We are excited to continue into our fifth year of Mackool Online CME. With the generous support of several ophthalmic companies, I am honored to have our viewers join me in the operating room as I demonstrate the technology and techniques that I have found to be most valuable, and that I hope are helpful to many of my colleagues. We continue to edit the videos only to either change camera perspective or to reduce down time – allowing you to observe every step of the procedure.

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Richard Mackool, MD, a world renowned anterior segment ophthalmic microsurgeon, has assembled a web-based video collection of surgical cases that encompass both routine and challenging cases, demonstrating both familiar and potentially unfamiliar surgical techniques using a variety of instrumentation and settings.

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- perform methods to deal with claustrophobic patients, and techniques to protect the cornea when the chamber is shallow.

Satisfactory Completion - Learners must pass a post-test and complete an evaluation form to receive a certificate of completion. You must listen to/view the entire video as partial credit is not available. If you are seeking continuing education credit for a specialty not listed below, it is your responsibility to contact your licensing/certification board to determine course eligibility for your licensing/certification requirement.

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in the orbit, causing enophthalmos and restriction of ocular motility, commonly known as scirrhous breast carcinoma.[4-6] The response to hormonal therapy is favorable for patients with ER+, PR+ findings in the tumor tissue. Estrogen receptor assay results from orbital metastases can differ from those of the primary lesion, so any orbital tissue studies should include their own separate assay.[5]

A retrospective review from the Cogan Ophthalmic Pathology Laboratory of the Massachusetts Eye and Ear Infirmary analyzed histopathologic correlations of breast cancer that metastasized to the orbit; it found that lobular breast cancer represents the cancer subtype with the highest prevalence among orbital metastases.[5,7] On immunophenotypical characterization, this was theorized to be due to the lack of intercellular cohesiveness in lobular breast cancers, because they lack the molecule E-cadherin. E-cadherin is normally expressed in many neoplastic cell types, including ductal breast carcinomas, limiting their dispersion.[5] REVIEW

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Xiidra (lifitegrast ophthalmic solution) 5%

Rx Only

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 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. In 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.

Shire

Manufactured for: Shire US Inc., 300 Shire Way, Lexington, MA 02421.
For more information, go to www.Xiidra.com or call 1-800-828-2088.

Patented: please see https://www.shire.com/legal-notice/product-patents
Last Modified: 01/2018 S33769

xiidra® (lifitegrast ophthalmic solution) 5%

THERE'S NO SWÏITCHING THIS

Xiidra is the only lymphocyte function-associated antigen-1 (LFA-1) antagonist treatment for Dry Eye Disease[1,2]

Xiidra, the first in a class of LFA-1 antagonists for Dry Eye Disease, is a prescription eye drop FDA-approved to treat both signs and symptoms of the disease.[1,3]

There's no substitute.[2,4] Check out patient resources, insurance coverage, and more at **Xiidra-ECP.com**

References:

1. Xiidra [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; November 2019. **2.** TFOS DEWS II Research Subcommittee. Report of the Research Subcommittee of the Tear Film & Ocular Surface Society Dry Eye WorkShop II (2017). *Ocul Surf.* 2017;15(3):269-649. **3.** FDA approves new medication for dry eye disease. FDA News Release. July 2016. http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm510720.htm. Accessed July 12, 2016. **4.** Food and Drug Administration. Electronic Orange Book. http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf. Accessed June 26, 2018.

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.

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

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