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New Technologies in the Diagnosis and Treatment of Anterior Segment Diseases

How corneal cross-linking, cryopreserved amniotic membrane, and epithelial thickness mapping are changing patient care

Highlights from a panel discussion held during the 2019 ASCRS Annual Meeting

Faculty

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Optovue, **Avedro**, and **Bio-Tissue**, three pioneering ophthalmic companies, welcomed surgeons to a thought-provoking symposium on new technologies in the diagnosis and treatment of anterior segment diseases, held during the American Society of Cataract and Refractive Surgery 2019 meeting in San Diego. The cosponsored symposium features five ophthalmic thought leaders who discussed how breakthrough technologies have influenced diagnosis and treatment for patients seeking cataract or refractive surgery, as well as care for corneal disease. For each company, there is a standout area of expertise: Optovue with the first FDA-approved OCT for Epithelial Thickness Mapping, Avedro with the first and only FDA-approved therapeutic treatment for progressive keratoconus, and Bio-Tissue with cryopreserved amniotic membrane.

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Epithelial Thickness Mapping: A New Tool for Anterior Segment

BY MAX PARIKH, MD

In my practice, Epithelial Thickness Mapping (ETM) with the Avanti Widefield OCT system (Optovue) serves several purposes. I use it to aid in keratoconus diagnosis and assess cross-linking patients pre- and post-operatively.

I also use ETM for dry eye diagnosis and management before refractive surgery. Acquiring an epithelial thickness map doesn't disrupt patient flow — it's a noncontact test, so technicians can do it — and it provides a great deal of useful data.

Normal ETM versus Keratoconus

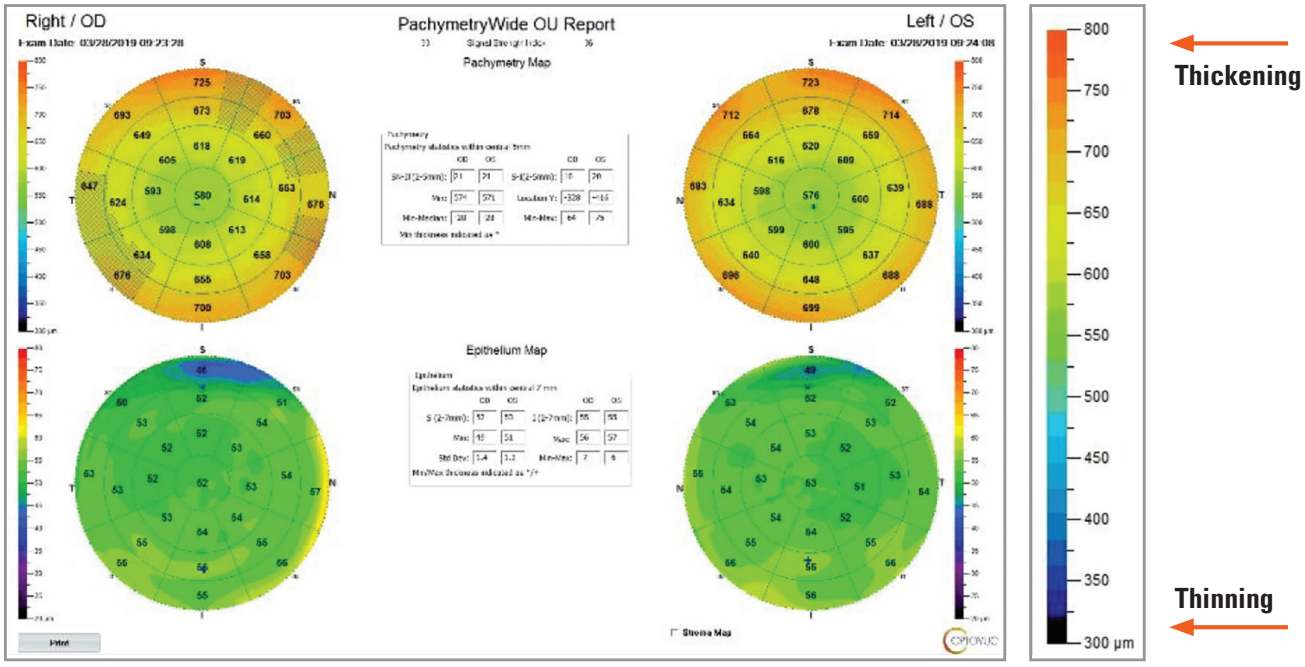
Once data is obtained from the OCT system, I get a map of the right eye and left eye that shows the total corneal thickness and the epithelial thickness. In a cross-sectional view, the software clearly identifies the epithelial layer, showing the posterior of the epithelium as well as the posterior corneal surface, which can be important when trying to locate landmarks.

On a normal map, we'll see a corneal thickness of approximately 550 microns and a corneal epithelium of about 50 microns pretty much all the way through. In an eye with untreated keratoconus where the diagnosis is obvious on the topographic maps, the ETM will show a little blue thinning of the epithelium over the apex of the cornea where the cone protrudes. When the ETM shows thinning of the epithelium on only one eye, I might observe the fellow eye for a little while as opposed to aggressively recommending treatment.

Evaluation Before LASIK

When we see a patient for LASIK evaluation and there is inferior steepening or a borderline cornea, we need to determine if the person is at an above-average risk for ectasia.

ETM in Normal Eyes Average Thickness ~50µm



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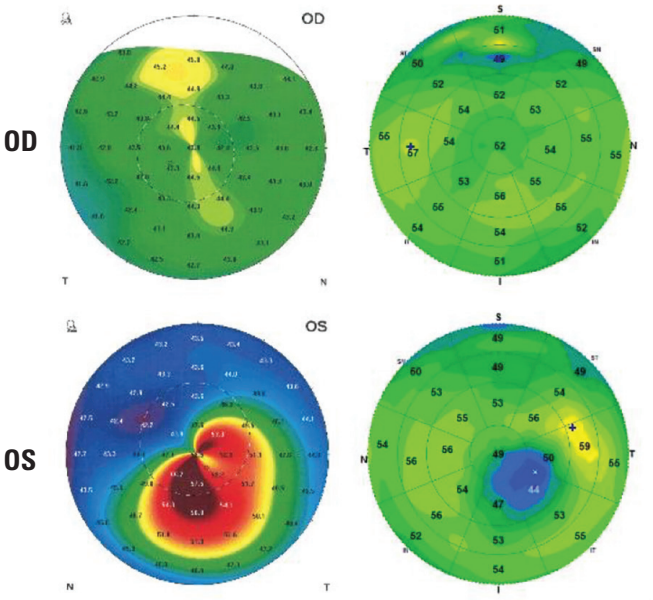
Unilateral Keratoconus
ETM aids in cross-linking decisions



Most patients prefer LASIK over PRK when given a choice, but LASIK may not be the best choice if the risk of ectasia is heightened. ETM offers another tool to help us feel more confident about whether to recommend LASIK, because epithelial thinning over the central cornea could indicate increased risk of ectasia.

ETM also helps us evaluate and address ocular surface issues, such as dry eye, before surgery. We might see a patient who has relatively normal topography, a cornea that looks pretty good clinically, and perhaps a little fluorescein staining on the cornea. But when we look at the ETM, the epithelium has a very irregular pattern caused by dryness. OCT is very useful for detecting this irregularity, which indicates that the surface is not pristine.

Post-LASIK Follow Up

When we perform LASIK surgery and outcomes are less than perfect, ETM can help us decide if and when to perform an enhancement. For example, I performed LASIK on a high myope. After surgery, the patient's topography looked pretty good, showing some flattening of the cornea.

The patient was happy with his overall vision, but still hoped for 20/20 or better without glasses, and his vision in the uncorrected eye was 20/30-20/40. We thought maybe we would enhance him when he was stable, but when we followed him for 6 months, the ETM showed some interesting changes.

As we commonly see with a myopic ablation, there is a flattening of the cornea with a relatively normal ETM after surgery. Over time, the epithelium in the central cornea where the ablation was flattened demonstrated epithelial thickening (hyperplasia). This thickening occurs very often in patients who need enhancements. Before I enhance the patient, I want to see not only a stable refraction, but also a stable ETM. When it is unstable, I delay enhancement — sometimes as long as 9 months or 1 year — which was the case with this patient.

For more information on the Avanti Widefield OCT system, visit ***optovue.com***

When we use ETM to follow patients after LASIK, we can also see how the epithelium fills in after surgery, which helps us understand cases where the post-op refractive error changes. Changes in refraction often correlate to changes in the corneal epithelium, which can alter as it heals.

ETM is a great diagnostic tool to help us identify keratoconus (clear-cut cases or forme fruste), evaluate patients before and after cross-linking, and diagnose and manage dry eye disease. ❖

DISCUSSION

DR. FRAM: Sometimes, contact lens wearers come seeking keratoconus evaluation or cross-linking. How can a clinician use ETM to determine if the problem is keratoconus or simply contact lens warpage?

DR. PARIKH: Whenever we see an irregular cornea, we use Pentacam (Oculus) topography, which provides a good anterior and posterior float evaluation. In addition, we obtain ETM from OCT. If we see thinning of the epithelium, then we're concerned that it might be forme fruste keratoconus. In patients with contact lens warpage, interestingly enough, we don't often see that pattern. We see a normal corneal epithelium or even a bit of thickening. That difference is important, because it points us either to contact lens warpage or to forme fruste keratoconus. Either way, we keep these patients out of contact lenses, allowing the cornea issues to resolve, and repeat the test before proceeding.

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Implementing Corneal Cross-Linking in Practice

BY KATHRYN HATCH, MD

Keratoconus is a progressive condition, therefore, early detection is critical. Patients can progress at any age, but younger patients from their pre-teens to their 20s have the highest risk, because their tissues are very elastic. Screening is essential, as is early intervention using corneal cross-linking to slow or prevent progression of keratoconus.

In 2016, Avedro received FDA approval for corneal cross-linking for the treatment of progressive keratoconus and corneal ectasia following refractive surgery. Cross-linking is the only approved therapeutic treatment for progressive keratoconus. Based on my experience in the last few years, I can share the following tips on how to implement this treatment into your practice.

Education and Expectations

Implementing cross-linking is a whole office effort, from the staff answering the phone, to the technicians, coordinators, and physicians. I have a staff member who is a dedicated cross-linking coordinator. Her primary role is to meet with patients, answer inquires, schedule the procedure, and obtain insurance prior authorization. The coordinator also reviews what patients should expect, from the eye drops to the procedure itself, including how long they'll spend in the office, and any post-op prescriptions.

For more information on corneal cross-linking, visit ***www.avedro.com***

I ensure patients understand that managing keratoconus is a team effort. Patients occasionally ask if I personally perform the procedure. I explain that I am in charge of the procedure, but I have technicians who help by handling specific steps and who will be with them throughout the procedure. While I'm explaining this approach, I introduce one of my cross-linking champion technicians, all of whom have a very calming effect on patients and are pros as setting expectations for a variety of patient types.

For example, I see many teenage keratoconus patients, and I tell them they're welcome to listen to their music during the procedure. If someone seems nervous, we might give a tour of the laser suite where the procedure will take place. Many keratoconus patients with special needs come to our offices, and a tour with staff introductions can be particularly helpful for them to prepare. The mother of one patient with Down syndrome put together a book to help patients with special needs understand what's ahead. It includes pictures of the laser suite, staff, and physicians. We spend a great deal of time communicating because we think it's important to make everyone feel confident in our team and comfortable with the process.

Cross-linking and Monitoring

The cross-linking procedure itself can be a difficult concept for some patients. Many still ask me the day after surgery, "Am I going to see better?" We must keep reiterating to patients that cross-linking is not a refractive procedure. The purpose is to stabilize the cornea and prevent future progression. This point is especially important to emphasize to patients whose keratoconus was detected when they presented seeking LASIK or other vision enhancement. Avedro offers many resources for patients on their educational website, LivingWithKC.com.

On treatment day, I start by giving patients a bit of benzodiazepine. I then see patients several times during their procedure, but I'm not with them every moment. I explain to them, "I'm going to see you after we load the cornea, again before the light treatment, and then at discharge." The technicians guide the patient through each step of the cross-linking procedure while I'm seeing patients in the clinic. We can treat up to four or five eyes a day in our clinic with this approach.

After cross-linking, it's important that patients are monitored. We usually see them day 1 and frequently — sometimes daily — until the epithelium is fully healed. At that point, we remove the bandage contact lens, and patients typically return to their referring providers. I start to assess the results of cross-linking around 3 to 4 months and again

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at 6 to 9 months. One month is too early because the cornea can actually get steeper as a result of epithelial hypertrophy.

Referrals and Reimbursement

It's essential to work with optometrists and other ophthalmologists in the community to reinforce the importance of early diagnosis for keratoconus and to emphasize that cross-linking is the standard of care and is FDA approved to slow or halt progression. It is crucial that they tell keratoconus patients about cross-linking and refer them for consultation.

> "It's essential to work with optometrists and other ophthalmologists in the community to reinforce the importance of early diagnosis for keratoconus."

In my practice, we share these messages with eyecare professionals in the community, referring optometrists and ophthalmologists, and through continuing education programs. These programs help to build these essential relationships and educate our partners on the process of referring patients to us for treatment, after which we return patients to their primary eyecare providers. After the procedure, most patients will need a new contact lens fitting and possibly a new prescription, which is reassuring to their optometrists.

These programs are also a great opportunity to educate our network on insurance progress, which is essential to making this procedure accessible for their patients. We've had great success with commercial insurance coverage of corneal cross-linking. Two years ago, it was exclusively self-pay, but that's no longer the case.

On the rare occasion that I see a patient who is not covered by insurance, we work with the Avedro Reimbursement Customer Hub (ARCH), a patient assistance program that reaches out to insurers. We need this less and less as corneal cross-linking has become the standard of care for progressive keratoconus, making the procedure simple to manage from a billing perspective. ❖

DISCUSSION

DR. RAJPAL: *Insurance coverage and the reimbursement process have gotten dramatically better at our practice, but occasionally, patients try to obtain pre-authorization, which takes time, especially for younger patients. How do you counsel those patients about progression?*

DR. HATCH: Ideally, we don't want to wait long periods of time for prior authorization to perform treatment, especially in a pediatric population (< 18), who are at a high risk for rapid progression. I aim to treat patients as soon as possible, usually within several weeks or a month. When I explain the sight-preserving importance of the procedure to young patients and their parents, they understand.

DR. FRAM: Avedro has done a very good job of advocating for patients and physicians. They've also helped to educate our practice administrators and billing department.

DR. RAJPAL: *How do you document progression? Have insurance companies put any requirements in place?*

DR. PARIKH: Once we diagnose keratoconus, we create a standard document that goes to the insurance company. It includes a clinical vignette of the patient showing progressive keratoconus and the need for cross-linking. We usually get a response for pre-determination in 4 to 6 weeks. If a patient doesn't need or want cross-linking, we bring them back every 6 months. We see younger patients at much more frequent intervals because their condition can deteriorate very quickly.

DR. HATCH: Some insurers have specific guidelines for defining progression, whether it's an increase in Kmax, a change in refraction, or failure of the contact lens. Sometimes, we don't have this information available, but I know the patient is progressing based on the history and the refraction. Often, young patients aren't wearing vision corrective visual aids, aren't complaining, and they can't tell they're getting worse. I try to always clearly document the subjective decline. This way, if I am challenged by an insurance company, I can demonstrate that the condition is progressive.

DR. RAJPAL: Whenever possible, we document progression using topography, but otherwise we use refraction to demonstrate increasing myopia or cylinder. We augment that with prior documentation from the referring provider, as well as old prescriptions.

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Cryopreserved Amniotic Membrane to Accelerate Corneal Healing

BY JAY MATTHEIS, MD

Bio-Tissue has been in the amniotic membrane space for more than 30 years, pioneering its use in ophthalmology. And, thankfully, we have this wonderful regenerative platform with PROKERA's cryopreserved amniotic membrane, which is the only product recognized by the FDA as having anti-inflammatory, anti-scarring, and anti-angiogenic properties. In the fetal environment, the amniotic membrane exists to serve and protect; on the eye, it promotes healing and protects from infection, scarring, haze, and inflammation. That's very important for many applications.

Technology and Clinical Use

The extracellular matrix (ECM) components found in cryopreserved amniotic membrane regulate and promote regenerative tissue processes.[1-3] In a head-to-head comparison between cryopreserved and dehydrated amniotic membrane, only cryopreservation maintained the quantity, quality, and activity of fresh amnion's key biosignaling factors (Heavy Chain-Hyaluronic Acid/Pentraxin3).[4] Dehydration changes the heavy chain hyaluronic acid to the light chain hyaluronic acid, which is known to be pro-inflammatory, so it doesn't have the same clinical efficacy. The spectrum of clinical uses for PROKERA ranges from moderate corneal-involved dry eye disease all the way up to chemical burns and stem cell dysfunction. Any condition that disrupts the corneal surface, whether it's a disease state or iatrogenic problem, is a potential use for PROKERA.

For more information on PROKERA, visit ***www.biotissue.com***

We commonly treat dry eye using PROKERA in our practice. In one study, dry eye patients with "pain and stain" had significantly better symptoms and increased corneal nerve density with PROKERA.[5] Another study of frustrated dry eye patients with "pain but no stain," also known as neuropathic corneal pain, showed that 3 to 7 days with PROKERA produced a statistically significant reduction in pain by 73% on average.[6] Finally, in the DREAM study, patients using PROKERA were compared to patients with other standard dry eye therapies. All signs and symptoms were significantly more improved in patients using PROKERA at 1 month and out to 3 months.[7]

We also use PROKERA often in our practice after cross-linking to prevent infection and inflammation and control pain. We also prescribe an antibiotic, a steroid, and an NSAID. We could use a bandage contact lens, however, PROKERA supports all of these goals: it is anti-inflammatory, it helps the eye to heal, and it prevents and/or reduces hazing and scarring.

In my experience, patients using PROKERA don't complain about the ring. Their symptoms are reduced. They feel better. The corneal nerves continue to regenerate, which will help the cornea and ocular surface remain healthy. Infection is rare, even in patients who have had herpes simplex in the past. It's an exceptional technology that allows us to help patients in ways that were simply not possible in the past. ❖

DISCUSSION

DR. RAJPAL: You use PROKERA for a spectrum of conditions. Has your use evolved over time? Specifically, what has your experience been with limbal stem cell deficiency?

DR. MATTHEIS: Initially, we only used PROKERA for very difficult cases, such as alkali burns. Seeing how well patients responded in these difficult cases helped me realize that it was possible to use cryopreserved amniotic membrane in less severe situations. It has been very effective for dry eye disease, for example.

One thing that we always talk about is if PROKERA will be uncomfortable to the patient. I always tell my patients to expect it. "You're going to be uncomfortable, and you'll be upset with me when you come back, but then you'll be very happy with the results." That has been working out very well. What impresses me is that if I don't send a recall in time, patients call me and say, "I think I need another one." It made me realize that even patients with moderate dry eye disease want their PROKERA back; it is that effective.

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Tying it All Together: Advanced Management of Keratoconus

BY NICOLE FRAM, MD

A 24-year-old college student and his parents were referred by his optometrist after noticing worsening vision in both eyes due to increased astigmatism. This is often a high-anxiety situation and requires a thorough explanation of the imaging tests performed and the reason for the pathology.

The working diagnosis in this patient, keratoconus, was confirmed by increased inferior steepening on topography and irregular astigmatism. Based on his prior records, it was evident the refraction increased from 3 diopters to 5 diopters of astigmatism over the course of 1 year. Previously, we had nothing to offer these patients except observation and a hard contact lens. However, now we can perform FDA-approved corneal cross-linking to potentially stop the progression of keratoconus. The patient and family were educated regarding the risks and benefits. The main risks of this procedure include corneal haze and bacterial keratitis. However, I always explain that, if monitored closely and carefully, the procedure is safe and effective.

A Safe, Effective Procedure

Preoperatively, we perform a thorough slit lamp exam, corneal topography and tomography, as well as anterior segment OCT with Epithelial Thickness Mapping (ETM) to help correlate the epithelial thickness with pachymetry. The epithelium is typically thinnest over the steepest part of the cornea. The corneal thickness should be at least 400 microns for safe cross-linking. Throughout the process, highly trained technicians who are partners in the cross-linking preparation and procedure give patients a great deal of information and comfort.

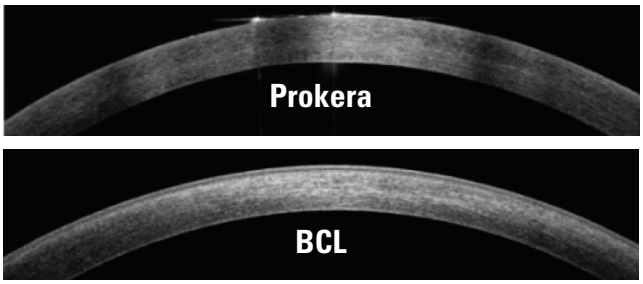
One pearl to avoid excessive dehydration of the cornea is to remove the lid speculum and close the eye during the loading of the riboflavin. If we were to keep the eye open with the speculum during the loading process, the cornea would dehydrate, causing the thickness to be <400 microns. If this occurs, we need to swell the cornea using Photrexa® (Avedro) until the corneal pachymetry measures >400 microns. Postoperatively, we customize care, but it always includes a topical antibiotic and a slow tapering of topical steroid. We bring patients back often, starting at day 1, day 3, and then 1 week. Once the epithelium heals, everyone can breathe a little easier, as the risk of infection is negligible.

Averting Corneal Haze and Bacterial Keratitis

The two things physicians should monitor for after cross-linking are corneal haze and bacterial keratitis. In addition to long-term low-dose steroid loteprednol ointment for 3 months, we bundle PROKERA into the cross-linking cost, so patients will also have the benefits of its anti-inflammatory effect.

My colleagues and I did an internal retrospective review of some cross-linking patients. Of 47 subjects, 24 had a bandage contact lens (BCL), while 23 patients received PROKERA immediately after surgery. PROKERA or the BCLs were all removed at day 4. We found that the PROKERA group epithelialized faster at day 7 (PROKERA 86%; BCL 73%). When we evaluated persistent corneal haze (grade 1+) at 3 months, we saw it affected 21% of eyes in the BCL group, but only 9% of PROKERA patients. The sample size is too small to be statistically significant, but the results are intriguing.

Patients who use PROKERA Slim will feel as if something is in their eye. The key is to give appropriate expectations and be there for patients if they are having trouble. I prepare patients in advance, telling them, "For 4 days, you're going to feel like something's in your eye. I'm here with you. If you really can't



Case Presentation: 1 month post operatively

These OCTs represent bilateral eyes of a patient who had PROKERA in the first eye and a BCL in the second eye. The patient had significantly more haze in the BCL eye and needed prolonged steroid treatment to clear the corneal haze.

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handle it, I'll take it out. But, please try to see it through." When they understand how this approach benefits their eye health, they are more motivated to use the technology.

An Exciting Future

Tying it all together, I think these technologies help us care for patients in a more systematic and clinically relevant way. We will use ETM as a baseline, and we'll look at topography and tomography. Then, we'll use epithelial thickness mapping again for post-op surveillance. It is exciting to see what we can do for patients with today's innovations. ❖

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DISCUSSION

DR. RAJPAL: Dr. Fram, you apply PROKERA in the OR on the day of the cross-linking procedure and bundle it. But cross-linking doesn't have a global post-op period. Do you sometimes apply it in the follow-up visits if the epithelium isn't healing? If so, are you able to bill for both separately?

DR. FRAM: If we need to, we can charge separately for PROKERA. In many cases, we will bundle this into our pricing to avoid issues with billing. Alternatively, one can apply PROKERA on day 1 or 2, noting a non-healing epithelial defect and billing the patient's insurance appropriately.

DR. RAJPAL: Dr. Mattheis, how has OCT enhanced your ability to follow your patients?

DR. MATTHEIS: When we treat dry eye prior to LASIK, we can flip through patients' repeated OCT maps each time they come back and say, "This is what you started out with. It is getting better, but not completely resolved." We can do the same thing if patients have dry eye post-LASIK. It's an objective tool for following patients, and the graphic colors and numbers make any differences very clear. We can even see very quick responses with artificial tears or prescription dry eye medications.

DR. RAJPAL: Dr. Fram, are you using Pentacam (Oculus) for the diagnosis of keratoconus as well as monitoring for progression?

DR. FRAM: Yes, I think Pentacam is the standard of care. It's important to understand how to correlate the steepening of topography with the thinning in the pachymetry, and now the epithelial thickness mapping that matches the thin area on pachymetry is important. I think we're providing a better level of care because we have this technology.

DR. RAJPAL: Whether we're using OCT or topography or Pentacam in particular for diagnosis, we all agree that early diagnosis is beneficial, as is following patients afterward.

DR. PARIKH: I encourage local optometrists that if they see new onset myopia or hyperopia refractive error, especially in a younger patient, they should perform or refer for a baseline topography and epithelial thickness map. If it doesn't reveal a problem, the patient should have a second one a few years later.

DR. RAJPAL: I've started telling some of the doctors we work with that if they see an increasing refractive shift — more cylinder or a dramatic increase in myopia — they should send those patients to me for imaging. And I think epithelial thickness mapping is going to help us diagnose keratoconus even earlier.