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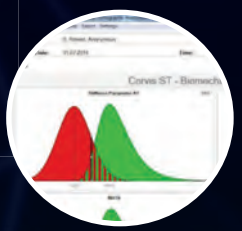

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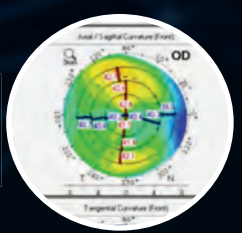
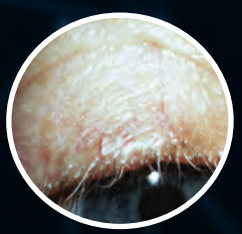


PREMIUM IOLS IN PATIENTS WITH CORNEAL CONDITIONS



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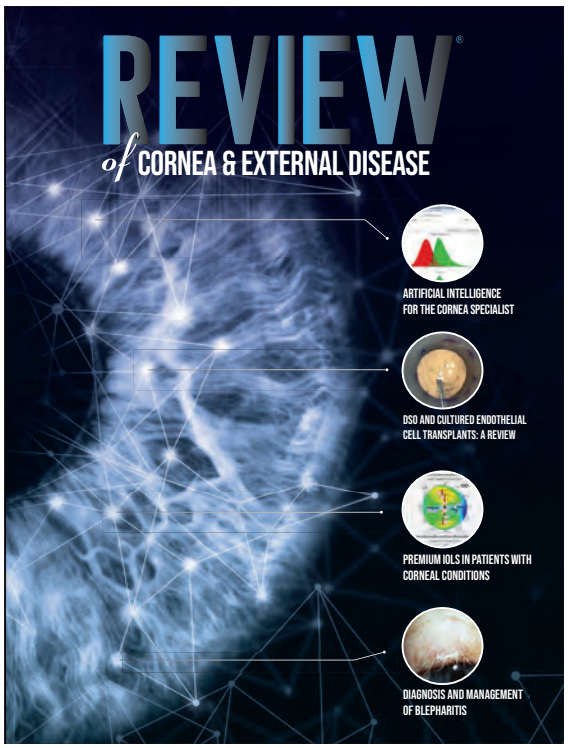

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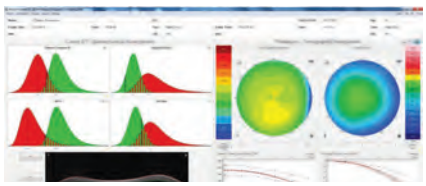


ARTIFICIAL INTELLIGENCE FOR THE CORNEA SPECIALIST

By
Christine Yue Leonard
Senior Associate Editor

The cornea subspecialty enjoys a variety of complementary technologies that rely on artificial intelligence to process vast amounts of generated data and aid clinical decision-making. In fact, AI algorithms for early keratoconus detection have been around since the development of computerized corneal topography in the late 1980s and early 1990s.

"The algorithms are widespread and performing well," says Bernardo T. Lopes, MD, MPhil, PhD, MRCS, FICO, of the University of Liverpool School of Engineering in the United Kingdom, the department of ophthalmology at Federal University of São Paulo and member of the Rio de Janeiro Corneal Tomography & Biomechanics Study Group. "As with everything in life, we're always seeking to improve what we have or coming back to already established machine learning algorithms to implement them into commercially available devices or websites. Algorithms and AI databases are supporting ophthalmologists around the world."

In this article, AI developers and experts share how AI is being used for corneal conditions, offer tips for working alongside algorithms and discuss future directions.

THE STATE OF CORNEAL AI

There are many types of AI processes used in cornea today. "Virtually any AI process can be involved in diagnosis, grading or treatment," Dr. Lopes says. "Some AI processes include algorithms using different neural network architectures for vector machine decision trees or random forests, with different degrees of success *(see sidebar for terms)*. We use these not only for screening but also for corneal surgeries. We have algorithms that were designed to predict visual outcomes after refractive surgery and to optimize intracorneal ring implantation and limbal relaxing incisions."

Much of the buzz in the news around AI innovation in recent years has been centered on the advent of two autonomous AI systems, IDx-DR and EyeArt, for large-scale diabetic retinopathy screening. AI experts say it's possible but less likely that corneal AI will follow this autonomous path. "Before the AI era, we had already been doing a lot of screening for retinal conditions such as DR, glaucoma suspects, AMD and myopia, so adding AI just made sense," explains AI expert Daniel Shu Wei Ting, MD, PhD, of the Singapore Eye Research Institute at the Singapore National Eye Centre. "Having said that, compared with retinal conditions, there aren't as many corneal conditions that require repeated screening, especially at a population level. Corneal conditions usually require specialist evaluations. Based on horizon scanning of the market size for ophthalmology, corneal diseases make up less than retinal diseases, so most R&D funding is going toward the posterior segment."

One goal that AI developers share is what Dr. Ting refers to as the "democratization of expertise." "There's a lack of corneal specialists in many parts of the world," he says. "If we build AI algorithms around the top experts, package and embed them into different laser and refractive technology, that would be a powerful way of making refractive surgery really safe for many more patients. Developing better segmentation algorithms, for example, will lead to better diagnoses and detection of abnormal areas in the scan.

"Machines are getting smarter," he continues. "We need to ask ourselves: How do we use AI and data to make things simple yet safe? This is a major trend in health care overall." Dr. Ting is currently involved with several industry and imaging companies looking in this direction.

As an editorial member of several peer-reviewed journals, many corneal AI projects come across his desk. "Most of the projects in corneal diagnosis are focused on the classification domain," he says. "Building a classifier involves datasets and a yes/no response for presence of disease. I also see many segmentation algorithms for corneal layers, which will aid in planning operations as well as postop surveillance—how's the graft doing? Are there signs of early rejection, inflammation or infection?"

KERATOCONUS DETECTION

The progressive nature of ectasia makes early detection key.[1] "We don't need an AI algorithm to tell us whether a patient has frank keratoconus," says corneal specialist Jodhbir S. Mehta, MBBS, FRCOphth, FRCS(Ed), PhD, of the Singapore Eye Research Institute. "Instead, we want these algorithms to differentiate cases of subclinical keratoconus from normal eyes. This is often a gray area."

"AI can help us differentiate subclinical cases because it makes sense of subtle signs that may not otherwise be highlighted in the amount of data we collect," Dr. Lopes says. "When you analyze this information with artificial intelligence, you build the whole picture."

Diagnostic imaging usually includes corneal topography with Placido disc-based imaging systems, 3-D tomographic or Scheimpflug imaging and AS-OCT.[2] AI algorithms integrate data from these systems to differentiate cases of keratoconus and forme fruste keratoconus from normal eyes, using AI approaches such as feedforward neural networks, convolutional neural networks, support vector machine learning and automated decision-tree classification of corneal shape.[2] All of these algorithms are highly precise for keratoconus detection, experts say, with accuracy, sensitivity and specificity rates ranging from 92 to 97 percent.[2] Machine learning has been shown to improve imaging devices' ability to diagnose subclinical disease.[3]

Subclinical differentiation remains challenging, however, despite the fact that AI algorithms have made great leaps. One study conducted in 2017, with no company ties, examined the diagnostic ability of three Scheimpflug devices—Pentacam (Oculus); Galilei (Ziemer); and Sirius (Costruzione Strumenti Oftalmici, Florence, Italy)—in differentiating normal and ectatic corneas.[4] Direct comparison wasn't possible since each machine uses different indices for keratoconus screening. All three devices were effective for differentiating keratonic eyes from normal eyes, but the researchers noted that the cutoff values provided by earlier studies and by manufacturers aren't adequate for differentiating subclinical cases from normal corneas.

The study included 42 normal eyes, 37 subclinical keratoconic eyes and 51 keratoconic eyes. A keratoconus diagnosis

ARTIFICIAL INTELLIGENCE TERMS

Here are some brief descriptions of AI processes mentioned in this article:[17]

- **Feedforward neural network (FNN)** is a type of AI network that processes information in one direction.
- **Convolutional neural network (CNN)** is a deep learning algorithm used primarily to analyze images. The algorithm takes an input image, assigns importance to certain aspects of the image and then differentiates one image from another.
- **Support vector machine learning (SVM)** is a type of supervised learning model that analyzes data for classification and regression analysis. Using "hyperplanes," or decision boundaries, the AI classifies data points. Support vectors are the data points closer to the hyperplane. They influence the hyperplane's position and orientation, and define the margins of a classifier.
- **Automated decision-tree classification** is a type of predictive modeling that moves from observations to conclusions to classify a variable. These algorithms use if/else questions to arrive at a decision.
- **Random forests or decision forest models (DFM)** use multiple individual decision trees that operate simultaneously to classify data. Each decision tree produces a class prediction and the class prediction occurring most often is the random forest's prediction. Multiple trees protect against individual errors.
- **Random survival forests (RSF)** are a type of random forests method usually used in risk prediction.

sensitivity of 100 percent was observed in six parameters on Pentacam and one parameter on Galilei. For subclinical keratoconus, 100-percent sensitivity was observed for two Pentacam parameters. All parameters were strong enough to differentiate keratoconus (AUC>0.9). The authors found that the AUC of the Belin/Ambrosio enhanced ectasia total derivation and the inferior-superior value of Pentacam were statistically similar to the Galilei's keratoconus prediction index and keratoconus probability (Kprob) (p=0.27), and to the Sirius' 4.5-mm root mean square per unit area (RMS/A) back (p=0.55). For subclinical differentiation, BAD-D was similar to the Galilei's surface regularity index (p=0.78) and significantly greater than the Sirius' 8-mm RMS/A (p=0.002).

In 2018, an unsupervised machine learning algorithm developed by Siamak Yousefi, PhD, and colleagues, labeled a small number of normal eyes as having mild keratoconus.[5] The researchers hypothesized that these eyes may have had FFKC. The algorithm was trained on 12,242 SS-OCT images and analyzed 420 principal corneal components. A total of 3,156 eyes with Ectasia Status Indices of zero to 100 percent were analyzed in the study. The algorithm had a specificity of 97.4 percent and a sensitivity of 96.3 percent for differentiating keratoconus from healthy eyes.

A 2020 study identified a possible predictive variable for subclinical disease differentiation. The study described an automated classification system using a machine learning classifier to distinguish clinically unaffected eyes in patients with keratoconus from normal control eyes.[6] A total of 121 eyes were classified by two corneal experts into normal (n=50), keratoconic (n=38) and subclinical keratoconus (n=33). All eyes underwent Scheimpflug and ultra-high-resolution OCT imaging, and a classification model was built using all features obtained on imaging. Using this classification model, the algorithm was able to differentiate between normal and subclinical keratoconic eyes with an AUC of 0.93. The researchers pointed out that variation in thickness profile of the corneal epithelium, as seen on UHR-OCT, was the strongest variable for differentiating subclinical keratoconic from normal eyes.

A review of machine learning's accuracy in assisting in detection of keratoconus, published in the *Journal of Clinical Medicine* this year, reported that machine learning has the potential to improve diagnosis efficiency but "Presently, machine learning models performed poorly in identifying early keratoconus from control eyes and many of these research studies didn't follow established reporting standards, thus resulting in the failure of clinical translation of these machine learning models." The authors suggested this is due in part to a lack of large datasets and differences between corneal imaging systems.[7]

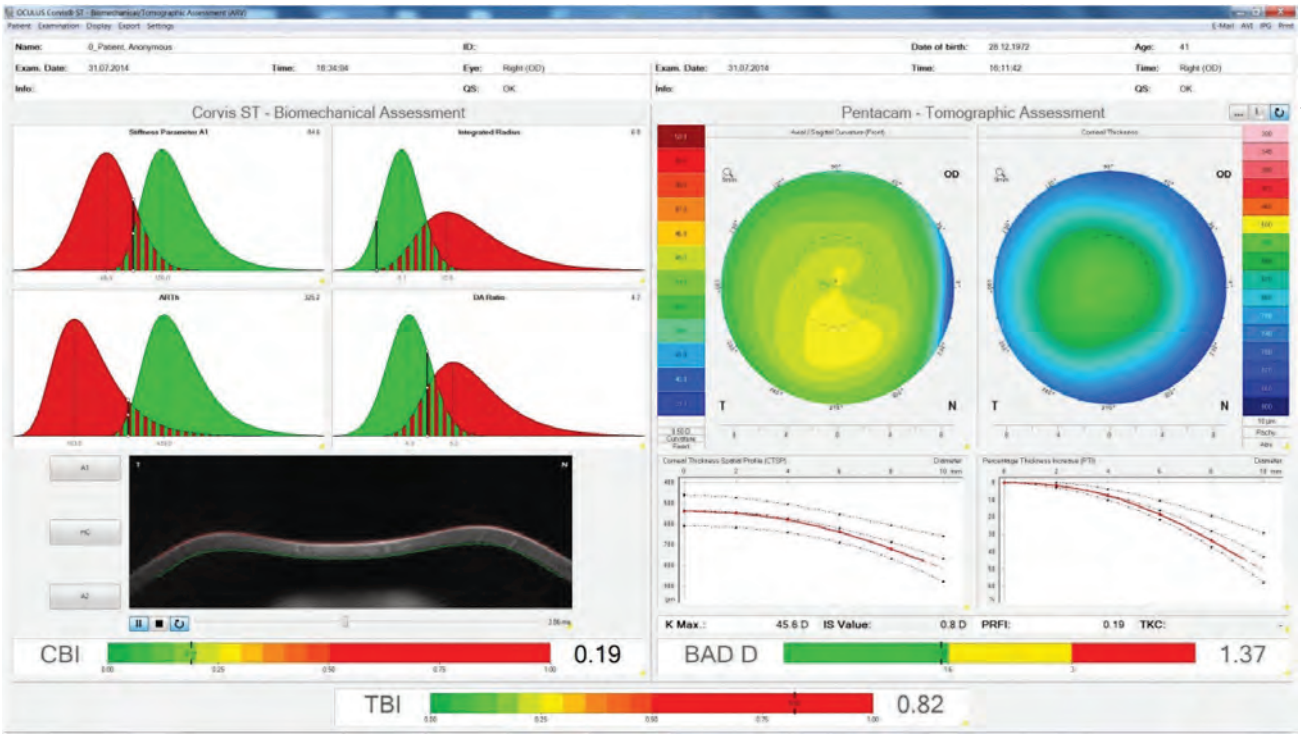
Experts point out that while the AI algorithms in your diagnostic imaging devices are powerful and consider a host of variables, it's still a good idea to consider the raw data and confirm the AI's analysis with other diagnostic testing. AI still isn't a replacement for a physician's judgment, they say.

REFRACTIVE SURGERY

Uncorrected refractive error is a leading cause of decreased vision around the world. Experts say that AI-based refractive surgery screening will play an important role as more patients seek refractive surgery. Current data shows that AI-based screening models are effective at identifying good surgical candidates.[8] "I use AI the most for refractive surgery screening," says Dr. Lopes. "It's useful for when you have a challenging case and you're in doubt as to whether the cornea would tolerate LASIK surgery."

Tyler Hyungtaek Rim, MD, MBA, a clinical scientist at the Singapore Eye Research Institute, and colleagues developed a machine learning clinical-decision support architecture to determine a patient's suitability for refractive surgery.[9] Five algorithms were trained on multi-instrument preoperative data and the clinical decisions of highly experienced experts for 10,561 subjects. The machine learning model had an accuracy of 93.4 percent for LASIK and SMILE. The model (ensemble classifier) with the highest prediction performance had an AUC of 0.983 (95% CI, 0.977 to 0.987) and 0.972 (95% CI, 0.967 to 0.976) on the internal (n=2,640) and external (n=5,279) validation sets, respectively.

The researchers reported that the machine learning models performed statistically better than classic methods such as the percentage of tissue ablated and the Randleman Ectasia Score. They noted that machine learning algorithms that use a wide range of preoperative data can achieve results comparable to physician screening and can serve as safe and reliable clinical decision-making support



This is the contralateral unoperated right eye of a patient who developed post-LASIK ectasia in the left eye. You can see that the while the individual tomographic and biomechanical indices are normal (BAD-D and CBI), the evaluation of them in combination using AI shows the high risk of this case.

for refractive surgery.

AI algorithms are also being used to predict refractive surgery outcomes, including risk of post-LASIK ectasia.[1] So far, the literature suggests that AI performs similarly to experienced surgeons in terms of safety, efficacy and predictability.

A decision forest model created from feature vectors extracted from 17,592 cases and 38 clinical parameters from patients who underwent LASIK or PRK surgeries at a single center effectively assessed risk with high correlation between actual and predicted outcomes (p<0.001).[10] The researchers reported efficacy (the ratio of preop CDVA and postop UDVA) of 0.7 or greater and 0.8 or greater in 92 percent and 84.9 percent of eyes, respectively. Efficacy less than 0.4 and less than 0.5 was achieved in 1.8 percent and 2.9 percent of eyes, respectively.

Interestingly, they noted that eyes in the low efficacy group had statistically significant differences compared with the high efficacy group but were clinically similar. For example, patients in the lower efficacy group were somewhat older, had smaller scotopic pupil size and lower treatment parameters for sphere and cylinder. Preoperative subjective CDVA was the most important variable in the model. The researchers also reported that correlations analysis showed significantly decreased efficacy with increased age, central corneal thickness, mean keratometry and preoperative CDVA (all p<0.001); and increased efficacy with pupil size (all p<0.001).

AI-based cataract diagnosis and severity grading using slit-lamp photography and fundus photos have also demonstrated success with high accuracy, sensitivity and specificity.[1] One group created a validated deep-learning model that could differentiate cataract and IOL from a normal lens (AUC>0.99) and detect referable, grades III-IV cataract (AUC>0.91), subcapsular cataract and PCO.[10]

CORNEAL ULCERS

AI has strong potential for use in diagnosing corneal ulcers and dystrophies because these conditions are easy to image with photography or other diagnostics. "The most common cause of corneal ulcers around the world is bacteria, followed by viruses, and in certain rural regions and countries such as India and China you see high levels of fungal keratitis," says Dr. Mehta. "We're training AI algorithms to differentiate these conditions."

Dr. Mehta was involved in a study of corneal ulcers that demonstrates the potential for AI's democratization of expertise. "We were involved in a study where ophthalmologists around the world were randomly shown a series of patient photographs from India that were culture-positive for either bacterial or fungal keratitis," he says. "We measured diagnostic accuracy and then compared the results of the surgeons based in India with those based outside of India, such in the United States, United Kingdom, Europe and other Asian countries. Basically, we were able to show that when you look at it as a cohort, the surgeons who were best able to pick up fungal keratitis were, unsurprisingly, the surgeons who saw the most cases of fungal keratitis—the doctors in India. The AI software, based only on a slit-lamp imaging protocol, was

BLOCKCHAIN TECHNOLOGY FOR AI EVALUATION

You've probably heard about blockchain in the context of cryptocurrencies like Bitcoin. Blockchain is a decentralized, immutable ledger that records digital assets with encryption technology. Each "block" is timestamped, providing proof that a data transaction occurred when a block was published. Each block contains information about the previous block. They're chained together and can't be altered retroactively.

How does this relate to AI technology? "There's a term called privacy preserving technologies or PPT, which helps to mitigate data-sharing problems," says Daniel Shu Wei Ting, MD, PhD, of the Singapore Eye Research Institute at the Singapore National Eye Centre. "Different countries have different data sharing and data privacy rules. The United States, the United Kingdom, the EU and Asian-Pacific countries all have different sets of rules. How can you facilitate cross-border collaborations without sharing data? How do you share without needing it to be physically transferred from one country to another?

"This is where blockchain comes into play," he says. "Blockchain is secure and it's an immutable platform. Once something is published on it, it can't be changed. If there's an update, there's always a trail to show the order in which something was changed.

"We've piloted a project examining how we can use a blockchain platform to govern the AI testing process," Dr. Ting continues. "I receive a lot of AI papers for peer-review, and one of the challenges I often face, especially when I'm reviewing articles as an editor, is that I don't know how true the result is. The studies all report something like an AUC of 98 percent or a sensitivity more than 95 percent, and everyone claims to have the best software. How do you actually appraise these studies? How do you test the algorithms? Some journals such as *The Lancet* or *Nature* have a data availability statement or an AI algorithms availability statement. So, if you request the data, the researchers will send it to you.

"I tried this once and reached out to the researchers," he says. "I said, 'I'd like to test the algorithm's reproducibility against what was submitted to be published.' I ran into problems with data privacy rules. Researchers would tell me, 'I can't send you the data because my tech transfer office told me it's against such-and-such rule' or the AI is licensed. So your hands are tied: Do you trust the people or reject the paper? These are things that are happening with many AI papers right now."

He says that using a blockchain ecosystem could help create a trusted environment. "It's a bit like an audit for your taxes," he explains. "You may submit your tax return and everything's fine and no one bothers you. But when something unusual happens, we need to investigate. If an AI algorithm gets FDA approval, and then hits its implementation space and the AUC is still consistently showing something like 96 or 97 percent, then no problem. No one's going to open up the black box of your algorithm and look. But if the paper submitted claims a 98 percent AUC and when it hits its real-world implementation its performance is significant lower, we want to know why so we can fix it. It might be an honest mistake, but we need to see what was done in the past.

"To do this, we would go back to the original algorithm and the data sets used, but if you go back three or four years, many researchers aren't able to provide you with the same dataset or the same algorithm because there have been new versions and updates but no permanent records of past changes," he says.

"We can use blockchain to help correct problems that might arise," he says. "If you submit an AI to the FDA, a hash value comes with your algorithms and datasets. If I do an audit of the algorithm and dataset four years later, it'll match the original hash values and we can see that maybe it was just bad luck and fix the problem."

superior to all of the doctors.

"So, what this shows is that diagnostic accuracy for doctors not working in areas with high levels of fungal keratitis is lower," he continues. "In the U.K., we probably see only a few fungal keratitis cases each year. In Singapore, we see many more cases of bacterial infection, even though we're in a tropical climate zone.

"This type of AI software will help improve diagnostic accuracy," Dr. Mehta says. "Bacterial samples can take days to culture, and fungal samples often take weeks before we get a response. Of course, you have to treat the patient in the meantime. Typically, we treat patients empirically, but with the software, we're able to get an idea of diagnostic accuracy sooner. This could help many patients, especially when there isn't access to a laboratory."

Dr. Mehta says artificial neural networks (ANN) have the potential to turn around results faster and more accurately than traditional diagnostic methods, which involve corneal scraping, microscopy, staining and culturing, and have a culture positivity rate of only 33 to 80 percent.[11] One ANN was able to classify 39 out of 43 bacterial and fungal ulcers correctly with an accuracy of 90.7 percent, compared with a clinician rate of 62.8 percent ($p<0.01$), and a specificity of 76.5 percent and 100 percent for bacterial and fungal ulcers, respectively.[12]

A 2020 report in *Nature* described a novel deep learning algorithm for slit-lamp photography that had high sensitivity and specificity for detecting four common corneal diseases: infectious keratitis; non-infectious keratitis; corneal dystrophy or degeneration; and corneal neoplasm.[13] The algorithm was trained to detect fine-grained variability of disease features on 5,325 ocular surface images from a retrospective dataset. It was tested against 10 ophthalmologists in a prospective dataset of 510 outpatients. The AUC for each disease was more than 0.91, and sensitivity and specificity were similar to or better than the average values for all the ophthalmologists. The researchers noted that there were similarities in misclassification between the human experts and the algorithm. Additionally, they cited a need for improvement to

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overcome variations in images taken by different systems, but concluded that this algorithm may be useful for computer-assisted corneal disease diagnosis.

One of the challenges that AI will need to overcome in corneal infection diagnosis is concomitant disease. "About 40 to 50 percent of cases are mixed infections, and that's going to be much more challenging for us to program and for an AI to pick up," says Dr. Mehta. "How do you differentiate a viral infection on top of a bacterial infection, or a bacterial infection on top of a viral infection, or polymicrobial bacteria and fungus? Right now, the software also won't give you an idea about resistance, though it could provide some guidance on antibiotics or other treatments. Understanding the dynamics of how this will affect treatment will be challenging. To do this, we'll need very large datasets to examine response rates to drugs."

He says that AI may be advantageous for analyzing *in vivo* confocal microscopy images. "Confocal microscopy machines are fantastic, but they produce a lot of images and data," he says. "Analyzing and screening these images is something that can be done using AI software. The software could pick up Acanthamoeboid cysts or hyphae filaments.

"An additional challenge is that confocal pictures of infection are often very light-colored, so you need to understand the granularity of the software to be able to pick up good images and areas of interest from a background that's very white or inflamed or scarred," he explains. "Sometimes the software will miss things, so again, big datasets are needed to refine training algorithms and perform validation."

"An AI algorithm is only as good as the data it's trained with," Dr. Lopes agrees. "The main problem we have now is the size of the datasets used to train algorithms. You'll see papers published with as few as 30 days of training to perform a complex task, such as combining topography and tomography to detect ectasia. That will almost certainly overfit the training data and won't be able to perform as well.

"Another challenge lies in the very nature of corneal data," Dr. Lopes continues. "Like most biological data, it's noisy. There are random fluctuations that interfere with the signal effect or the feature or pattern you're trying to detect. If you measure the same eye twice, you won't have the same outcome because of these random fluctuations. They can be as high or as important to mask an actual feature you're trying to detect. So, dealing with noise is a challenge for algorithms to handle, and it's hard to get big samples to correct for this."

"THERE'S BEEN A DIGITAL TRANSFORMATION, AND NOW THERE'S MORE ACCEPTANCE OF VIRTUAL DIAGNOSES AND TELEHEALTH. THESE MAY REVOLUTIONIZE THE WAY CORNEAL DIAGNOSES ARE MADE."

—DANIEL SHU WEI TING, MD, PHD

CORNEAL TRANSPLANTS

One of the well-known difficulties with DMEK is getting the graft to adhere to the endothelium with as little manipulation as possible. "There's some work using AI software and machine learning models that's trying to understand which grafts will stick and which ones won't, and the behavior of grafts—whether or not they need to go back for rebubbling after basic surgeries," says Dr. Mehta.

A study presented at ASCRS in 2020 reported successful graft rejection diagnosis with a novel autonomous AI algorithm.[14] A total of 36 eyes with corneal grafts were imaged using AS-OCT, and a deep learning AI algorithm from Bascom Palmer was used to evaluate the graft scans. The researchers compared the AI's results to clinical diagnoses of Bascom Palmer corneal experts. The corneal experts diagnosed 22 grafts as healthy and rejected 14 of them. The AI algorithm correctly diagnosed all healthy grafts and 12 of 14 rejected grafts. For rejection diagnosis, the AUC was 0.9231 with a sensitivity of 84.62 percent and specificity of 100 percent.

Another study published in *Cornea* reported positive early results with a deep-learning-based method to automatically detect graft detachment after DMEK.[15] The researchers trained an algorithm on 1,172 AS-OCT images (609 attached, 563 detached) to create a classifier. The mean graft detachment score was 0.88 ±0.2 in the detached group and 0.08 ±0.13 in the attached graft group ($p<0.001$). Sensitivity was 98 percent, specificity was 94 percent and accuracy was 96 percent. The authors say further work is needed to include the size and position of the graft detachment in the algorithm.

The Singapore National Eye Centre published a paper in June of this year using machine learning to analyze factors associated with 10-year graft survival in Asian eyes.[16] The algorithm included donor characteristics, clinical outcomes and complications from 1,335 patients who underwent DSAEK (n=946) or PK (n=389) for Fuchs' dystrophy or bullous keratopathy. The researchers used random survival forests analysis to determine the optimal Cox proportional hazards regression model. They found that male sex (HR: 1.75, 95% CI: 1.31 to 2.34; $p<0.001$) and poor preoperative visual acuity (HR: 1.60, 95% CI: 1.15 to 2.22, $p=0.005$) were associated with graft failure.

"AI is also being developed for monitoring patients after transplants," Dr. Mehta says. "We look at the endothelial cell count to get an idea of how healthy the cells are, and this gives us a surrogate marker of how long the graft will survive. There are now several tools available with software to perform cell counting. The problem is that sometimes imaging can be poor, and you need really good-quality images, or you won't have a true idea of

how the graft is functioning. AI software may help to provide better cell data, even if the image quality is poor. However, this has all been done in a research setting so far, not in a clinical setting, so how useful this AI tool will be for monitoring post-corneal transplant patients remains to be seen."

Dr. Mehta says advances in our understanding of the genetics of Fuchs' dystrophy may aid AI-customized transplant procedure planning. "We have much more genetic information on the disease now, and I think there's an opportunity to link imaging to genetics," he says. "From a surgical standpoint, we're working toward approaches that don't require removal of the whole endothelium, but rather just in a specific area around the disease pathology. AI is helping us diagnose and understand who will be a good candidate for a procedure such as DSO. An algorithm could guide you with respect to how much tissue to strip and where the diseased area is, specifically. We never imaged the endothelium much before because we were just stripping the whole thing off."

BUY-IN

Many of these newer algorithms need a lot of work and validation on larger datasets before they're ready for clinical prime time. Dr. Ting says an additional obstacle they may face is acceptance by corneal specialists. "Speaking with corneal specialists before COVID, many didn't seem to think that AI can do a better job than a Gram stain or current culture sensitivities, so a few years ago I would have said that the buy-in from corneal specialists may take some work," says Dr. Ting. "But as you know, technology is getting smarter, and the aging population has resulted in a shortage of medical expertise, and then we had a pandemic, so there's a lot that's changed in people's mindsets in the past two years. There's been a digital transformation, and now there's more acceptance of virtual diagnoses and telehealth. These may revolutionize the way corneal diagnoses are made."

What's most important for a clinician to keep in mind when using a tool that has AI? "It's not perfect," says Dr. Mehta. "There's no software that I've seen with an AUC of 0.9999, so there will always be an error rate. Some people are worried about being replaced by AI. In radiology, for example, AI can pick up things from CT scans and the like, and AI may be better at that than humans. But will it replace the doctor making clinical decisions? I don't think so.

"Consider all the machines we have now for tomography or biomechanics," he continues. "Those systems help you make a better decision for your patient and improve their outcome. I think that's the role of AI—to help the clinician make the best decision, not to dominate the process. The ultimate decision will be with the surgeon. That's a responsibility that's never going to go away. You won't say, 'Oh, but the AI software told me to do such and such.' That's not going to happen. There are limitations to using AI, and it's important to understand that it's a tool to guide you with as much knowledge as possible."

THE FUTURE

"In the future, but probably not in the very near future, we may have completely automated diagnostic systems for different corneal conditions, like in other areas of medicine," says Dr. Lopes. "Refractive screening is probably closest to this. We already have similar tools for retinal disease screening.

"The main challenge of reaching this future is data," he says. "You need hundreds of thousands of cases to train an algorithm well. We need more centralized data centers with good-quality information if we want proper automated diagnostics or more advanced surgical planning tools. But AI has been around for more than 30 years now, and there's high acceptance of current tools. I'm optimistic about the future."

Dr. Mehta has no financial ties to AI-related technology. Dr. Ting is the co-inventor of a deep learning system for retinal disease. Dr. Lopes is a consultant for Oculus.

"THE ULTIMATE DECISION WILL BE WITH THE SURGEON. THAT'S A RESPONSIBILITY THAT'S NEVER GOING TO GO AWAY."

— JODHBIR S. MEHTA, MBBS, PHD

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DSO AND CULTURED ENDOTHELIAL CELL TRANSPLANTS: A REVIEW

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The past 15 years have seen a lot of change in corneal transplantation for conditions such as Fuchs' endothelial dystrophy, with endothelial transplant methods taking over from penetrating keratoplasty. However, there's an even newer wave of transplant techniques on the horizon, which may help decrease the amount of tissue needed to treat patients while maintaining safety and efficacy. Here, we'll detail the latest techniques surgeons are working on to circumvent this problem, as well as to help decrease tissue rejection.

THE PUSH FOR NEW TECHNIQUES

Human corneal transplantation has substantially evolved due to the improvement of surgical technique since its first successful attempt in 1905. The paradigm of the surgical approach has shifted from full-thickness transplant to partial-thickness transplantation for specific diseased tissue layers. Over the past few decades, endothelial keratoplasties have begun to supplant penetrating keratoplasty as the most common corneal transplant procedure. Descemet's membrane endothelial keratoplasty is a particularly common EK procedure that involves selective transplantation of only the endothelium and Descemet's membrane without stroma. The transplantation of less tissue in DMEK allows for minimal surgical manipulation, more predictable outcomes and enables faster restoration of the corneal anatomy with fewer complications. However as one may predict, the increasing success of EKs comes with an increasing demand for donor corneas, for which there is currently a severe global shortage.

DESCEMET'S STRIPPING ONLY

To circumvent the need for donor tissue and risk of possible graft rejection, the procedure of Descemet Stripping Only was introduced. It involves a descemetorhexis to remove the dysfunctional endothelial cells without a graft. The peripheral endothelial cells then migrate to the stripped area and regenerate the central posterior cornea.[1,2] The DSO procedure is considered a viable treatment option for patients who have localized endothelial disease within the central 5 mm of the cornea and have a clear periphery endothelial layer with cell density >1,000 cells/mm^2. Compared to an 8-mm descemetorhexis traditionally performed in DMEK, the descemetorhexis in DSO is usually only 4 to 5 mm. Another benefit of this procedure is that there's no need to use long-term topical corticosteroids to prevent graft rejection, and hence there is no potential risk of steroid-induced intraocular pressure elevation.

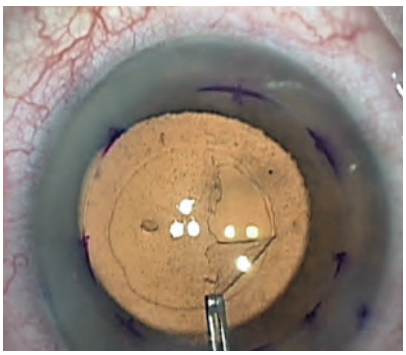
The feasibility of this procedure is based on prior *ex vivo* studies and clinical observations.[1-3,5-10] Endothelial cells derived from Fuchs' endothelial cell disease patients have been shown to proliferate *in vitro* without viral transduction.[3] The cells are generally thought to proliferate until they come into contact with one another, e.g., contact inhibition, at which point they go into cell cycle arrest. When comparing endothelial

cells isolated from the central cornea vs peripheral cornea, peripheral cells have a higher proliferation rate when grown *ex vivo* or *in vitro*. Hence, these peripheral cells are thought to migrate to the central cornea after DSO and then proliferate in the space. Clinically, this has been observed by one group of researchers, who reported migration of endothelial cells into denuded corneal stroma after DMEK in five patients with Fuchs' endothelial dystrophy.[1]

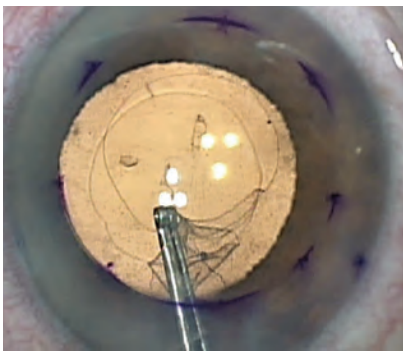
A recent review has summarized the outcomes of 47 eyes with Fuchs' endothelial cell disease that underwent DSO.[4] The patient population had an average age range from 34 to 91 years, and the diameter of the descemetorhexis ranged from 4 to 9 mm. Postop, a clear cornea was observed in 65 percent of eyes, with improvement noted within a month. However, the success rate has been variable. One study reported a corneal clearing with improved visual acuity in three of eight cases that underwent DSO with cataract surgery,[5] although all patients eventually underwent EK.

On the other hand, another study reported 10 of 13 eyes with resolution of corneal edema with an intact central endothelial mosaic at six months and only three eyes had to eventually undergo EK.[6] Similarly, in nine patients who underwent DSO with or without cataract surgery, the average time to achieve recovery of vision was 6.5 weeks.[7] However these patients also had a 10-percent decrease in peripheral endothelial cell count over the 12-month postop period. A separate group performed a retrospective study to determine predictive factors that may lead to better outcomes after DSO.[8] However, their review failed to show any significant predictive factors between success and failure groups based on age, pachymetry and endothelial cell count. Nonetheless, many authors have suggested there are better outcomes in general when a smaller central descemetorhexis (4 mm) is performed.

Overall, DSO is a relatively new treatment option with early data suggesting that it's effective in Fuchs' patients with localized endothelial disease within the central 5 mm of the cornea. While DMEK or DSEK remains the gold standard, DSO provides an alternative if donor tissue isn't readily available, graft rejection is a concern or postoperative steroid use is undesirable. Surgeon experience and focus are important when performing the gentle descemetorhexis necessary to reduce any roughening of the posterior stroma that could impede endothelial cell migration and repopulation.



The initial part of the Descemet's Stripping Only procedure. Also seen is the pre-existing anterior capsulorhexis opening.



The completed DSO procedure and the surgically detached disc of Descemet's membrane with compromised endothelial cells. The pre-existing capsulorhexis opening is also visible.

Images courtesy Mark A. Terry, MD

CULTURED ENDOTHELIAL CELL TRANSPLANTS

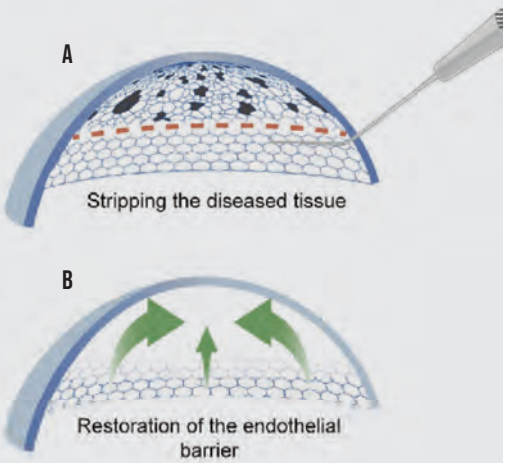
Another new treatment option as an alternative to replacing damaged endothelial cells is the transplantation of engineered corneal tissue created through endothelial cells expansion.[11] This novel approach relies on the *in vitro* proliferation of isolated corneal endothelium cells (CECs), which is an attractive way of providing an unlimited source of cells to overcome the donor cornea shortage. However, the engineering technology used to promote endothelial cell proliferation *in vitro* and facilitate *in vivo* transplantation is challenging. Although human corneal endothelial cells have limited proliferative capacity as the cell cycle held in the G1 phase *in vivo*, studies showed that they can expand *in vitro*.[12-14] Understanding endothelial cell biology and using promoting factors can thus provide an effective way to master the engineering technique.

Corneal endothelium engineering procedures include crucial steps such as tissue removal, cell isolation, culture and implantation to the recipient's eyes with or without a carrier. Different sources of autologous or heterologous cells have been used in corneal endothelium expansion.[14-20] The crucial requirement for endothelial cell culture is a source of viable, proliferative cells. Primary corneal endothelial cells isolated from cadaver donors, peripheral corneal endothelial stem cells or organ-specific adult stem cells can be used as good sources for corneal endothelial cell culture.

Cadaver donor characteristics such as age, proliferative capacity and cell density significantly determine the success of cell culture. Of note, in one study, young donors showed higher endothelial cell density, better proliferative capability and cell homogeneity than old-aged donor corneas.[14] The study categorized young donor corneas as being from donors under age 30 and the old-aged cornea as those from donors older than 50. The endothelial cell density at age 20 to 40 is about 3,000 cells/mm^2, and decreases to around 2,700 cells/mm^2 at 50 to 70 years of age. In addition, young donors have more proliferative cells (47 percent) than the older donor group (23 percent). While human corneal endothelial cells from young donors expressed "Ki-67" 36 hours after wounding, indicating that cells were active in the late G1 phase through to the M phase to represent cell proliferation, the endothelial cells from older donors delayed cell proliferation until 48 hours. A study revealed that endothelial cells from donors could be expanded up to the third passage while maintaining their polygonal cell shape.[21-23] However, cultured human corneal endothelial cells from old donors lost their unique polygonal morphology and presented more heterogeneity in the fourth and fifth passages when compared to young donors. Although corneal endothelial cells from young donors are preferred to optimize *in vitro* cell culture, most young donor corneas won't be easy to obtain because they are consumed in clinical corneal transplantation. Thus, *in vitro* culturing

DESCEMET'S STRIPPING ONLY

- 4 to 5 mm descemetorhexis to remove the dysfunctional endothelial cells without a graft
- Peripheral endothelial cells then migrate to the void and regenerate the central posterior cornea
- Useful for patients with localized endothelial disease within the central 5 mm of the cornea and have a clear periphery endothelial layer with cell density >1,000 cells/mm^2



cells from old-aged donors becomes relatively challenging.[24]

The cells from the peripheral endothelium (2.75 mm) can be an alternative resource other than the central cornea (8.25 mm). Peripheral corneal endothelial cells with the proliferative potential to differentiate into mature endothelial cells have been referred to as human corneal endothelial progenitor cells. These progenitor cells, expressed neural crest cell markers, p75 Neurotrophin receptor, SOX9, FOXC2, stem/progenitor markers (Sox2, Lgr5, CD34, Pitx2, and telomerase), are found in the peripheral and transition zones of the cornea. Other specific stem cell markers (Nestin, ALP, and telomerase) are found at the trabecular meshwork and the transitional zone between trabecular meshwork and the peripheral area of the cornea.[25] After wounding, peripheral corneal endothelial cells presented proliferative marker expression (BrdU and TGF-β), and increased differentiation markers (Pax6, and Sox2), whereas Oct-3/4 was found in the trabecular meshwork and Wnt-1 in both trabecular meshwork and transitional zones.

As immune-mediated graft rejection can be avoided by providing cultivated autologous corneal endothelium cells, we focus on autologous, easily accessible adult stem cells. Studies reported that organ-specific adult stem cells used for endothelial cell culture are from adipose tissue, umbilical cord blood or bone marrow, directed differentiation competent embryonic stem (ES) cells, induced pluripotent stem cells (iPSC), skin-derived precursors (SKP) and mesenchymal stem cells (MSCs).[14-20] However, the concerns with culturing these stem cells are that both mechanisms of corneal endothelial cell embryonic developmental steps and cell reprogramming-differentiation pathways remain unclear. They may present heterogeneous proliferative and differentiation capacities and unexpected morphological results after differentiation, thus hindering the development of the various culturing protocols.[26]

Currently, the most established protocol for cell isolation consists of peel-and-digest method.[27] In this method, the Descemet's membrane endothelial donor is peeled from the stroma, followed by dissociation of cell junctions to separate the corneal endothelial cells from the membrane.

Enzymatic or nonenzymatic tissue digestion strategies are employed. The tissues are treated with collagenase, trypsin or dispase in the enzymatic digestion procedures, while the nonenzymatic digestion uses ethylenediaminetetraacetic acid (EDTA) to break cell–cell junctions. The main composition of extracellular matrix (ECM) collagens, which help human CECs adhere to DM, is type IV collagen. Therefore, the most promising enzyme for isolating endothelial cells is collagenase. More viable cells are isolated after collagenase digestion than after trypsin digestion. Collagenase induces a selective reduction of the intercellular matrix with minimal damage to cell membranes, whereas trypsin mainly acts on the intracellular mucoproteins, thus affecting the cell membrane. The mechanism of action of EDTA is to release cell junctions but it also enhances cell division upon exposure to mitogens. Not surprisingly, EDTA is often used with trypsin to disrupt cell contacts to separate cell-to-cell contact and to separate cells from the ECM without undesirable effects on cell viability.

The isolated cells are then collected and plated onto coated plates in the medium that enhances attachment. Studies reported optimal seeding plate densities ranging widely from 10,000 to 25,000 cells/cm^2 to maintain morphology but obtain a sufficient number of cells in the endothelial cells' passages.

In corneal tissues, endothelial cells adhere to DM via ECM components. ECM comprises a range of structural proteins (collagen I, elastin), adhesive proteins (collagen IV, VIII, fibronectin, laminin) and glycosaminoglycans (GAG). They construct a scaffolding to provide mechanical support for cell adhesion and organization. To mimic a physiological environment for endothelial cell plating and growth, the cell adhesion coating derived from these ECM proteins is applied on the surface of the tissue culture substrate. Tissue culture plates are coated with different combinations of ECM proteins and compared to uncoated plates to assess the effects on the cultivated endothelial cells.[28-33] However, due to different techniques and applied cell culture protocols, some studies showed conflicting results.

Although there is no consensus on the optimal coating, all proteins (fibronectin, poly-D-lysine, collagen type I, fibronectin/collagen I, collagen IV, and FNC coating mix, laminin) demonstrated increased endothelial cell adhesion compared to uncoated controls. Fibronectin-coated culture plates have been shown to improve cell spreading, reduce cell loss after rinsing, and promote better cell confluence and morphology compared to cultures grown on fibronectin-coated plates, collagen IV-coated plates and uncoated plates. Thus, currently the most used coating is the fibronectin coating mix (a mixture of fibronectin, collagen, and albumin).

Synthetic and semi-synthetic materials are being developed to provide a stable, well-defined, easily usable polymer scaffold to facilitate initial cell adhesion and detachment of cultivated cells.[30, 33] However, the drawbacks of synthetic and semi-synthetic

materials include fragility, requiring another biomaterial for transplant; unpredictable results on cells affected by temperature change; and difficulty in scaling them up.

Many endothelial cell culture media combinations, including base media, essential and nonessential amino acids, growth factors and vitamins, have been described.[34-37] However, no single medium is superior. A study introduced dual media that uses both maintenance and proliferation media. Maintenance media consist of basal media but without growth factors, whereas proliferation media is basal media with growth factors. After cell isolation, endothelial cells are cultured in maintenance media overnight, followed by proliferation media to promote cell growth. Maintenance media has replaced proliferation media for stabilizing the cells after the cells reach confluence. Studies have shown that the endothelial characteristics were maintained in the dual but not the single media.[36] For cultured endothelial cells to be applied in clinical transplantation, preventing endothelial-to-mesenchymal transition (EMT) is crucial. EMT leads to irreversible transdifferentiation from an endothelial to a mesenchymal phenotype, resulting in a fibroblastic phenotype and a loss of cell-cell contacts and hexagonal morphology. One study showed that EMT is induced by TGF-β, FGF-2 and IL-1β.

During EMT, the presence of α-smooth muscle actin (α-SMA) promoted by TGF-β indicates reorganization of the cytoskeleton and fibrosis.TGF-β arrests the cell cycle at the G1 stage, inhibiting proliferation and inducing differentiation. Hence, anti-TGF-β inhibitor SB-431542 avoids EMT by blocking the TGF-β receptor in cultivated endothelial cells to allow cell expansion.[38] Adding an anti-TGF-β inhibitor to the culture media can promote cell proliferation and prevent EMT. In addition, the antioxidation derivative of ascorbic acid, L-ascorbic acid 2-phosphate (A-2P), can stimulate the barrier function in endothelial cell monolayers and enhance various cell growth effectively. Fibroblast growth factor-2 (FGF-2) is a well-known growth factor used to supplement the culture media of many cell types. However, FGF-2 may induce EMT despite some studies showing that combining A-2P and FGF-2 significantly increased the growth of cultivated endothelial cells. Other studies have shown success of culturing CEC monolayers derived from collagenase digestion of stripped Descemet's membrane in modified embryonic stem cell medium supplemented with p120 and Kaiso siRNAs.[40-45] This reprogramming approach circumvents the need of using iPSCs or embryonic stem cells. Overall, there are many combinations of cell culture techniques and there continues to be development of new techniques to avoid EMT and promote cultivated cell growth.

After the successful cell culture, the cultivated corneal endothelial cells can be directly injected into the eye. Alternatively, the formed cell sheet from cultivated cells is transferred to substrates or carriers that provide mechanical support for the transplantation. For the direct cell injection method, the patient must remain in a prone position for hours to allow cell adherence to the posterior cornea.

To promote endothelial cell adhesion, researchers have injected a Rho-kinase (ROCK) inhibitor along with the cultivated cells.[39] (The RAS homologous [Rho] protein family is a member of the RAS superfamily of small guanosine triphosphatases [GTPases]). Animal studies proposed that Y-27632, a selective ROCK inhibitor, promoted cell proliferation and inhibited cell apoptosis in corneal endothelial cells. A recent clinical study using ROCK inhibitor-supplemented cell suspension demonstrated endothelial cell density increment and formation of a monolayer sheet of the endothelium. Despite these encouraging results, this direct cell injection method may be limited by clinical feasibility and raises concern about the systemic dissemination risk. The carrier implantation method, on the other hand, is still in the preclinical stage.

An ideal carrier would facilitate cultivated endothelial cells' adhesion to the posterior stroma and mimic the characteristics of the DM to support the interaction between the endothelial cells and the recipient stroma. Different carriers have been extensively investigated. They include:

- biologically derived (such as amniotic membrane, silk fibroin, human anterior lens capsules, decellularized DM or stroma, fish scales or plastic compressed collagen/gelatin);
- synthetic (such as chitosan blends, Poly-ε-lysine peptide, Polymethylmethacrylate hydrogel, Polylactic-co-glycolic acid, Polycaprolactone); and
- semisynthetic (Gelatin methacrylate, chitosan).

Despite carrier materials advancement, cellular properties remain a limiting factor in terms of transparency, permeability, sufficient mechanical strength, flexibility to adjust to the corneal curvature and biocompatibility.[40] The carrier with cultivated endothelial cells is implanted into the anterior chamber using a DMEK surgical technique. The placement of the fragile monolayer endothelial cell sheet in the anterior chamber and firmly fixing it to the posterior cornea is one of the main surgical challenges.

After attachment of cultivated endothelial cells to the recipient's posterior stroma, the carrier needs to enhance endothelial cells' DM production to ensure stromal transparency after transplantation. Further *in vivo* and animal studies can investigate surgical transplantation or implantation of cultivated endothelial cells with or without carriers, postsurgical DM production, immune tolerance and long-term outcomes.

In conclusion, new advancements targeting endothelial donor tissue shortage

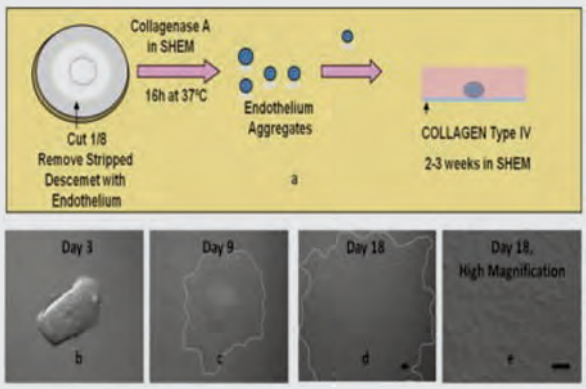
THE IMPORTANCE OF THE ENDOTHELIUM

Corneal endothelial cells are embryonically derived from cranial neural crest cells and form a single monolayer of hexagonal cells lining Descemet's membrane. These cells play a pivotal role in regulating corneal stromal hydration and hence transparency by exerting effective barrier and pump functions. Unlike endothelial cells from other species, human endothelial cells have limited proliferative capacity *in vivo*. Hence, the loss of cells or cell dysfunction has a dramatic impact on the overall transparency of the cornea as newer cells are hard to replicate and maintain the pump and barrier function. When the cell density decreases to <500 cells/mm^2, the endothelial cell pump function underperforms and the cornea becomes edematous. The current treatment for corneal blindness caused by dysfunctional endothelial cells usually resorts to transplantation, wherein new endothelial cells are brought into replace the lost or dysfunctional cells.

'CELL-BASED' HUMAN CORNEAL ENDOTHELIAL CELLS (HCEC)

- HCEC have limited proliferative capacity *in vivo*, but studies show that they can expand *in vitro*
- HCEC are isolated from cadaveric corneas using EDTA or collagenase and expanded *in vitro* on different substrates
- Optimization is based on substrates, cell seeding density and cell media

A. Isolation and Expansion



with DSO and cultivated endothelial cells are emerging. This review highlights *in vitro* expansion of corneal endothelial cells isolated from cadaver donors, peripheral corneal endothelial cells or organ-specific adult stem cells. Collagenase digestion is an effective way to isolate the corneal endothelial cells. Cell plating density can be different between studies.

Combined culture media have also been described, including dual media or use of siRNAs with various growth factors attempted to promote cell growth and inhibit EMT. However, it remains challenging to culture corneal endothelial cells on the coating surface while maintaining their characteristics. Although several types of carriers and surgical techniques have been proposed for cultivated EC transplantation, further studies need to develop ways to resolve biocompatibility issues.

Dr. John is in private practice in the Chicago area, and is a clinical associate professor, Loyola University at Chicago. Dr. Cheng is a resident at Broward Health, Department of Ophthalmology, Fort Lauderdale, and a voluntary clinical associate professor at Florida International University, Department of Ophthalmology in Miami, and a clinical assistant professor at Florida International University.

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PREMIUM IOLS IN PATIENTS WITH CORNEAL CONDITIONS

By
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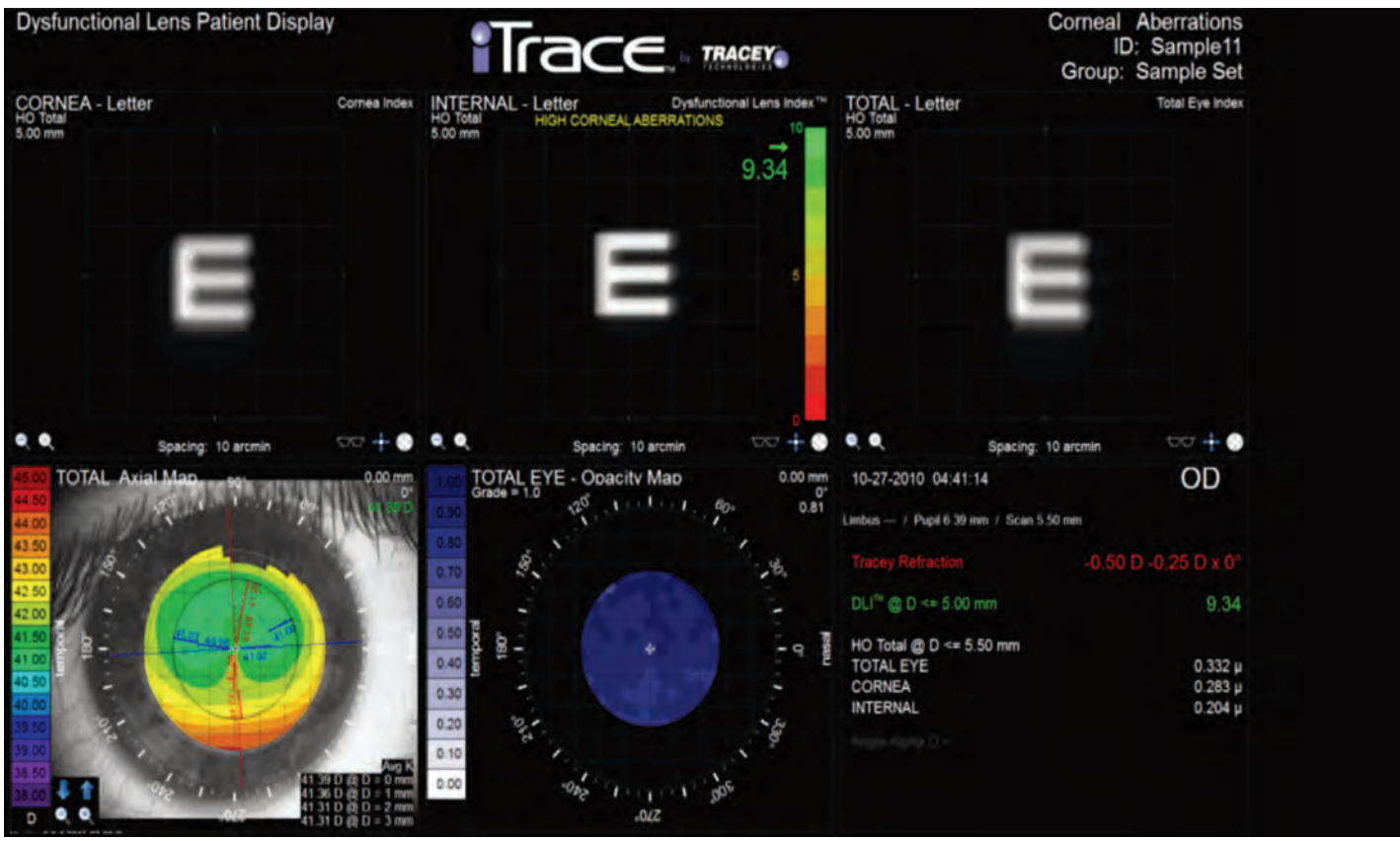


Figure 1. The image above shows the wavefront measurements of the eye and a combined placido disc image of the anterior corneal surface. The iTrace separates the total HOAs of the eye into the corneal and internal aberrations. The internal aberrations are assumed to be from the natural lens or IOL. In this case, the corneal aberrations make up the majority of the total HOAs (which is from corneal ectasia s/p LASIK) and therefore cataract or lens exchange surgery wouldn't be beneficial for this patient; instead, the corneal aberrations should be addressed].

Since I started implanting premium IOLs in 2002, I've learned when to offer these lenses and when to avoid them. To come to that decision, we evaluate the patient from front to back—from the ocular surface to macula—and address any findings with them preoperatively in order to avoid any mistrust or surprises postoperatively.

In this article we'll focus on the anterior segment/cornea conditions that can affect the outcomes of premium IOLs, namely ocular surface disease, Salzmann's nodular degeneration, epithelial basement membrane dystrophy, Fuchs' endothelial dystrophy and irregular astigmatism.

WHY THE IOL DECISION IS IMPORTANT

There are many reasons to avoid MF or even EDOF lenses in patients that have limited visual potential: (1) loss of contrast sensitivity from the IOL, (2) the perceived lack of value of a premium IOL if the patient is paying extra out-of-pocket and not achieving their best potential vision, (3) remove the confusion postoperatively as to the cause of decreased vision—i.e., is it the IOL or some other ocular pathology?

If there are any findings on the anterior segment or dilated fundus exam that will limit the patient's visual potential, we typically recommend monofocal IOLs with or without monovision. By using monofocal IOLs we can provide our patients their best quality of vision possible.

ROOT OUT THE CAUSE OF POOR VISION

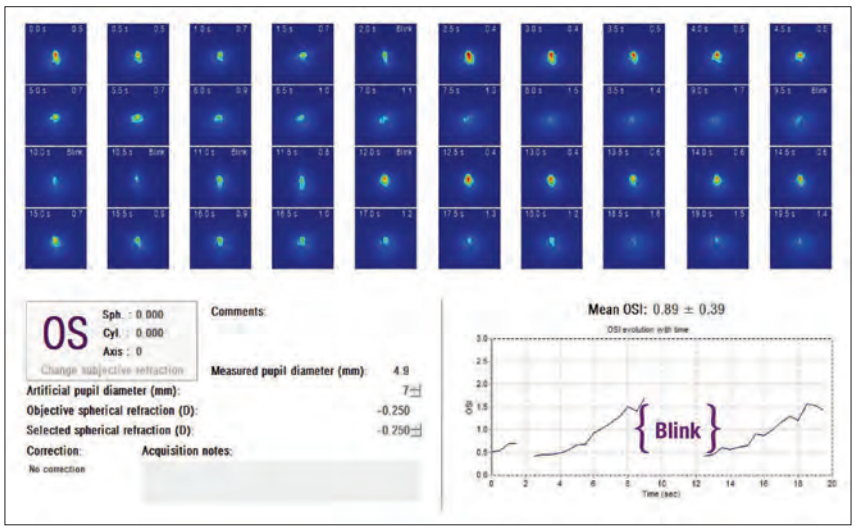
First, we determine if the vision loss is from corneal pathology or internally (i.e., the lens). An easy way to determine if it's a cornea or lens issue is by performing wavefront measurements (Tracey's iTrace and Nidek's OPD-III are common instruments available in the United States). We also use an RGP CL over-refraction in cases of irregular astigmatism and compare that to the manifest refraction; if the RGP over-refraction improves the BCVA then we know the cornea is the source of poor vision.

If we determine that the cornea is responsible for the loss in vision, we'll focus on treating the corneal pathology first before recommending a lens implant. Figure 1 on page 17 shows an example of the cornea HOAs from corneal ectasia affecting the vision more than the internal HOAs.

Here's a look at the main corneal causes of dissatisfaction with premium IOLs postop:

• ***Ocular surface disease.*** Dry eye is the most common corneal condition that must be addressed prior to recommending premium IOLs. Dry eye not only affects the quality of vision, but also the IOL calculations and the ability to perform enhancements for any residual refractive error. Dry eye can also alter the topography and A-scan measurements. An evaluation of the placido image on the topography, the keratometric image on the A-scan and the ocular scatter index (OSI) on the HD analyzer can help determine the clinical significance of the dry eye. If the images aren't clear, we pretreat the patients with artificial tears, mild steroids and anti-inflammatory drops. We also recommend lid hygiene, and we still encourage oral omega-3 FAs. In severe cases, we recommend autologous serum drops. If the dry eye is significant enough to be a contraindication for LVC, we wouldn't recommend any MF/EDOF lenses. Figure 2 shows an example of pre- and post-dry eye treatments on the OSI measurements.

Pre-treatment:



Post-treatment:

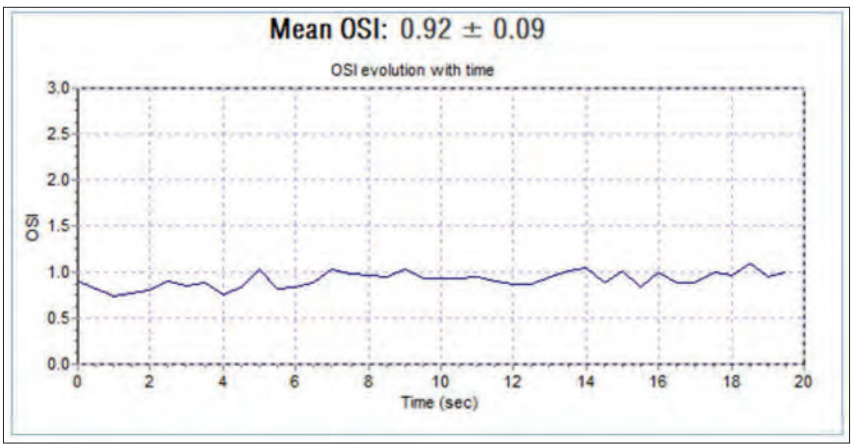


Figure 2. Top: The OSI gradually increases as the patient focuses on a target without blinking, then once they blink the OSI improves before it increases as the patient focuses on the target again. This is consistent with an unstable tear film and lid margin disease. Bottom: After treatment, the OSI is low and stays low as they fixate on a target, showing a more stable tear film.

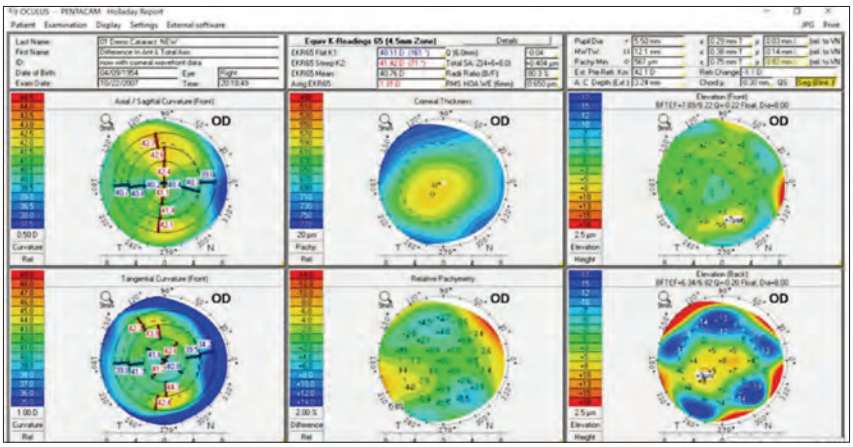


Figure 3. An example of the Holladay Report on the Oculus Pentacam showing the mean equivalent K reading for IOL calculations, total cornea HOAs, estimated refractive change from previous LVC, and chord μ values.

• ***Epithelial basement membrane dystrophy and Salzmann's nodular degeneration.*** These conditions affect the refractive outcome of surgery, limit LVC enhancement options and create HOAs/irregular astigmatism. If present, we recommend addressing these conditions preoperatively and allowing the vision and topography to stabilize before proceeding with lens implantation.

Our treatment approach includes initiating dry-eye treatment first and then performing superficial keratectomy with a diamond burr.

The dry-eye treatment consists of artificial tears, lid hygiene, oral supplements (omega 3 FAs), and prescription dry-eye treatments. We don't prefer one prescription dry-eye treatment over others; we typically start with what's best covered by their health insurance and often use an independent pharmacy to assist us in this process.

Diamond burr superficial keratectomy for EBMD is performed under topical anesthesia in our laser suite or ASC. I like using a Took blade to test and remove all loose epithelium and then a diamond burr to gently treat the basement membrane. We then place a BCL soaked in a NSAID and sized appropriately to their K values, the postop management is the same as PRK/surface ablation treatments. SK for EBMD is curative, but recurrent corneal erosions can occur if all the abnormal basement membrane isn't treated. Postoperatively, we wait until the ocular surface is normalized and the topography is stable and regular. Once they're stable, we can then offer premium lenses and astigmatism treatment at the time of their cataract/refractive lens exchange surgery. Although LASIK can be offered once they are fully healed, I prefer surface ablations if an enhancement is needed.

For SND, the only difference in the procedure is finding the plane of the nodule(s), dissecting it off the Bowman's layer and then using the diamond burr to create a smooth surface. Care is used to avoid removal of any stromal tissue. I also use MMC 0.02% for 30 seconds to reduce recurrence of nodules. SND patients typically also have significant dry eyes. Nodules can also recur over time even with the use of MMC and long-term dry-eye treatment. If you follow these patients postoperatively long enough, you'll see continued OSD and changes in their refraction from the recurrence of nodules. LVC may also be contraindicated due to their dry-eye condition and irregular astigmatism. For these reasons, I rarely recommend premium IOLs in these patients.

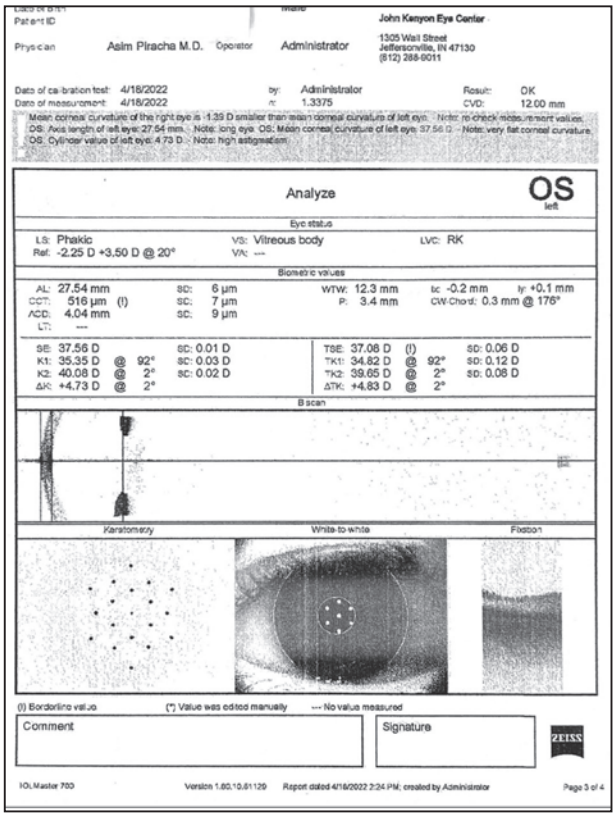


Figure 4. This is the IOLMaster 700's analysis of data that includes the telemetric K values with image quality, visual axis and Chang-Waring chord μ value; and K and total K values with the amount and axis of astigmatism. In this case the TK measures 4.83 D at 2 degrees.

A retrospective review of 20 consecutive EBMD cases discussed in the April 2010 *Review of Ophthalmology* article "The Benefits of Pretreating Corneas" found that the average change in MRSE was 0.64 D (range: 0 to 1.25 D of change). The average change in MRSE for SND was 1.7 D sphere (range: 0.5 to 6.5 D) and 1.57 D of cylinder (range: 0.25 to 4.5 D).

• ***Irregular astigmatism.*** This is another condition that can be a contraindication for a premium lens implant. Irregular astigmatism can be diagnosed by corneal topography and tomography. The most common causes include post-corneal refractive surgery ectasia (following LASIK, RK, PRK, etc.), keratoconus, pellucid marginal degeneration and corneal scars or opacities.

If the irregular astigmatism is caused by ectasia, one can't confidently determine if the ectasia is stable or if it'll progress. In these cases, I'll review their past topographies and refractions

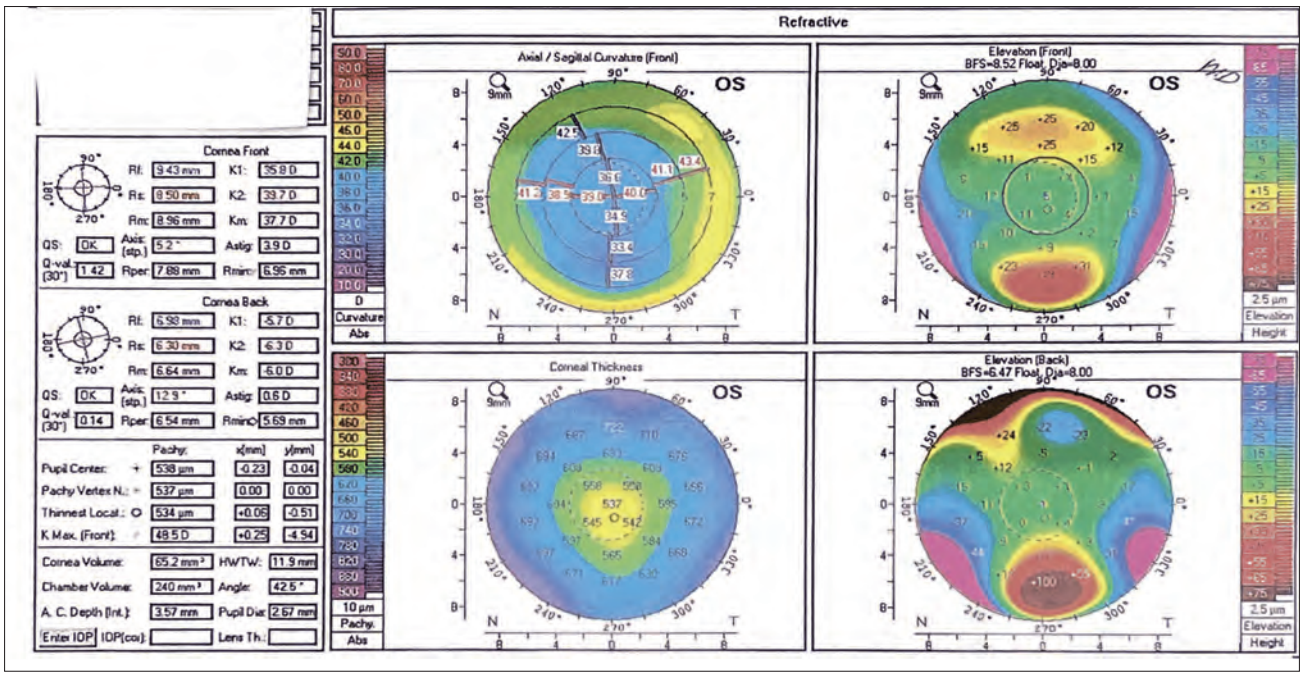


Figure 5. An Oculus 4 Map Refractive evaluation showing the front and back elevation, axial/sagittal curvature and central corneal thickness. The front curvature shows 3.9 D of astigmatism, with the steep meridian at 5.2 degrees.

and then, based on these findings as well as their age, history of eye rubbing and/or floppy eyelid conditions, make a surgical plan with the patient. If they're older (over 40 for KCN, over 50 for PMD), I'll consider a toric IOL. For post-surgical ectasias, however, I'm more hesitant.

For irregular astigmatism from injuries or infection, on the other hand, I'm more comfortable with toric lenses or even MF/EDOF lenses, as long as the patient's corneal higher-order aberrations are low.

I especially like the Holladay cataract report on the Pentacam to determine if a patient is an appropriate candidate for premium lenses. This report shows the following, as described by the Holladay Report Interpretation Guidelines 2018 in the Pentacam manual:

• total spherical aberration to help pair the correct aspherical lens from 0 for hyperopic LVC to -0.27 for myopic LVC and RK;

• RMS (root mean square) HOA at 6 mm to measure corneal irregularity, if over 0.66 µm, a MF/EDOF lens may not be ideal, since the quality of vision may already be compromised;

• chord µ (analogous to angle kappa) to measure the chord distance from the corneal vertex to the pupil center; any value over 0.42 mm can cause worse uncorrected near vision and more night vision disturbances (glare and halos around lights); and

• predicted refractive change from previous cornea refractive surgery, to help with the IOL calculations. There are several other devices that we use in our clinic to measure the chord µ length, including the iTrace (Tracey Technologies), OPDIII (Marco Ophthalmic), and the IOLMaster 700 (Zeiss Meditec).

If the RMS and chord µ values are outside of the normal range, I'm very cautious about using a MF lens. If the values are borderline and the patient understands how these findings can affect the performance of premium lenses, then I'm more comfortable with EDOF lenses like the Alcon Vivity, Johnson & Johnson Vision Symfony OptiBlue, or J&J Vision's Eyhance.

I've been very happy with the quality of vision and function when pairing the Eyhance with previous myopic KRS. In patients with larger pupils, my experience is slightly better for the Symfony OptiBlue compared to the Alcon Vivity (a larger pupil affects the near function).

I've had success with toric lenses in patients with ectasia. If the ectasia is unstable, I'd recommend corneal cross-linking first and then a toric IOL once they're stable after CXL. Some patients need more than CXL and benefit from intracorneal ring segments (ICRS) to reduce the corneal astigmatism and make it more regular.

• ***Fuchs' endothelial corneal dystrophy.*** We also avoid MF IOLs in patients with Fuchs' dystrophy. If the condition is clinically significant (i.e., diffuse central guttae and increased CCT) then we recommend a combined epithelial keratoplasty with phaco and implantation of a monofocal IOL. Even if the patient is relatively young (under 50) with mild guttae and normal CCT, we're still very cautious with using a MF lens, since the condition can progress, it can affect the quality of vision and cause some refractive changes. I also prefer to avoid MF lenses in patients with Fuchs' since the condition can progress after phaco or refractive lens exchange, limit their quality of vision due to the cornea, and limit the postop enhancement options.

If a Fuchs' patient is highly motivated to have premium lens, however, we'd consider an EDOF lens and perform DMEK to treat their condition. My experience with DMEK and DSEK (nano-thin, <60 µm), is

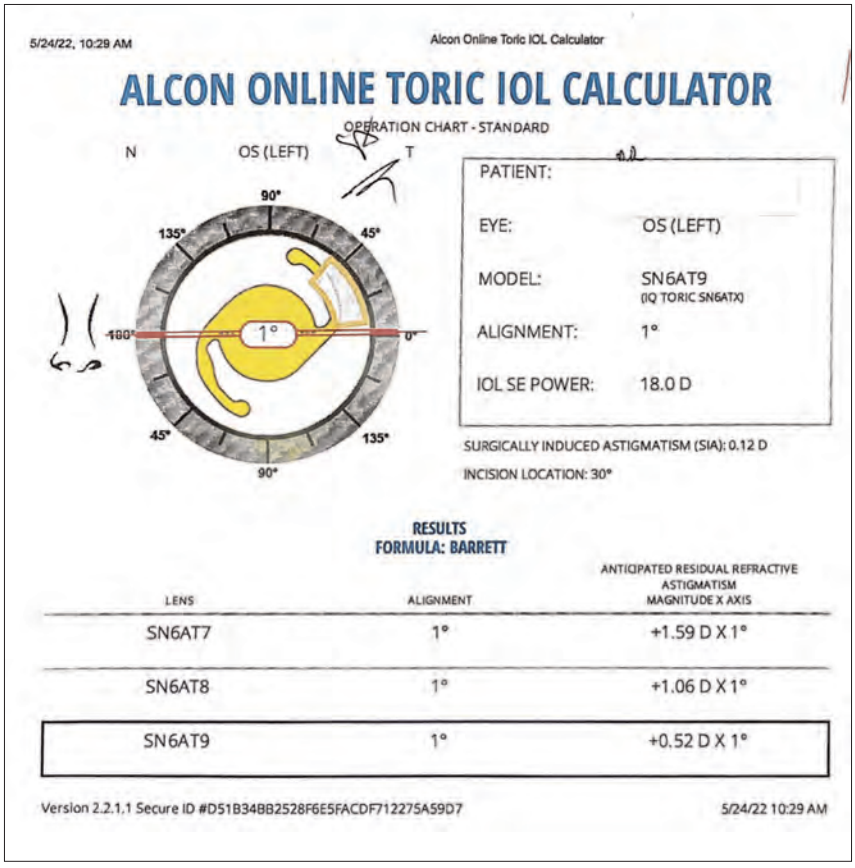


Figure 6. In this example, using the TK values, the Alcon Toric calculator recommends using the SN6AT9 (highest toric power) to treat the corneal astigmatism with an anticipated residual astigmatism of +0.52 D at 1 degree.

that the corneal treatment can still induce an unpredictable refractive change. Although we target about -1 D for DSEK and -0.75 to -1 D for DMEK, we still frequently see outliers. In a recent case in which I performed a triple procedure (DMEK, phaco, IOL), the patient was +2.5 D MRSE and we targeted -1 D. When combining an EK with a premium IOL in this case, the patient will require a LVC enhancement, IOL exchange or a piggyback IOL.[1,2] Note also that any intraocular surgery can damage the EK tissue and vision. Since this approach can be unpredictable and could take two or more surgeries to achieve good UCDVA, we recommend using monofocal aspheric IOLs and targeting good near or distance vision, but not both.

CASE STUDY

The case is that of a 62 year-old male professional golfer, with previous RK surgery, cornea ectasia, BCVA of 20/50 and more than 4 D of irregular astigmatism (his images appear in Figures 4, 5 and 6). His topography and manifest refraction were stable, and he was very motivated to improve his UCVA and to reduce his dependence on glasses and contact lenses. After explaining that a toric IOL was off-label for him due to his irregular astigmatism, previous refractive surgery and the unpredictability of the refractive outcome, he was still very motivated to have toric lenses. His results were better than expected: UCVA 20/30+ and BCVA of 20/20. He was very pleased with the outcomes and is ready to get back on the tour.

In this example, using the TK values, the Alcon Toric calculator recommends using the SN6AT9 (highest toric power) to treat the corneal astigmatism with an anticipated residual astigmatism of +0.52 D at 1 degree.

FINAL THOUGHTS

So, can you use premium IOLs (specifically MF and EDOF lenses) in patients with pre-existing corneal pathology? The answer is … it depends. If the condition can be treated preoperatively to the point where the quality of vision isn't affected by the cornea, the corneal topography/tomography is stable, there's a low risk of the condition recurring or progressing, and they're good candidates for LVC for enhancements after surgery, then the answer is "Yes." The reason I'm so conservative with these cases is that if the refraction changes over time (as can occur with SND) the UCVA and BCVA will decrease, and the patient will be unhappy with their visual outcomes. What can add insult to injury for these patients is that there may not be a good surgical solution to improve their vision.

Since refractive surprises can occur with cataract and RLE surgery, the surgeon must be able to enhance them to correct any residual refractive error. Residual refractive errors with multifocal IOLs (bifocal or trifocal) can have a significant effect on their function for near, distance and low-light conditions. If a patient isn't a candidate for LVC preoperatively for premium IOL surgery then, in my mind, they're poor candidates for premium lens surgery too. Note that contraindications for LASIK include EBMD, SND, dry eyes and FCD. Advanced surface ablation is a better option in patients with clinically significant dry eyes or untreated FECD since interface fluid and poor flap adherence can occur with LASIK. LASIK, however, is an option for EBMD that's responded to treatment.

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DIAGNOSIS AND MANAGEMENT OF BLEPHARITIS

By
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Just because we see something every day in our offices, doesn't make it any less confounding. Blepharitis is a good example: It's not rare by any means, but it remains a challenge to successfully diagnose and treat, since the overlap of symptoms and signs and the association with dermatologic conditions including rosacea, seborrheic dermatitis, and eczema can lead to misdiagnosis, underreporting of the condition and variable management protocols with variable outcomes. Here, I'll review how I approach this condition, and share pearls for managing it.

THE CONDITION

Blepharitis is a common, chronic ophthalmologic condition characterized by inflammation of the eyelid margins associated with recurrent symptoms of eye redness, tearing and irritation. It occurs in people of all ages, ethnicities and in either sex.

The etiology of this complex disease includes infectious (bacterial; viral herpes simplex, zoster, molluscum), immune (atopic dermatitis, contact dermatitis, mucus membrane pemphigoid, Stevens-Johnson Syndrome), dermatologic (rosacea, psoriasis) traumatic (chemical and thermal) and neoplastic including benign (papilloma, actinic keratosis) and malignant (sebaceous cell, melanoma, squamous cell, basal cell) eyelid tumors.

Ulcerative forms are usually infections, like herpes simplex or zoster, while inflammatory disease is usually non-ulcerative.

Blepharitis may differ based on the location of eyelid inflammation (posterior versus anterior). *Demodex* blepharitis is frequently overlooked in the assessment of blepharitis in part because *Demodex* can also be asymptomatic. Other skin conditions like rosacea may also be associated with posterior blepharitis and meibomian gland dysfunction. Like most ocular diseases, careful consideration must also be given to normal age-related changes that occur in the eyelid and ocular surface.

According to a 2009 survey, the prevalence of blepharitis in the United States probably lies between 37 percent, reported by ophthalmologists, and 47 percent, as reported by optometrists.[1] Associated dry-eye disease (DED) is present in 5 to 30 percent of patients over age 50 with MGD as one of the leading causes of evaporative DED (EDED).[2,3] MGD is responsible for 66 to 78 percent of DED making it a clinically significant condition.[4]

There have been many proposed classification systems for blepharitis. The most recent system comes from the International Workshop on MGD: In the report of the Definition and Classification Subcommittee, the term blepharitis refers to inflammation of the eyelid as a whole whereas marginal blepharitis refers to inflammation of the lid margin and includes anterior and posterior blepharitis *(discussed in more detail under "Clinical Evaluation," below)*.[5]

WHAT CAUSES IT

Blepharitis is multifactorial, involving the eyelid margin, meibomian glands, bulbar and tarsal conjunctiva, cornea and the lacrimal gland. These structures all

contribute to the normal homeostatic state of the ocular surface and normal tear film. With the presence of disease, the integrity of the ocular surface is disrupted, leading to a cycle of eyelid and ocular surface disease that's often difficult to break. Altered lipid composition of the meibomian gland secretions can lead to instability of the tear film. These abnormal secretions can have a direct toxic effect on the ocular surface.[6] Additionally, because the microbiota of the tear film is dependent upon proper meibomian gland function, a proliferation of pathogenic microbes may take place, including the proliferation of Staphylococcus, Streptococcus, Corynebacterium and Cutibacterium species.

Blepharitis can also result from activity of the mite *Demodex folliculorum*, a parasite that has been identified in 30 percent of patients with chronic anterior blepharitis affecting the base of the lashes, but which is also found with approximately the same prevalence in asymptomatic people. It's present in more than 75 percent of adults over 70, and it's clearly a contributing factor in some patients as evidenced by the symptomatic improvement seen in the response to therapy.

In a 2018 study, with 500 patients, *Demodex* was identified in almost 80 percent of blepharitis patients but also in 31 percent of controls.[7] The researchers found *Demodex* in 40 percent of 229 patients with dry-eye symptoms.[8]

The prevalence of *Demodex* also increases with age (with or without the associated diagnosis of blepharitis) and so should be ever present in the differential diagnosis of patients with chronic ocular surface disease.[9,10]

A second species, *Demodex brevis*, has been associated with posterior blepharitis and occupies the meibomian glands.[11] The altered tear-film integrity and the proliferation of these organisms lead to a generalized inflammation of the ocular surface. Long-term inflammation leads to gland dysfunction, hyper-keratinization and fibrosis, as well as damage to the eyelid and ocular surface.

Hyper-keratinization, therefore, is an early finding in patients with posterior blepharitis and diagnosing and grading this change is critical to staging the severity of the disease. These changes result in worsening meibomian gland function, perpetuating the cycle.

FIGURE 1. A SYSTEMATIC APPROACH TO THE POTENTIAL BLEPHARITIS PATIENT

1. Patient History
2. Symptom Questionnaire (OSDI, DEQ-5, SPEED, NEI-VFQ25)
3. External Examination (rosacea, seborrhea, blink pattern)
4. Tear Osmolarity (if available)
5. Meibography and Lipid Layer Thickness (LLT) (if available)
6. Corneal Sensation (Luneau Cochet-Bonnet aesthesiometer)
7. Anterior Eye Assessment (Slit Lamp Exam)
   a. Meibomian Gland Assessment (volume, thickness, plugging)
   b. Corneal Integrity Assessment (fluorescein)
   c. Conjunctival Integrity (Lissamine Green)
8. Tear Film Assessment
   a. Tear-film Breakup Time (TFBUT)
   b. Tear Volume Assessment (Schirmer I)
   c. Inflammatory Mediators (InflammaDry)
9. Additional Testing
   a. *Demodex*
   b. Cultures
   c. Biopsy (neoplasia)

Underlying inflammatory skin conditions such as rosacea and seborrheic dermatitis may also be associated with posterior blepharitis, although these conditions commonly occur in their absence. Blepharitis in patients with underlying chronic dermatoses tends to be more severe.

Chronic infection may also play a role in posterior blepharitis, although this manifestation has been studied less than in anterior blepharitis. The bacteria that comprise the lid and conjunctival flora in posterior blepharitis are the same as those on normal skin but are present in greater numbers.[12] They include coagulase-negative staphylococci, Corynebacterium species, and *Cutibacterium acnes*. *D. brevis* should also be included in the etiology of posterior blepharitis. Bacterial lipase produced by colonizing bacteria on the ocular surface may contribute to the differences in lipid composition in the tear film in patients with blepharitis.

Other possible causes of blepharitis include contact (allergic) dermatitis, eczema and psoriasis. Contact allergic blepharitis is an acute inflammatory reaction of the skin of the eyelids, usually occurring as a reaction to an inciting agent found in some cosmetics.

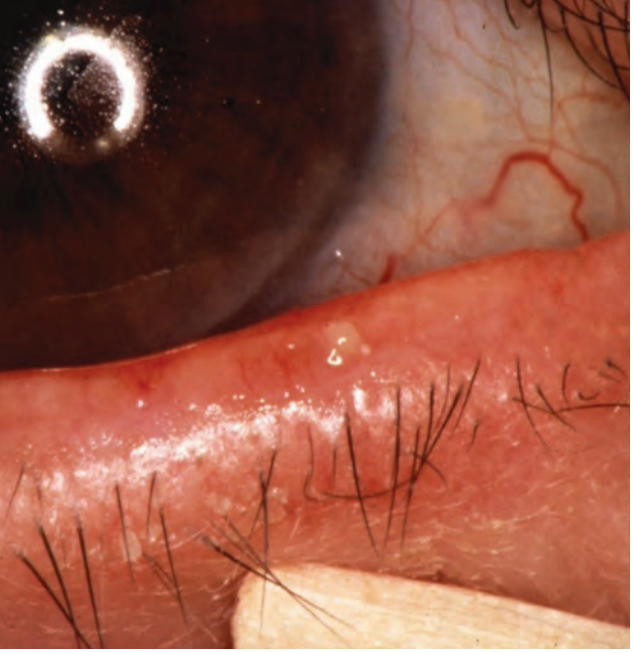
CLINICAL EVALUATION

Your diagnosis and evaluation of blepharitis should consist of a comprehensive multi-step process that involves both subjective and objective measures *(See Figure 1)*. Many cases of chronic blepharitis are associated with evaporative dry-eye disease and meibomian gland dysfunction, and so are a part of a broader category of ocular surface disease. More severe and chronic eyelid disease can also be a risk factor for sight-threatening corneal inflammatory disease.

When a patient presents in your office with possible signs of blepharitis, here's how to home in on the right diagnosis:

• ***Symptoms.*** Patients with blepharitis typically complain of irritation, redness, burning, crusting, sticking eyelids and sometimes tearing. They may also complain of blurred vision that improves with blinking and some photophobia. The symptoms are usually chronic, and wax and wane over time; they're often worse in the morning upon awakening.

• ***Dermatologic evaluation.*** Facial rosacea should always be assessed, since about a quarter of patients with blepharitis also suffer from rosacea. Telangiectasias,



Rosacea with MGD. Shown is a blocked meibomian gland undergoing gentle expression.

papules and pustules of the face, glabellar and chin regions are typical signs, along with prominent sebaceous glands. I always look for signs of rosacea in every patient who complains of ocular irritation.

• ***Anterior blepharitis.*** Anterior blepharitis refers to eyelid inflammation anterior to the gray line and is associated with eyelash inflammation often connected to squamous debris and collarettes. Anterior blepharitis is less common than posterior blepharitis and is characterized by inflammation at the base of the eyelashes. Patients with anterior blepharitis are often female and tend to be younger than those with posterior blepharitis.

Anterior blepharitis can be further separated into staphylococcal or seborrheic types, although *Demodex folliculorum* has also been implicated.[13] Staphylococcal blepharitis is characterized by lid margin erythema, mild edema, inflammation, telangiectasias, scaling of the skin and loss of lashes (madarosis). Whitening (poliosis) and lash misdirection can also occur. Characteristic scaling that results in the formation of "collarettes" around the bases of the lashes may be present. (These differ from the more tightly bound "sleeves" characteristic of *Demodex folliculorum*.) The fibrinous scales and crusts around the eyelashes are caused by colonization by *Staphylococcus aureus* and coagulase-negative staphylococci. In addition, Staphylococci may alter meibomian gland secretion and cause blepharitis via various mechanisms, including direct infection of the lids, production of staphylococcal exotoxin, and by provoking an allergic reaction. It's likely that a combination of these factors is responsible for the manifestations of anterior blepharitis.

The seborrheic type is characterized by dandruff-like skin changes and greasy scales around the base of the eyelids associated with the sebaceous glands of Zeiss. The oily scale and crusting can also be found on the retroauricular, glabellar and nasolabial fold areas as well.

• ***Demodex.*** The diagnosis of Demodex blepharitis can be made from clinical evaluation as well as epilating suspicious lashes, placing the eyelashes on a glass slide and then examining the organism under a cover slip after a drop of fluorescein has been added.

The definitive diagnosis can also be made through confocal microscopy.[14,15] Epilation of the eyelashes for microscopic examination to detect *Demodex* mites is warranted when the clinical presentation (e.g., presence of cylindrical dandruff or "sleeves" on the eyelashes) is suggestive of this diagnosis, or when there's severe or refractory blepharitis.

• ***Posterior blepharitis.*** Posterior blepharitis refers to inflammation associated with the posterior lid margin, meibomian gland dysfunction, conjunctival inflammation and other causes, including *D. brevis*.[11]

By way of quick review, MGD is a chronic, diffuse inflammation of the meibomian glands commonly associated with terminal duct obstruction and/or abnormalities of the secreted meibum. The new classification system proposed by the International Workshop on MGD differentiates the various MGD subgroups on the basis of the level of secretion, with obstructive MGD being the most common type.[5]

In the clinic, posterior blepharitis patients will have dilated or obstructed meibomian glands, with thickened turbid secretions associated with telangiectatic vessels and lid margin scarring in severe cases.

• ***Carcinomas and other serious conditions.*** Critically important is the careful assessment of the eyelids and ocular surface for potentially severe sight- and life-threatening diseases, including basal cell carcinoma and sebaceous cell carcinoma. You should have a strong index of suspicion if the patient has a history of chronic eyelid inflammation that's been unresponsive to aggressive treatment, including corticosteroids.

Severe corneal complications can also develop with rosacea blepharokeratoconjunctivitis including punctate epitheliopathy, corneal neovascularization, infectious keratitis and thinning—even perforation. These patients should be referred early to a cornea specialist.

DIAGNOSTIC TESTING

In addition to your exam and patient history, certain diagnostic tests can help you zero in on the problem. The complete list of our diagnostic process (including history, etc.) appears in Figure 1. The recommended list of a standardized sequence of ocular surface clinical and diagnostic assessments should provide valuable diagnostic, quantitative information to properly assess blepharitis and meibomian gland-related ocular surface disease. Here, however, we'll expand on a couple of the tests to explain what we're looking for:

• ***Tear osmolarity.*** It's generally accepted that a tear osmolarity measurement greater than 308 mOsm/mL is abnormal, as well as a difference between the eyes of 8 mOsm/mL. We don't rely on this too heavily, but it's an important theoretical factor, because when the quality of tears is abnormal, the hyperosmolarity that results provides an insult to the surface, leading to low-grade inflammation.

• ***Meibography and lipid layer thickness (if available)***. The Heiko Pult Meiboscale provides a good visual grading system of Meibomian Gland Dropout that helps patients understand the condition better (https://www.heiko-pult.de/media/files/MEIBOSCALE-2016--Einseiter-ADD-Sec.pdf). The LipiView device also provides a quantitative measure of the lipid layer thickness (LLT), with normal being over 65 µm. Both these values help in assessing the presence and severity of the MGD.

• ***Blink rate/staining.*** It can be very useful to observe the patient's blink rate. The LipiView device will also document incomplete blinks, though I'm not entirely sure of its reliability for diagnosis. How-

ever, you can use the results from a device such as the LipiView to show patients that they're not closing their eyes completely when they blink. In these patients, most (but not all) will also have inferior punctate staining. Importantly, if you lift the upper lid and there isn't superior punctate corneal staining, that's a good sign. If there's staining under the upper lid in these patients, however, that would suggest a toxic etiology, and you may want to look at other drops they're taking, such as those for glaucoma.

• ***Corneal sensation.*** As a follow-up to the previous point about blinking, if a patient blinks a lot that's often a good sign that their corneal sensation is normal. If someone doesn't blink a lot, be sure to do a test of corneal sensation, since it may be abnormal. Normal sensation is critical for normal epithelial healing.

• ***Tear-film breakup time.*** This is the most important diagnostic tool for the diagnosis of tear dysfunction syndrome (TDS), and is probably more important than Schirmer test and punctate staining. It's critical that this measurement be carefully performed and documented.

TREATMENT

Once you've settled on a diagnosis, you can embark on the path to treatment. Following are the best routes to take for the various causes of the patient's problem:

• ***Chronic blepharitis.*** For chronic blepharitis, many important interventions often have only marginal effects, and for this reason I always try to set realistic expectations regarding the outcome of the treatments *(See our practice's handout on Tear Dysfunction Syndrome, available with the online version of this article on reviewofophthalmology.com).* I tell patients that they have to decide whether the various treatments help or not and that we'll need to try to establish the most effective dose/regimen.

Understanding the chronic nature of the disease is critical to the management. Since the incidence of depression and anxiety in patients with chronic eye disease is high, some patients will fixate on their eye problem until it feels overwhelming. It's important to explain to patients that you're not going to solve the problem and make it go away—it's chronic. In fact, a Cochrane Database Systematic Review of 34 interventions failed to demonstrate a cure of blepharitis, so it's important to communicate to patients that this will be a chronic and recurrent condition.[16] I tell them our job is to figure out which treatments will make their eyes feel a little better—emphasis on "a little." They must have a mindset that we're going to try these treatments in an effort to get some marginal improvement.

Although there have been many published reports on the benefits of a variety of interventions, lid hygiene, including lid scrubs and warm compresses remain the mainstay of treatment for this chronic condition (e.g., Ocusoft Lid Scrub, Sterilid, Cliradex, I-Lid 'N Lash Pro and the TheraPearl Eye Mask). The duration of the heat should be emphasized, as well as the chronic nature of the condition, both of which necessitate regular/daily/weekly management schedules. Remind them that the shampoo should be diluted and be sure to demonstrate the specific gentle meibomian gland massage technique.

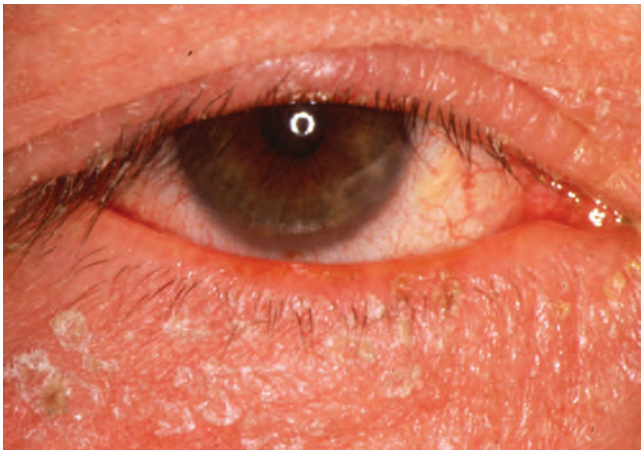
For uncontrolled meibomian gland dysfunction, oral antibiotics, including tetracyclines, are recommended.

Newer treatments for managing chronic blepharitis include mechanical devices including Thermal pulsation (LipiFlow, Systane iLux2, TearCare, MiBo Thermoflo), intense-pulsed light (Lacrystim IPL, OptiLight, Epi-C Plus), and microblepharoexfoliation (MBE) devices that mechanically scrub the eyelids, eyelashes, and skin with a gentle mechanical brushing system (NuLids, BlephEx) which remove scales and potentially blocked meibomian gland orifices. Finally, meibomian gland probing has been reported to be effective in some cases especially for the more severe disease (e.g., Stevens-Johnson Syndrome). Topical steroids should also be an option for more severe disease.

Topical preservative-free lubricants can also be useful for those patients with a component of aqueous tear deficiency. Start with aggressive lubricant treatment (q.i.d.) in the beginning and then taper it to the most effective dose that requires the least amount of lubricant.

Oral Omega-3 fatty acids are another theoretically effective approach to the management of posterior blepharitis and MGD. However, the 2018 Dry Eye Assessment and Management (DREAM) study, a prospective, randomized study that analyzed the role of 3,000 mg of n-3 fatty acids/day for 12 months, failed to demonstrate a statistically beneficial effect over the placebo group.[17]

• ***Acute cases.*** For acute infectious disease, topical antibiotic drops and ointment at bedtime (erythromycin or bacitracin) can be effective. Systemic antibiotics are occasionally indicated for their anti-inflammatory, antibiotic and oil gland composition-altering effects. Topical corticosteroids (such as Klarity-L, Lotemax, Inveltys and Eysuvis) or combination steroid/antibiotic drops can also be very effective to control acute inflammation, with the cautionary discussion with the patient of potential for elevating their intraocular pressure with chronic use.



Seborrheic dermatitis with blepharitis.

• ***Demodex blepharitis.*** For *Demodex* infection, the critical clinical feature is the cylindrical sleeves at the base of the eyelashes, which is found in 50 to 90 percent of *Demodex* patients.[18] Management with tea tree oil, with its active component terpinen-4-ol, has demonstrated good outcomes in eradicating the organism and reducing the inflammation, as demonstrated in a 2020 meta-analysis.[19] It's important to impress on the patient that treatment must be

maintained for six to eight weeks.

Other current treatments including ivermectin, metronidazole, selenium sulfide, as well as conventional lid hygiene.[11]

Waiting in the wings for *Demodex* treatment is Tarsus' anti-parasitic drug TP-03. It's due to finish Phase III trials this year, and the company may submit its New Device Application to the FDA shortly afterward.

PEARLS

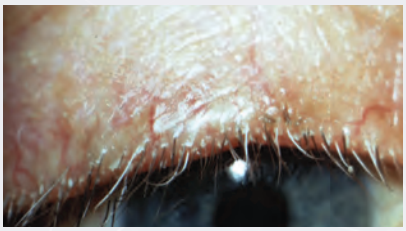
After having seen many patients with blepharitis and TDS over the years, I've developed certain strategies and approaches that work, such as the following:

• ***Show them images.*** Something I've found helpful is to have a number of laminated images depicting varying degrees of severity of a variety of anterior segment diseases, e.g., the Meiboscale to demonstrate the different grading levels of meibomian gland loss right there in the clinic. I can show patients the photos and identify their personal level of loss and they get the idea immediately—they love it.

I also show them a standard grading system for *Demodex* (mild, moderate and severe) and where they land on it. They learn their lid anatomy and can then look in the mirror and see their own condition reflected in the images. Similarly, I have images depicting conjunctival injection and various levels of lipid layer thickness.

Along with these images of disease signs, I also have cards illustrating symptoms. They see the images and they can relate to questions such as: Is it burning like soap in your eye? Is it scratching like sand in your eye? Is it itching like a mosquito bite? Is it a tearing problem?

• ***"Telephone" diagnosis.*** You'd be surprised how much you can learn just by listening to a patient's chief complaint and history of the present illness, even if they're not in front of you for an exam. I often tell residents this is like being able to do a "telephone" diagnosis in which you can rule out certain diseases and triangulate the problem just by obtaining a detailed and focused history. For instance, knowing how long the condition's been bothering the patient (years, months, days, hours), whether it's one eye or both eyes that are affected or if the redness in the eye is diffuse or sectoral can eliminate some



***Demodex* with typical cylindrical sleeves on lashes. Here, lashes were pulled and examined.**

diagnoses. I also ask which treatments have been helpful and which ones haven't worked. I press them to admit whether they actually helped, even a little bit for a short period of time. Response to therapy provides important information to help isolate the diagnosis.

• ***Treat monocularly first.*** As a kind of corollary to the previous point, I always begin treatment in one eye first. Why? Because, as mentioned, this patient population can be fixated on their eye problem and be depressed and anxious. They need to see and feel improvement. If you start treatment in both eyes and there is actually some improvement, it'll be difficult for them to remember how their eyes felt weeks ago and notice the difference now. If you just treat one eye, though, and leave the other eye untreated, they'll definitely notice the difference between their eyes.

• ***The sunburn analogy.*** I also try to impart upon patients the idea that their problem is chronic and it will never completely resolve. As such, prophylactic treatment is key. Just like putting sunblock on after you've gotten a sunburn won't work, it's harder to make your eyes better if you wait for the irritation to use a drop or treatment. They've got to manage their lids and ocular surface constantly in order to prevent and/or reduce the irritation.

In summary, blepharitis is a common, chronic, ocular surface disease with multiple etiologies and complex pathophysiology than can be effectively managed through an interprofessional team of technicians, optometrists and ophthalmologists, supported by a thoughtful patient education program. Regular and careful eyelid hygiene is the most important chronic therapy, with topical antibiotic and immunosuppressive agents are used for acute exacerbations. *Demodex* is an important diagnostic challenge and, now that we're armed with a higher index of suspicion for it, should be better managed in the future. Always rule out more serious eyelid disease including sebaceous cell and squamous cell carcinoma for those more severe and usually chronic conditions that are unresponsive to conventional therapy. I hope the techniques and pearls I've shared can help you more accurately diagnose and effectively treat your blepharitis patients.

Dr. Bouchard is the John P. Mulcahy Professor of Ophthalmology and Chair of the Department Ophthalmology at Loyola University in Chicago. He has no financial interest in any of the products mentioned.

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