

Applications of epithelial thickness mapping in corneal refractive surgery

Dan Z. Reinstein^{1,2,3,4}, Timothy J. Archer^{1,4}, Ryan S. Vida¹

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Abstract:

In this review, we discuss the applications of epithelial thickness mapping in corneal refractive surgery. The review describes that the epithelial thickness profile is nonuniform in the normal eye, being thinner superiorly than inferiorly and thinner temporally than nasally. It is postulated that this is due to the eyelid forces and blinking action on the superior cornea. Changes in the epithelial thickness profile have been found to be highly predictable, responding to compensate for changes in the stromal curvature gradient, using the eyelid as an outer template. This leads to characteristic changes in the epithelial thickness profile that can be used for early screening in keratoconus, postoperative monitoring for early signs of corneal ectasia, and for determining whether further steepening can be performed without the risk of apical syndrome following primary hyperopic treatment. Compensatory epithelial thickness changes are also a critical part of diagnosis in irregular astigmatism as these partially mask the stromal surface irregularities. The epithelial thickness map can then be used to plan a trans-epithelial photorefractive keratectomy treatment for cases of irregularly irregular astigmatism.

Keywords:

Epithelial thickness, keratoconus, mapping, refractive surgery

INTRODUCTION

The corneal epithelium is a highly active, self-renewing layer; a complete turnover occurs in approximately 5–7 days.^[1] Despite this high turnover rate, the epithelium must maintain the same thickness profile overtime to maintain corneal power and, hence, ocular refraction. As described by Alfred Vogt in 1921,^[2] it is known that the corneal epithelium has the ability to alter its thickness profile to compensate for changes in stromal surface curvature to try and re-establish a smooth, symmetrical optical surface. Understanding this epithelial compensatory mechanism is crucial to fully understand how the cornea will respond to different conditions and surgical procedures. As the refractive index of epithelium and stroma are sufficiently different (1.401 vs. 1.377),^[3] the epithelial-stromal interface constitutes an important refractive interface within the cornea, with a mean power contribution estimated at approximately -1.40 D.^[3] Therefore, knowledge

of the epithelial thickness profile and how it may change after corneal surgery could positively contribute to the accuracy of refractive corneal and intraocular lens surgery.

HISTORY OF THE MEASUREMENT OF EPITHELIAL THICKNESS

The first real measurement of the epithelium *in vivo* was made in 1979 by Brian Holden using optical pachymetry.^[4] In 1993,^[5] we started measuring epithelial thickness using very high-frequency (VHF) digital ultrasound and published a 3 mm diameter map in 1994.^[6-9] By 2000, we had improved this method to generate a 10 mm map.^[10-27] VHF digital ultrasound was further developed and is now commercially available as the Artemis Insight 100 VHF digital ultrasound arc-scanner (ArcScan Inc, Golden, CO), which has been previously described in detail.^[6,10,14]

During the 1990s, optical pachymetry was used for a number of studies measuring epithelial thickness.^[28-30] Epithelial thickness was studied using histology from 1992,^[31-34] Torben

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¹London Vision Clinic, London, ⁴School of Biomedical Sciences, Ulster University, Coleraine, United Kingdom, ²Department of Ophthalmology, Columbia University Medical Center, New York, USA, ³Department of Ophthalmology, Sorbonne Université, Paris, France

Address for correspondence:
Dr. Dan Z. Reinstein,
London Vision Clinic, 138
Harley Street, London W1G 7
LA, United Kingdom.
E-mail: dzr@londonvisionclinic.com

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Moller-Pedersen^[35-37] started using confocal microscopy in 1997, and optical coherence tomography (OCT) was first used for measuring the epithelium in 2001.^[38-41] Epithelial thickness maps in an 8 mm diameter using OCT were published by Haque in 2008,^[42] followed by David Huang's group in 2012,^[43] which are now commercially available using the RTVue/Avanti OCT (Optovue, Fremont, CA). Since then, other OCT devices have been developed that include epithelial thickness mapping, such as the MS-30 OCT (CSO, Florence, Italy) and Cirrus HD OCT (Carl Zeiss Meditec, Jena, Germany).

NORMAL CORNEAL EPITHELIUM

Before looking at more complicated situations, it is useful to consider the epithelial thickness profile in a population of normal eyes.^[14] Somewhat surprisingly, we demonstrated using VHF digital ultrasound that the epithelium was not a layer of homogeneous thickness as had previously been thought, but followed a very distinct pattern [Figure 1a]; on average the epithelium was 5.7 μm thicker inferiorly than superiorly, and 1.2 μm thicker nasally than temporally, with a mean central thickness of 53.4 μm . This nonuniformity seems to provide evidence that the epithelial thickness is regulated by eyelid mechanics and blinking, as we suggested in 1994.^[5] We postulated that the eyelid might effectively be chafing the surface epithelium during blinking and that the posterior surface of the semi-rigid tarsus provides a template for the outer shape of the epithelial surface. During blinking, which occurs on average between 300 and 1500 times per hour,^[44] the vertical traverse of the upper lid is much greater than that of the lower lid. Doane^[45] studied the dynamics of eyelid anatomy during blinking and found that during a blink the descent of the upper eyelid reaches its maximum speed at about the time it crosses the visual axis. As a consequence, it is likely that the eyelid applies more force on the superior than the inferior cornea. Similarly, the friction on the cornea during lid closure is likely to be greater temporally than nasally as the outer canthus is higher than the inner canthus (mean intercanthal angle = 3°), and the temporal portion of the lid is higher than the nasal lid (mean upper lid angle = 2.7°).^[46] Therefore, it seems that the nature of the eyelid completely explains the nonuniform epithelial thickness profile of a normal eye.

EPITHELIAL PROFILE AFTER ORTHOKERATOLOGY

Further evidence for this theory is provided by the epithelial thickness changes observed in orthokeratology.^[18] In orthokeratology, a shaped contact lens is placed on the cornea overnight that sits tightly on the cornea centrally but leaves a gap in the mid-periphery. Therefore, the natural template provided by the posterior surface of the semi-rigid tarsus of the eyelid is replaced by an artificial contact lens template designed to fit tightly to the center of the cornea and loosely paracentrally. We found significant epithelial thickness changes with central thinning and mid-peripheral thickening showing that the epithelium had remodeled according to the template provided

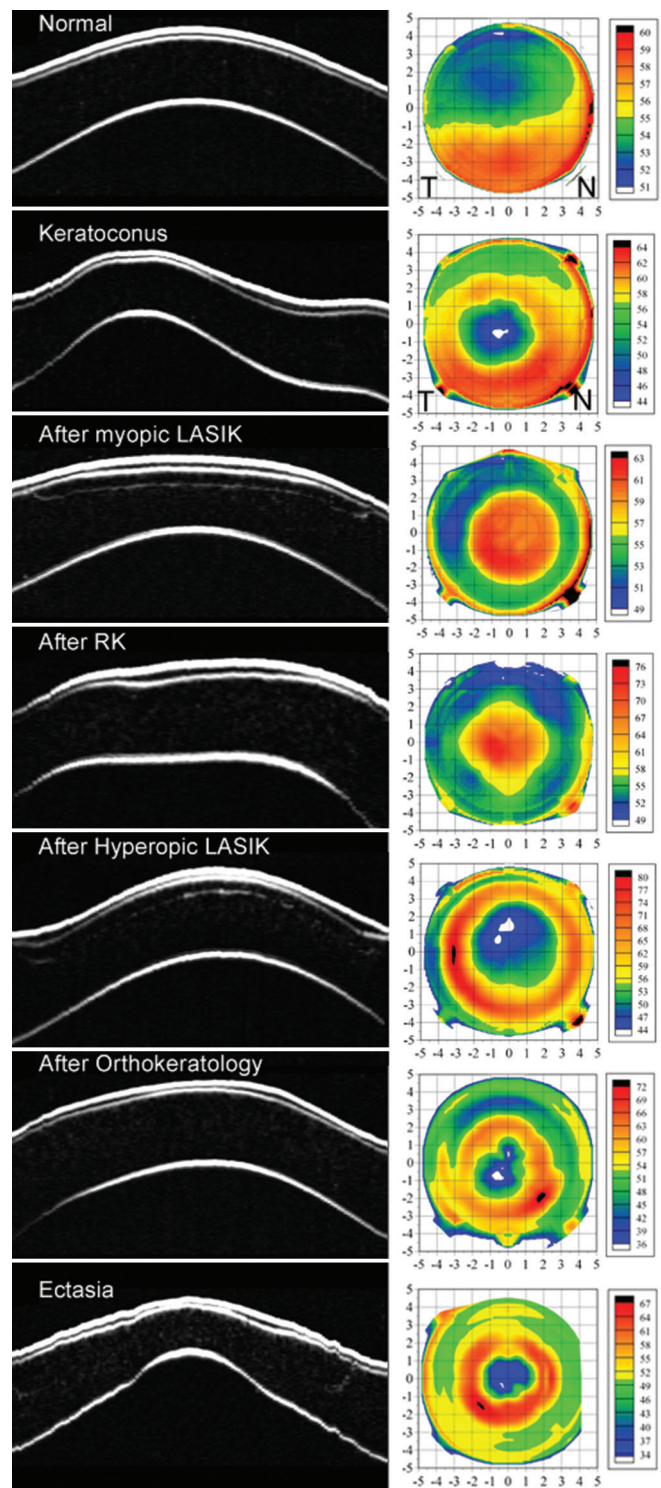


Figure 1: B-scan and epithelial thickness map in a population of normal eyes (1), keratoconic eyes (2), after myopic LASIK (3), after RK (4), after hyperopic LASIK (5), after orthokeratology (6), and in ectasia (7)

by the contact lens [Figure 1b], i.e. the epithelium is chafed and squashed by the lens centrally while the epithelium is free to thicken paracentrally where the lens is not so tightly fitted.

This epithelial change has a lenticular concave shape, which contributes the majority of the achieved refractive effect. This

change is forced on the epithelium by the shape of the contact lens template, but once the lens is removed the epithelium will return to its original shape according to the natural template provided by eyelid forces due to blinking and closure. This explains the temporary nature of orthokeratology.

EPITHELIAL THICKNESS CHANGES AFTER MYOPIC REFRACTIVE SURGERY

The importance of epithelial changes in corneal refractive surgery has probably been underestimated. Significant changes in epithelial thickness profiles after both myopic photorefractive keratectomy (PRK)^[28,34] and myopic laser *in situ* keratomileusis (LASIK)^[15,25,47-50] have been demonstrated and implicated in regression as well as in the inaccuracy of topographically guided excimer laser ablation.^[9,13,27,51-53] A lenticular epithelial thickness change has been shown after myopic laser ablation; central epithelial thickening partially compensates for the ablated stromal tissue [Figure 1c].^[15,25,47-50] A similar change is seen after radial keratotomies (RK) [Figure 1d] although the epithelium responds to changes in curvature alone after RK without tissue removal.^[24] In our study, these epithelial thickness changes were present in eyes up to 26 years after the RK procedure, which indicates that epithelial changes are a permanent response to corneal curvature changes.

As well as central epithelial thickening after myopic LASIK, there is peripheral epithelial thinning in an annulus immediately outside the optical zone. As the central epithelial thickening is partially compensating for stromal tissue removal, the peripheral epithelial thinning is partially compensating for the expansion of the peripheral stroma as the lamellae relax having been severed by the creation of flap and ablation. This peripheral stromal expansion has been measured by VHF digital ultrasound^[10] and also observed using Orbscan tomography after phototherapeutic keratectomy (PTK).^[54]

Given the different refractive index between the epithelium and stroma, unpredicted changes in the epithelial lenticule after surgery as described will result in unplanned refractive shifts. This is one of the reasons why current ablation depths and profiles (“nomograms”) differ from theoretical ablation profiles—they incorporate the average change of epithelial power for a given level of stromal surface flattening (level of myopia treated). This made an immediate impact on corneal refractive surgery when the first results of PRK were found to be undercorrected, due to the fact that the Munneryn *et al.* ablation profile formula had assumed that the epithelial thickness would not change after surgery.^[55]

EPITHELIAL THICKNESS CHANGES AFTER HYPEROPIC REFRACTIVE SURGERY

Compensatory epithelial thickness changes are also seen after hyperopic laser ablation, characterized by central epithelial thinning and paracentral epithelial thickening overlying the

location of maximum ablation [Figure 1e].^[21] As for myopic ablations, the degree of epithelial changes increased for higher corrections, with more central thinning and peripheral thickening as the hyperopia treated increased [Figure 2]. Of note also is that the magnitude of the epithelial thickening was greater than that observed after myopic ablations; the maximum epithelial thickness was 80 μm after a myopic ablation compared with 120 μm after a hyperopic ablation in our studies using VHF digital ultrasound.

Knowledge of the epithelial thickness also has other applications. It is currently assumed that hyperopic LASIK should be limited according to postoperative curvature as too much steepening can result in epitheliopathy or apical syndrome; it is generally accepted that the postoperative curvature should not exceed 49.00–50.00 D.^[56] However, we have previously suggested that central epithelial thickness may be a more useful indicator as it is a direct measurement of the potential risk of the apical syndrome, which occurs once the epithelium is too thin (<25 μm).^[21] For example, in one case from our study,^[21] the maximum simulated keratometry of 50.80 D would most likely prevent the surgeon from treating further hyperopia; however, the central epithelial thickness of 41.7 μm would suggest that the cornea could be steepened further without resulting in an epithelial breakdown. On the other hand, another case from this study demonstrates that the epithelial thickness can be thin (33.7 μm) although the cornea was still relatively flat postoperatively (46.40 D). The curvature limit would allow further hyperopic ablation, whereas the thin, central epithelium would indicate that further steepening might increase the risk of apical syndrome. Therefore, using epithelial thickness measurements, hyperopic retreatments might be performed without risk of apical syndrome while also allowing some patients to have retreatment who would otherwise have been rejected for further surgery due to high keratometry postoperatively.^[57]

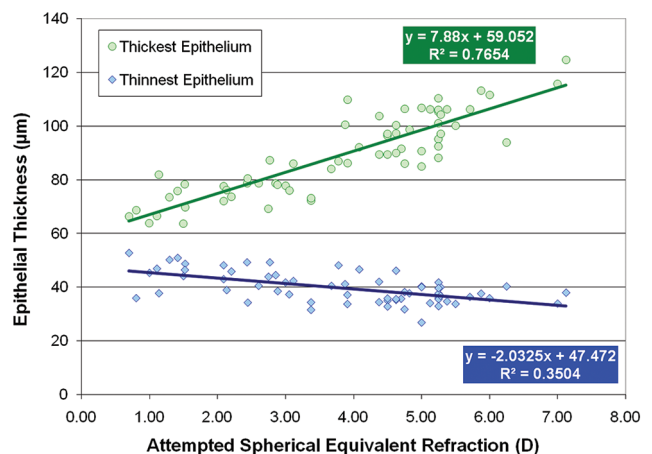


Figure 2: Scatter plot showing the minimum and maximum epithelial thickness plotted against the attempted spherical equivalent refraction, showing that the thinnest point was thinner and the thickest point was thicker for higher hyperopic corrections^[21]

KERATOCONIC EPITHELIUM

In keratoconus, the epithelium is known to thin in the area overlying the cone,^[58-60] and in advanced keratoconus, there may be excessive epithelial thinning leading to a breakdown in the epithelium. The average epithelial thickness profile in keratoconus revealed that the epithelium was significantly more irregular in thickness compared to the normal population [Figure 1b].^[19] The epithelium was thinnest at the apex of the cone and this thin epithelial zone was surrounded by an annulus of thickened epithelium, which we refer to as an epithelial doughnut pattern. The location of the thinnest epithelium within the central 5 mm of the cornea was displaced 0.48 mm (± 0.66 mm) temporally and 0.32 mm (± 0.67 mm) inferiorly with reference to the corneal vertex. The mean epithelial thickness for all eyes was 45.7 ± 5.9 μm (range: 33.1–56.3 μm) at the corneal vertex, 38.2 ± 5.8 μm at the thinnest point (range: 29.6–52.4 μm), and 66.8 ± 7.2 μm (range: 54.1–94.4 μm) at the thickest location. The epithelial thickness was outside the range observed in the normal population in both the thinnest and thickest regions, demonstrating the extent of the change in epithelial thickness in keratoconus.^[19] The degree of epithelial compensation was found to be correlated with the severity of the keratoconus. A similar epithelial thickness profile has also been reported using OCT.^[43,61-65]

EPITHELIAL PROFILE AFTER ECTASIA

In ectasia, epithelial changes observed are similar to those seen in keratoconus with an epithelial donut pattern of epithelial thinning over the ectatic cone surrounded by an annulus of thicker epithelium [Figure 1g].^[22]

RULES FOR EPITHELIAL REMODELING

All of the examples described above demonstrate how the epithelial thickness remodels following any change to the stromal surface. As well as after myopic excimer laser ablation, hyperopic excimer laser ablation, RK, orthokeratology, keratoconus, and ectasia, epithelial thickness changes have also been described to compensate for intra-corneal ring segments,^[11] irregularly irregular astigmatism after corneal refractive surgery,^[9,13,27,51-53] Figure 1 shows the epithelial thickness profile in a number of different situations.

In all of these cases, the epithelial thickness changes are clearly a compensatory response to the change to the stromal surface and can all be explained by the theory of eyelid template regulation of epithelial thickness. Compensatory epithelial thickness changes can be summarized by the following rules:

1. The epithelium thickens in areas where tissue has been removed or the curvature has been flattened (e.g., central thickening after myopic ablation^[15,25,29,47-50] or RK^[18] and peripheral thickening after hyperopic ablation^[21])
2. The epithelium thins over regions that are relatively elevated or the curvature has been steepened (e.g., central

thinning in keratoconus,^[19,43,61-65] ectasia^[22] and after hyperopic ablation^[21]).

3. The magnitude of epithelial changes correlates to the magnitude of the change in curvature (e.g., more epithelial thickening for higher myopia,^[15,29,47] higher hyperopia,^[21] more advanced keratoconus^[19,43,61-65])
4. The amount of epithelial remodeling is defined by the rate of change of curvature of an irregularity; there will be more epithelial remodeling for a more localized irregularity^[9,13,27,51-53] The epithelium effectively acts as a low pass filter, smoothing small changes almost completely, but only partially smoothing large changes.

The rate of change of curvature is really the key to understanding the entirely predictable epithelial response. This can be appreciated by the fact that there is almost twice as much epithelial thickening after a hyperopic ablation^[21] compared with a myopic ablation,^[15] and the total epithelial compensation for small, very localized stromal loss such as after a corneal ulcer [Figure 3].^[21] Similarly, the effectiveness of a trans-epithelial PTK (TE-PTK) procedure increases as the localization of the irregularities increases (see more later).^[13,27,51,52] This also explains why the amount of refractive regression decreased as the optical zone diameter was made larger during the 1990s.^[66,67] Another example of this is that the epithelial thickness profile becomes more regular following a combined topography-guided and cross-linking treatment for keratoconus; stromal elevation of the cone is reduced both by the ablation and the flattening effect of cross-linking, which results in a more regular stromal surface and hence a more regular epithelial thickness profile.^[68]

FACTORS INFLUENCING THE EPITHELIUM

There are some exceptions to these rules as the epithelium can

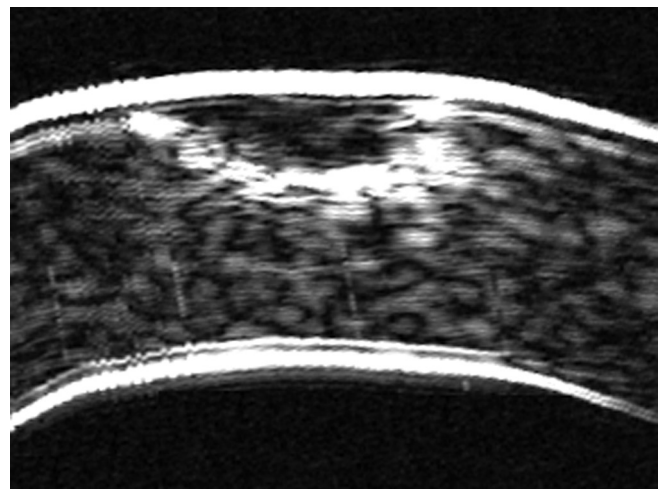


Figure 3: B-scan of a cornea after a corneal ulcer. The total corneal thickness is 536 μm and the epithelial thickness in the location of the corneal ulcer is 209 μm . The epithelial thickening over the region of the corneal ulcer has maintained a consistent curvature of the anterior surface of the cornea

be influenced by some other physiological factors. Epithelial changes associated with anterior basement membrane dystrophy (ABMD) may cause focal areas of a thickening that can be identified on clinical slit-lamp examination. These clinical findings will often have corresponding changes in the epithelial thickness map [Figure 4]. If there is paracentral thickening, the epithelial thickness profile can resemble a keratoconus pattern as shown in Figure 5. In addition to ABMD, dry eye can also affect the epithelium. Kanellopoulos and Asimellis^[69] found the central epithelial thickness in dry eye patients to be $59.5 \pm 4.2 \mu\text{m}$ compared to $53.0 \pm 2.7 \mu\text{m}$ in the control group. Figure 6 shows an extreme example of this in a patient that had an episode of Bell's palsy resulting in an incomplete blink. The right eye epithelium thickened by $14 \mu\text{m}$ centrally during the episode and subsequently returned to normal to match the left eye once blinking function recovered.

RATE OF CHANGE IN EPITHELIAL THICKNESS

The other aspect of the changes in the epithelial thickness profile described above is the speed at which the changes occur. This turns out to be extremely fast with dramatic

overnight changes having been demonstrated after myopic LASIK [Figure 7]^[25] and complete epithelial remodeling 1 day after flap rotation of a free cap.^[12,70]

Orthokeratology is another example of this, as it has been shown that the refractive changes are mainly due to epithelial thickness changes; overnight, the lenses compress the central cornea to induce central epithelial thinning and allow paracentral epithelial thickening.^[18] Therefore, the temporary nature of the effect demonstrates the speed of epithelial remodeling as it returns to its natural state.

After myopic LASIK, we have previously shown that the epithelial thickness continues to change during the first 3 months, after which it remains completely stable [Figure 7].^[25] Overnight, there is central epithelial thickening of approximately $1\text{--}2 \mu\text{m}$, but paracentral epithelial thinning of approximately $4\text{--}6 \mu\text{m}$ – we postulated that this thinning was in response to edema. Between 1 day and 1 month, the epithelium thickened across the entire 7 mm diameter zone by up to $5 \mu\text{m}$, with more pronounced thickening within the central 4 mm. Between 1 and 3 months, the epithelium continued to thicken in the central 7 mm diameter zone by approximately an additional $1 \mu\text{m}$. These epithelial changes partially explain the regression seen after

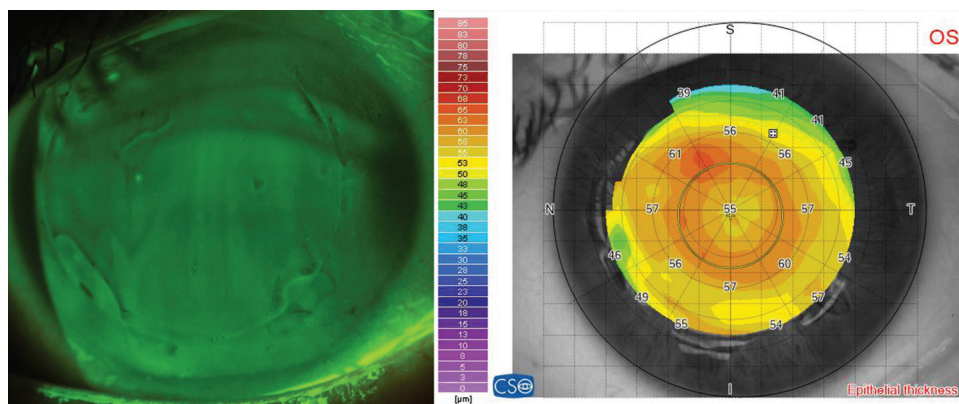


Figure 4: Slit-lamp photograph under heavy fluorescein staining showing focal anterior basement membrane dystrophy (left) and the associated thickening seen on the MS-39 epithelial map (right)

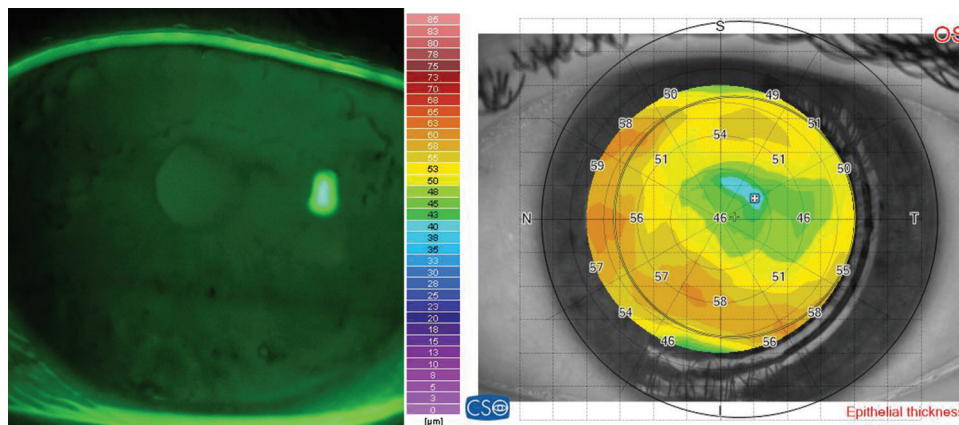


Figure 5: Slit-lamp photography under heavy fluorescein staining showing diffuse anterior basement membrane dystrophy (left) and the associated thickening seen on the MS-39 epithelial map (right). The epithelial pattern mimics that seen in keratoconus with an area of central thinning, surrounded by thickening

myopic LASIK in the first 3 months and agree with the common finding that refractive stability is attained after 3 months.^[71]

INFLUENCE OF THE EPITHELIAL THICKNESS PROFILE ON CORNEAL TOPOGRAPHY

Epithelial changes such as those described above will have an impact on the ocular refraction, however, the biggest clinical impact of epithelial changes is on corneal front surface topography; since the epithelium compensates for stromal irregularities, the presence of an irregular stromal surface is either partially or totally masked from corneal front surface topography. Therefore, corneal front surface topography does not always tell the whole story, and in some cases does not provide the necessary information to establish a correct diagnosis.

KERATOCONUS SCREENING

In keratoconus, the epithelium remodels to follow a distinctive epithelial donut pattern, characterized by a localized central zone of thinning surrounded by an annulus of thick epithelium, demonstrating that the epithelium compensates

for the underlying stromal cone by thinning over the cone and thickening around the cone.^[19,43,61-65] In early keratoconus, the epithelial donut pattern will act to minimize the extent of the cone on the front corneal surface and potentially fully compensate the stromal surface irregularity and render a completely normal front corneal surface.^[16] Therefore, epithelial thickness mapping has the potential to exclude the appropriate patients by detecting keratoconus earlier or confirming keratoconus in cases where topographic changes may be clinically judged as being “within normal limits.” Second, epithelial thickness profiles may be useful in excluding a diagnosis of keratoconus despite suspect topography; epithelial thickening over an area of topographic steepening implies that the steepening is not due to an underlying ectatic surface.

Based on this qualitative diagnostic method, we then set out to derive an automated classifier to detect keratoconus using epithelial thickness data, together with Ron Silverman and his group at Columbia University.^[72] We used stepwise linear discriminant analysis (LDA) and neural network (NN) analysis to develop multivariate models based on combinations of 161 features comparing a population of 130 normal and 74 keratoconic eyes. This process resulted in a six-variable model that provided an area under the receiver operating curve of 100%, indicative of complete separation of keratoconic from normal corneas. Test-set performance averaged over ten trials, gave a specificity of $99.5\% \pm 1.5\%$ and sensitivity of $98.9\% \pm 1.9\%$. Maps of the average epithelium and LDA function values were also found to be well correlated with keratoconus severity grade. Other groups have also been working on automated classification algorithms based on epithelial thickness data obtained by OCT.^[43,62] Figure 8 shows an example of early keratoconus in which the front surface topography and Pentacam tomography appear normal, however, the epithelial thickness profile demonstrates focal thinning which is identified as keratoconus by this automated algorithm.

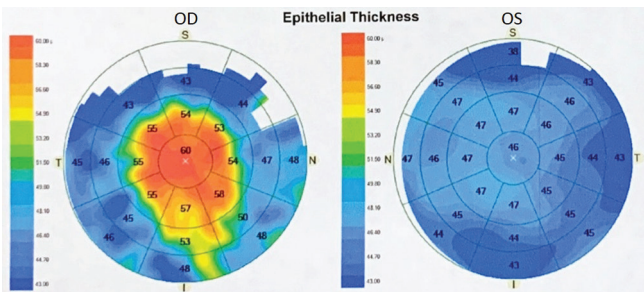


Figure 6: Cirrus HD optical coherence tomography epithelial thickness map showing thickening in the right eye due to decreased blinking ability during a Bell's palsy episode. The left eye epithelial thickness is normal

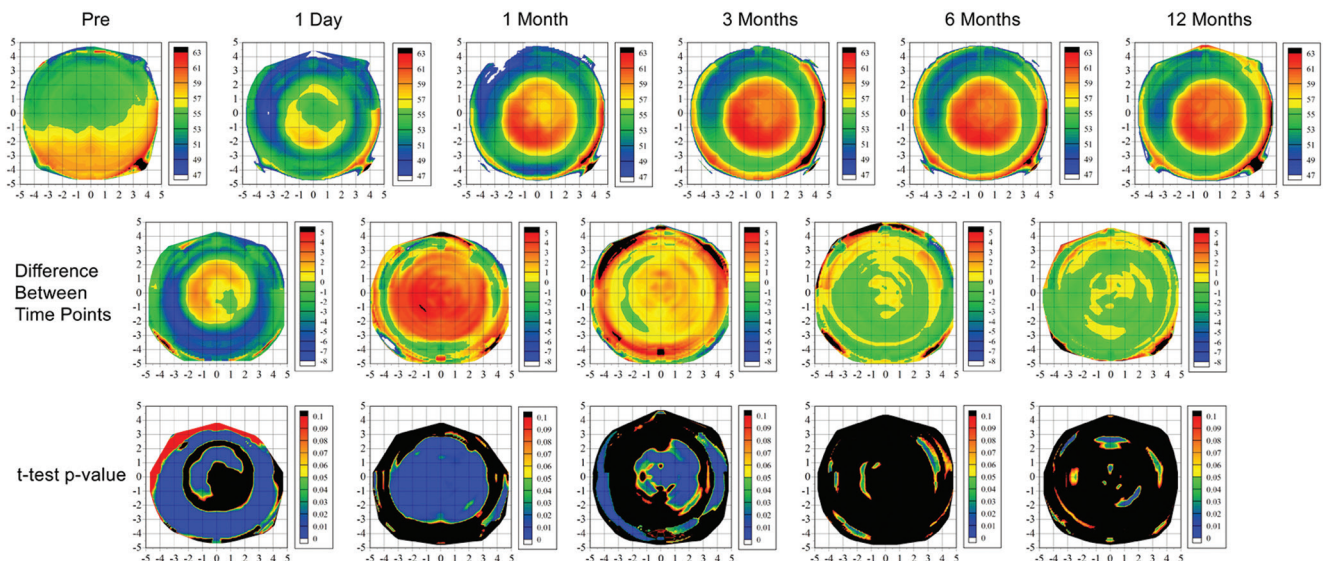
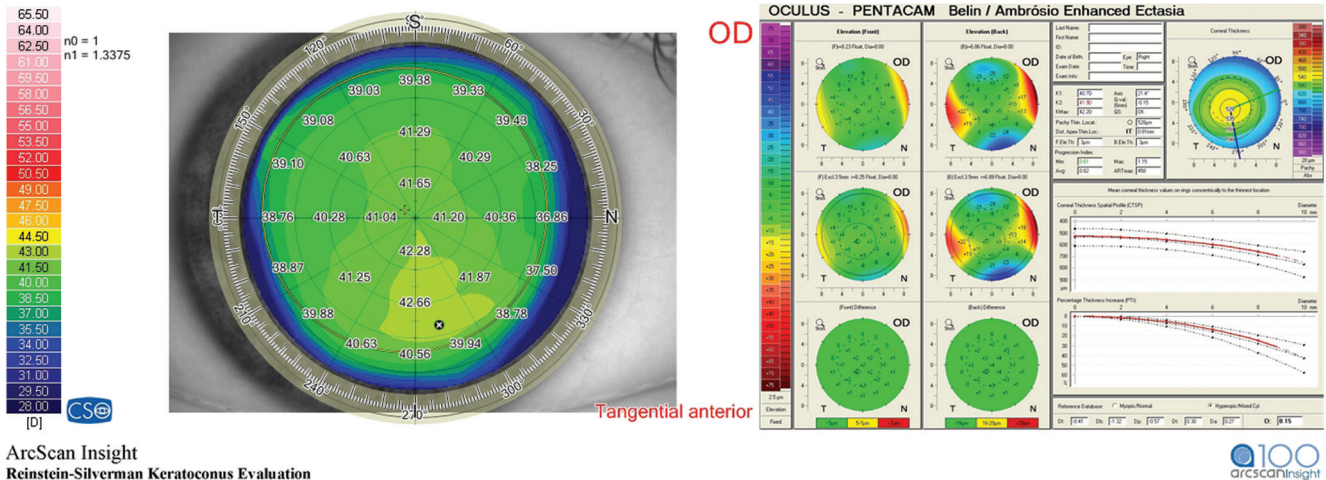
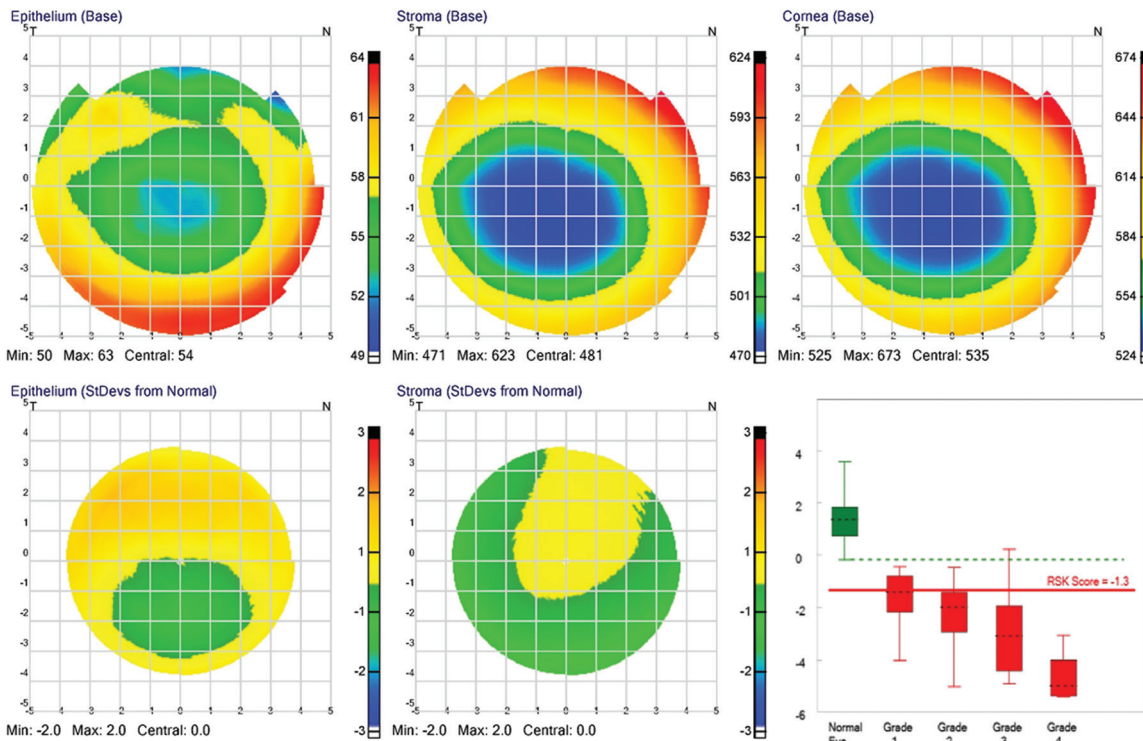


Figure 7: Longitudinal changes in epithelial thickness after myopic laser *in situ* keratomileusis^[25]



ArcScan Insight
Reinstein-Silverman Keratoconus Evaluation
 Patient:
 Scanned: Right eye (OD)



† Epithelial Remodeling as Basis for Machine-Based Identification of Keratoconus
 (Ronald H. Silverman, Raksha Urs, Arindam RoyChoudhury, Timothy J. Archer, Marine Gobbe and Dan Z. Reinstein)
Invest Ophthalmol Vis Sci. 2014;55:1580-1587. DOI:10.1167/iov.13-12578

Figure 8: MS-39 (top left) shows a relatively normal corneal curvature with a slight superior to inferior difference in keratometry. The corresponding Pentacam Belin Ambrosia Display (top right) shows a normal front and back surface elevation. The ArcScan Insight 100 shows an area of epithelial thinning with surrounding thickening. This is further highlighted in the bottom left map which shows the thickness standard deviations from the normal population. The epithelial map confirms that despite the topography and tomography findings, the patient has keratoconus

TRANS-EPITHELIAL PHOTOTHERAPEUTIC KERATECTOMY/ STROMAL SURFACE TOPOGRAPHY-GUIDED CUSTOM ABLATION

Despite all the advances in corneal topography and ocular wavefront measurement, it is not always possible to diagnose the cause of subjective visual complaints by these means alone because the compensatory epithelial thickness changes

act to partially mask the true stromal surface irregularity. In 1994, we coined *Reinstein's Law of Epithelial Compensation* for irregular astigmatism:^[73] "Irregular astigmatism results in irregular epithelium." If a patient presents with stable irregular astigmatism, by definition the epithelium has reached its maximum compensatory function by thinning over peaks and thickening over troughs in the stromal surface. As mentioned earlier, the epithelium can compensate almost completely for very localized irregularities. Therefore, topography or

wavefront-guided treatments may lead to a sub-optimal treatment plan and potentially make things worse.^[9,13,27,51-53] Instead, we need a method to target the irregularities masked by the epithelium, something that is achieved, by definition, by TE-PTK.^[13,27,51,52]

This is demonstrated by the following case example in which a short flap had occurred during the primary LASIK procedure, but the ablation was also carried out, resulting in irregularly irregular astigmatism and associated visual symptoms of diplopia, halos, and starbursts.^[27] The patient then underwent both a topography-guided and a wavefront-guided retreatment, which actually made the symptoms worse. On presentation at our clinic, the front surface topography showed a truncated optical zone, although it is feasible that this could have been interpreted as a decentration. An Artemis Insight 100 VHF digital ultrasound exam demonstrated the true diagnosis was a short flap with ablation: The flap was found to have a short nasal hinge and the stromal surface was indented near the hinge which had been compensated for by epithelial thickening and epithelial thinning over the ridge immediately nasal to the crevice [Figure 9]. The local difference in epithelial thickness was 36 μm within 0.7-mm demonstrating the severity of the localized irregularity caused by the double ablation of the stromal surface and the underside of the flap.

A TE-PTK procedure was performed and the postop result as shown in Figure 9. Prior to treatment, we use a technique called digital subtraction pachymetry,^[13,27,51,52] in which the breakthrough pattern and remaining epithelium at regular lamellar depths of TE-PTK ablation are simulated. These maps are used intraoperatively to calibrate the ablation depth that

has been achieved to avoid removing excess stromal tissue, which is often at a premium in repair cases.

The nasal ridge on the stromal surface had been almost completely smoothed, which could also be seen on the epithelial thickness map where the localized nasal 36 μm difference had disappeared and the postop epithelium showed a regular thickness profile. The truncation of the optical zone of the hyperopic ablation on topography had also been restored, with the difference map showing the significant change in the nasal region. The patient also reported a large improvement in the visual symptoms.

The only disadvantage of TE-PTK is that it is limited to treat only the proportion of the stromal irregularities compensated for by the epithelium (as defined by the rate of change of curvature of the stromal irregularity), so more than one procedure is often required. Given this limitation of TE-PTK, and the limitation that epithelial changes mask the true stromal surface irregularity from topography-guided custom ablation, there is still room for improvement in techniques to repair corneal refractive surgery complications. The final solution in repair treatments is going to be a custom ablation profile based on stromal surface topography, something which can be measured by subtracting the epithelial thickness profile from the front corneal surface topography.

REFRACTIVE EFFECT OF THE EPITHELIUM IN TRANS-EPITHELIAL PHOTOTHERAPEUTIC KERATECTOMY

TE-PTK is an excellent treatment option in irregularly irregular astigmatism. However, the refractive effect of the epithelium

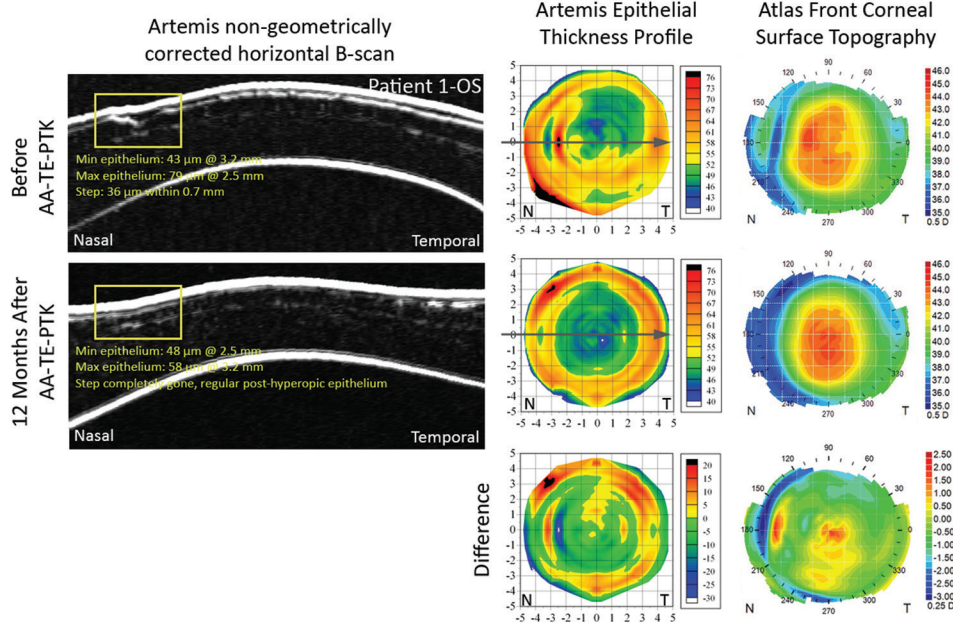


Figure 9: B-scan, epithelial thickness map and front surface topography before and after trans-epithelial phototherapeutic keratectomy to smooth a stromal irregularity caused by a short flap with ablation^[27]

should be considered to evaluate the predicted outcome and impact that this will have on future treatments. The stromal ablation is guided by the epithelial thickness profile, meaning that a TE-PTK ablation may induce a refractive change at the same time as regularizing the stromal surface. For example, if the epithelium is thinner centrally than peripherally, then a TE-PTK will act like a myopic ablation with deeper central ablation. Or it can act like an astigmatic correction if the epithelial thickness is orthogonally asymmetric, such as in this case report, where a TE-PTK induced a refractive change of $+2.24 - 3.97 \times 120$.^[51] This effect has been quantified in the analysis of our TE-PTK population.^[52] There was a change of more than 0.50 D in 59% of cases, in the hyperopic direction in 33%, and the myopic direction in 24% of eyes. Therefore, until we have a method for accurately predicting this change, patients should be counseled to expect that another treatment will be required to address the remaining refraction.

REDUCTION OF STROMAL SURFACE IRREGULARITY MEASURED BY EPITHELIAL THICKNESS CHANGES

As we know that a higher degree of epithelial compensation occurs in a more irregular stromal surface, the variability of epithelial thickness can be used as a parameter to measure of the extent of the stromal surface irregularity. We defined this as the within-eye epithelial thickness range, which was calculated as the difference between the minimum and maximum epithelial thicknesses in the location of the irregularity. In a population of 41 cases, the change in within-eye epithelial thickness range was calculated to quantify the change in stromal surface irregularities achieved by the TE-PTK procedure [Figure 10].^[52]

A reduction in epithelial thickness range was achieved in 89% of treatments, with a mean change of $-12 \pm 10 \mu\text{m}$ (range: -31 to $5 \mu\text{m}$), demonstrating the improvement in the stromal surface irregularity.

SUMMARY

Our work with VHF digital ultrasound mapping of epithelial thickness has demonstrated the dramatic and significant changes that occur whenever changes are made to the curvature of the stromal surface. Rather than the epithelium being a benign layer of little interest to refractive surgeons, understanding and compensating for epithelial thickness changes is one of the missing links in perfecting refractive surgery. For example, it was assumed that the epithelium would not change after an excimer laser ablation when the original ablation profiles were designed by Munnerlyn *et al.*,^[55] however it quickly became clear that these profiles were undercorrecting largely due to the epithelial response. We now know that the epithelium will always change if the stromal surface is changed, so we can now start to proactively use this knowledge to improve a number of areas of refractive surgery. Epithelial thickness mapping provides another method for detecting keratoconus, with the ability to detect keratoconus earlier than front surface

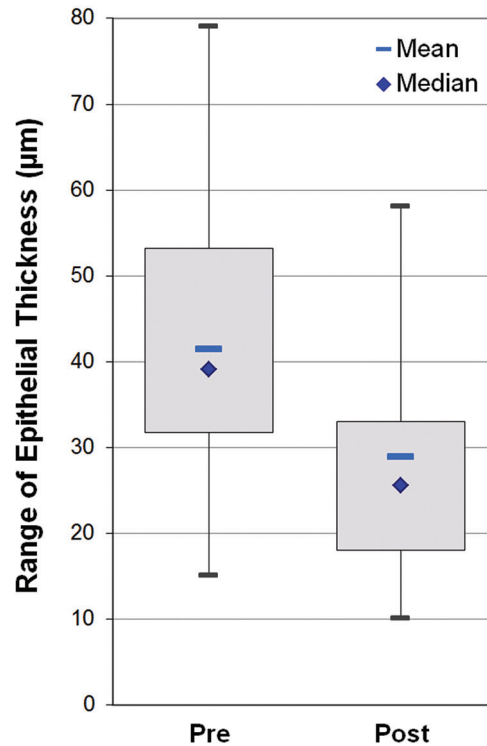


Figure 10: Epithelial thickness range before and after trans-epithelial-phototherapeutic keratectomy^[52]

topography and also to exclude keratoconus in cases with suspicious back surface elevations. Diagnosis and repair of irregularly irregular astigmatism are also being revolutionized by considering the epithelial thickness as this enables the stromal surface to be measured.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Hanna C, O'Brien JE. Cell production and migration in the epithelial layer of the cornea. *Arch Ophthalmol* 1960;64:536-9.
- Vogt A. *Textbook and Atlas of Slit Lamp Microscopy of the Living Eye*. Bonn: Wayenborgh Editions; 1981.
- Patel S, Marshall J, Fitzke FW 3rd. Refractive index of the human corneal epithelium and stroma. *J Refract Surg* 1995;11:100-5.
- Holden BA, Payor S. Changes in thickness in the corneal layers. *Am J Optom* 1979;56:821.
- Reinstein DZ, Silverman RH, Coleman DJ. High-frequency ultrasound measurement of the thickness of the corneal epithelium. *Refract Corneal Surg* 1993;9:385-7.
- Reinstein DZ, Silverman RH, Trokel SL, Coleman DJ. Corneal pachymetric topography. *Ophthalmology* 1994;101:432-8.
- Cusumano A, Coleman DJ, Silverman RH, Reinstein DZ, Rondeau MJ,

- Ursea R, *et al.* Three-dimensional ultrasound imaging. Clinical applications. *Ophthalmology* 1998;105:300-6.
8. Silverman RH, Reinstein DZ, Raevsky T, Coleman DJ. Improved system for sonographic imaging and biometry of the cornea. *J Ultrasound Med* 1997;16:117-24.
 9. Reinstein DZ, Silverman RH, Sutton HF, Coleman DJ. Very high-frequency ultrasound corneal analysis identifies anatomic correlates of optical complications of lamellar refractive surgery: Anatomic diagnosis in lamellar surgery. *Ophthalmology* 1999;106:474-82.
 10. Reinstein DZ, Silverman RH, Raevsky T, Simoni GJ, Lloyd HO, Najafi DJ, *et al.* Arc-scanning very high-frequency digital ultrasound for 3D pachymetric mapping of the corneal epithelium and stroma in laser *in situ* keratomileusis. *J Refract Surg* 2000;16:414-30.
 11. Reinstein DZ, Srivannaboon S, Holland SP. Epithelial and stromal changes induced by intacs examined by three-dimensional very high-frequency digital ultrasound. *J Refract Surg* 2001;17:310-8.
 12. Reinstein DZ, Rothman RC, Couch DG, Archer TJ. Artemis very high-frequency digital ultrasound-guided repositioning of a free cap after laser *in situ* keratomileusis. *J Cataract Refract Surg* 2006;32:1877-83.
 13. Reinstein DZ, Archer T. Combined Artemis very high-frequency digital ultrasound-assisted transepithelial phototherapeutic keratectomy and wavefront-guided treatment following multiple corneal refractive procedures. *J Cataract Refract Surg* 2006;32:1870-6.
 14. Reinstein DZ, Archer TJ, Gobbe M, Silverman RH, Coleman DJ. Epithelial thickness in the normal cornea: Three-dimensional display with Artemis very high-frequency digital ultrasound. *J Refract Surg* 2008;24:571-81.
 15. Reinstein DZ, Srivannaboon S, Gobbe M, Archer TJ, Silverman RH, Sutton H, *et al.* Epithelial thickness profile changes induced by myopic LASIK as measured by Artemis very high-frequency digital ultrasound. *J Refract Surg* 2009;25:444-50.
 16. Reinstein DZ, Archer TJ, Gobbe M. Corneal epithelial thickness profile in the diagnosis of keratoconus. *J Refract Surg* 2009;25:604-610.
 17. Reinstein DZ, Archer TJ, Gobbe M. Stability of LASIK in topographically suspect keratoconus confirmed non-keratoconic by Artemis VHF digital ultrasound epithelial thickness mapping: 1-year follow-up. *J Refract Surg* 2009;25:569-77.
 18. Reinstein DZ, Gobbe M, Archer TJ, Couch D, Bloom B. Epithelial, stromal, and corneal pachymetry changes during orthokeratology. *Optom Vis Sci* 2009;86:E1006-14.
 19. Reinstein DZ, Gobbe M, Archer TJ, Silverman RH, Coleman DJ. Epithelial, stromal, and total corneal thickness in keratoconus: Three-dimensional display with artemis very-high frequency digital ultrasound. *J Refract Surg* 2010;26:259-71.
 20. Reinstein DZ, Archer TJ, Gobbe M, Silverman RH, Coleman DJ. Repeatability of layered corneal pachymetry with the artemis very high-frequency digital ultrasound arc-scanner. *J Refract Surg* 2010;26:646-59.
 21. Reinstein DZ, Archer TJ, Gobbe M, Silverman RH, Coleman DJ. Epithelial thickness after hyperopic LASIK: Three-dimensional display with Artemis very high-frequency digital ultrasound. *J Refract Surg* 2010;26:555-64.
 22. Reinstein DZ, Gobbe M, Archer TJ, Couch D. Epithelial thickness profile as a method to evaluate the effectiveness of collagen cross-linking treatment after corneal ectasia. *J Refract Surg* 2011;27:356-63.
 23. Reinstein DZ, Archer TJ, Gobbe M. Very high-frequency digital ultrasound evaluation of topography-wavefront-guided repair after radial keratotomy. *J Cataract Refract Surg* 2011;37:599-602.
 24. Reinstein DZ, Archer TJ, Gobbe M. Epithelial thickness up to 26 years after radial keratotomy: Three-dimensional display with Artemis very high-frequency digital ultrasound. *J Refract Surg* 2011;27:618-24.
 25. Reinstein DZ, Archer TJ, Gobbe M. Change in epithelial thickness profile 24 hours and longitudinally for 1 year after myopic LASIK: Three-dimensional display with Artemis very high-frequency digital ultrasound. *J Refract Surg* 2012;28:195-201.
 26. Reinstein DZ, Archer TJ, Gobbe M. Stability of epithelial thickness during 5 minutes immersion in 33 degrees C 0.9% saline using very high-frequency digital ultrasound. *J Refract Surg* 2012;28:606-7.
 27. Reinstein DZ, Archer TJ, Gobbe M. Improved effectiveness of trans-epithelial phototherapeutic keratectomy versus topography-guided ablation degraded by epithelial compensation on irregular stromal surfaces. *J Refract Surg*. 2013;29:526-33.
 28. Gauthier CA, Holden BA, Epstein D, Tengroth B, Fagerholm P, Hamberg-Nyström H. Factors affecting epithelial hyperplasia after photorefractive keratectomy. *J Cataract Refract Surg* 1997;23:1042-50.
 29. Gauthier CA, Holden BA, Epstein D, Tengroth B, Fagerholm P, Hamberg-Nyström H. Role of epithelial hyperplasia in regression following photorefractive keratectomy. *Br J Ophthalmol* 1996;80:545-8.
 30. Gauthier CA, Epstein D, Holden BA, Tengroth B, Fagerholm P, Hamberg-Nyström H, *et al.* Epithelial alterations following photorefractive keratectomy for myopia. *J Refract Surg* 1995;11:113-8.
 31. Shieh E, Moreira H, D'Arcy J, Clapham TN, McDonnell PJ. Quantitative analysis of wound healing after cylindrical and spherical excimer laser ablations. *Ophthalmology* 1992;99:1050-5.
 32. Beuerman RW, McDonald MB, Shofner RS, Munnerlyn CR, Clapham TN, Salmeron B, *et al.* Quantitative histological studies of primate corneas after excimer laser photorefractive keratectomy. *Arch Ophthalmol* 1994;112:1103-10.
 33. Lohmann CP, Patmore A, Reischl U, Marshall J. The importance of the corneal epithelium in excimer-laser photorefractive keratectomy. *Ger J Ophthalmol* 1996;5:368-72.
 34. Lohmann CP, Reischl U, Marshall J. Regression and epithelial hyperplasia after myopic photorefractive keratectomy in a human cornea. *J Cataract Refract Surg* 1999;25:712-5.
 35. Li HF, Petroll WM, Møller-Pedersen T, Maurer JK, Cavanagh HD, Jester JV. Epithelial and corneal thickness measurements by *in vivo* Confocal Microscopy Through Focusing (CMTF). *Curr Eye Res* 1997;16:214-21.
 36. Møller-Pedersen T, Li HF, Petroll WM, Cavanagh HD, Jester JV. Confocal microscopic characterization of wound repair after photorefractive keratectomy. *Invest Ophthalmol Vis Sci* 1998;39:487-501.
 37. Møller-Pedersen T, Vogel M, Li HF, Petroll WM, Cavanagh HD, Jester JV. Quantification of stromal thinning, epithelial thickness, and corneal haze after photorefractive keratectomy using *in vivo* confocal microscopy. *Ophthalmology* 1997;104:360-8.
 38. Feng Y, Varikooty J, Simpson TL. Diurnal variation of corneal and corneal epithelial thickness measured using optical coherence tomography. *Cornea* 2001;20:480-3.
 39. Wirbelauer C, Pham DT. Monitoring corneal structures with slitlamp-adapted optical coherence tomography in laser *in situ* keratomileusis. *J Cataract Refract Surg* 2004;30:1851-60.
 40. Haque S, Fonn D, Simpson T, Jones L. Corneal and epithelial thickness changes after 4 weeks of overnight corneal refractive therapy lens wear, measured with optical coherence tomography. *Eye Contact Lens* 2004;30:189-93.
 41. Sin S, Simpson TL. The repeatability of corneal and corneal epithelial thickness measurements using optical coherence tomography. *Optom Vis Sci* 2006;83:360-5.
 42. Haque S, Jones L, Simpson T. Thickness mapping of the cornea and epithelium using optical coherence tomography. *Optom Vis Sci* 2008;85:E963-76.
 43. Li Y, Tan O, Brass R, Weiss JL, Huang D. Corneal epithelial thickness mapping by Fourier-domain optical coherence tomography in normal and keratoconic eyes. *Ophthalmology* 2012;119:2425-33.
 44. Bentivoglio AR, Bressman SB, Cassetta E, Carretta D, Tonali P, Albanese A. Analysis of blink rate patterns in normal subjects. *Mov Disord* 1997;12:1028-34.
 45. Doane MG. Interactions of eyelids and tears in corneal wetting and the dynamics of the normal human eyeblink. *Am J Ophthalmol* 1980;89:507-16.
 46. Young G, Hunt C, Covey M. Clinical evaluation of factors influencing toric soft contact lens fit. *Optom Vis Sci* 2002;79:11-9.
 47. Kanellopoulos AJ, Asimellis G. Longitudinal postoperative lasik epithelial thickness profile changes in correlation with degree of myopia correction. *J Refract Surg* 2014;30:166-71.
 48. Chen X, Stojanovic A, Liu Y, Chen Y, Zhou Y, Utheim TP. Postoperative changes in corneal epithelial and stromal thickness profiles after photorefractive keratectomy in treatment of myopia. *J Refract Surg* 2015;31:446-53.
 49. Rocha KM, Krueger RR. Spectral-domain optical coherence tomography

- epithelial and flap thickness mapping in femtosecond laser-assisted *in situ* keratomileusis. *Am J Ophthalmol* 2014;158:293-301.e1.
50. Tang M, Li Y, Huang D. Corneal epithelial remodeling after LASIK measured by Fourier-domain optical coherence tomography. *J Ophthalmol* 2015;2015:860313.
 51. Reinstein DZ, Archer TJ, Gobbe M. Refractive and topographic errors in topography-guided ablation produced by epithelial compensation predicted by 3D Artemis VHF digital ultrasound stromal and epithelial thickness mapping. *J Refract Surg* 2012;28:657-63.
 52. Reinstein DZ, Archer TJ, Dickeson ZI, Gobbe M. Transepithelial phototherapeutic keratectomy protocol for treating irregular astigmatism based on population epithelial thickness measurements by artemis very high-frequency digital ultrasound. *J Refract Surg* 2014;30:380-7.
 53. Reinstein DZ, Gobbe M, Archer TJ, Youssefi G, Sutton HF. Stromal surface topography-guided custom ablation as a repair tool for corneal irregular astigmatism. *J Refract Surg* 2015;31:54-9.
 54. Dupps WJ Jr, Roberts C. Effect of acute biomechanical changes on corneal curvature after photokeratectomy. *J Refract Surg* 2001;17:658-69.
 55. Munnerlyn CR, Koons SJ, Marshall J. Photorefractive keratectomy: A technique for laser refractive surgery. *J Cataract Refract Surg* 1988;14:46-52.
 56. Varley GA, Huang D, Rapuano CJ, Schallhorn S, Boxer Wachler BS, Sugar A, *et al.* LASIK for hyperopia, hyperopic astigmatism, and mixed astigmatism: A report by the American Academy of Ophthalmology. *Ophthalmology* 2004;111:1604-17.
 57. Reinstein DZ, Carp GI, Archer TJ, Buick T, Gobbe M, Rowe EL, *et al.* LASIK for the correction of high hyperopic astigmatism with epithelial thickness monitoring. *J Refract Surg* 2017;33:314-21.
 58. Scroggs MW, Proia AD. Histopathological variation in keratoconus. *Cornea* 1992;11:553-9.
 59. Haque S, Simpson T, Jones L. Corneal and epithelial thickness in keratoconus: A comparison of ultrasonic pachymetry, Orbscan II, and optical coherence tomography. *J Refract Surg* 2006;22:486-93.
 60. Aktekin M, Sargon MF, Cakar P, Celik HH, Firat E. Ultrastructure of the cornea epithelium in keratoconus. *Okajimas Folia Anat Jpn* 1998;75:45-53.
 61. Qin B, Chen S, Brass R, Li Y, Tang M, Zhang X, *et al.* Keratoconus diagnosis with optical coherence tomography-based pachymetric scoring system. *J Cataract Refract Surg* 2013;39:1864-71.
 62. Temstet C, Sandali O, Bouheraoua N, Hamiche T, Galan A, El Sanharawi M, *et al.* Corneal epithelial thickness mapping using Fourier-domain optical coherence tomography for detection of form fruste keratoconus. *J Cataract Refract Surg* 2015;41:812-20.
 63. Sandali O, El Sanharawi M, Temstet C, Hamiche T, Galan A, Ghouali W, *et al.* Fourier-domain optical coherence tomography imaging in keratoconus: A corneal structural classification. *Ophthalmology* 2013;120:2403-12.
 64. Kanellopoulos AJ, Aslanides IM, Asimellis G. Correlation between epithelial thickness in normal corneas, untreated ectatic corneas, and ectatic corneas previously treated with CXL; is overall epithelial thickness a very early ectasia prognostic factor? *Clin Ophthalmol* 2012;6:789-800.
 65. Rocha KM, Perez-Straziota CE, Stulting RD, Randleman JB. SD-OCT analysis of regional epithelial thickness profiles in keratoconus, postoperative corneal ectasia, and normal eyes. *J Refract Surg* 2013;29:173-9.
 66. O'Brart DP, Corbett MC, Lohmann CP, Kerr Muir MG, Marshall J. The effects of ablation diameter on the outcome of excimer laser photorefractive keratectomy. A prospective, randomized, double-blind study. *Arch Ophthalmol* 1995;113:438-43.
 67. O'Brart DP, Gartry DS, Lohmann CP, Muir MG, Marshall J. Excimer laser photorefractive keratectomy for myopia: Comparison of 4.00- and 5.00-millimeter ablation zones. *J Refract Corneal Surg* 1994;10:87-94.
 68. Kanellopoulos AJ, Asimellis G. Epithelial remodeling after partial topography-guided normalization and high-fluence short-duration crosslinking (Athens protocol): Results up to 1 year. *J Cataract Refract Surg* 2014;40:1597-602.
 69. Kanellopoulos AJ, Asimellis G. *In vivo* 3-dimensional corneal epithelial thickness mapping as an indicator of dry eye: Preliminary clinical assessment. *Am J Ophthalmol* 2014;157:63-8.e2.
 70. Reinstein DZ, Archer TJ, Gobbe M, Rothman RC. Epithelial thickness changes following realignment of a malpositioned free cap. *J Cataract Refract Surg* 2014;40:1237-9.
 71. Reinstein DZ, Archer TJ, Gobbe M. LASIK for myopic astigmatism and presbyopia using non-linear aspheric micro-monovision with the Carl Zeiss Meditec MEL 80 platform. *J Refract Surg* 2011;27:23-37.
 72. Silverman RH, Urs R, Roychoudhury A, Archer TJ, Gobbe M, Reinstein DZ. Epithelial remodeling as basis for machine-based identification of keratoconus. *Invest Ophthalmol Vis Sci* 2014;55:1580-7.
 73. Reinstein DZ, Aslanides IM, Silverman RH, Najafi DJ, Brownlow RL, Belmont S, *et al.* Epithelial and Corneal 3D ultrasound pachymetric topography post excimer laser surgery. *Invest Ophthalmol Vis Sci* 1994;35:1739.