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# Corneal densitometry as a tool to measure epithelial ingrowth after laser in situ keratomileusis

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**CORNEAL DENSITOMETRY AS A TOOL TO MEASURE EPITHELIAL**

**INGROWTH AFTER LASER IN SITU KERATOMILEUSIS**

by

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# CORNEAL DENSITOMETRY AS A TOOL TO QUANTIFY EPITHELIAL INGROWTH AFTER LASER IN SITU KERATOMILEUSIS

## DANIEL ADRAN

## ABSTRACT

A retrospective case study of 3 patients that developed epithelial ingrowth after laser in situ keratomileusis (LASIK). This study was conducted at Boston Eye Group in Brookline, Massachusetts.  The Oculus Pentacam was used to study corneal densitometry for each patient.  Corneal densitometry readings were obtained for each patient pre-operatively and post-operatively after ingrowth was discovered. Densitometry was recorded at the central nest of opacity and at the leading edges of the ingrowth.  For all patients, the most severe stages of epithelial ingrowth observed on slit lamp photographs correlated to the highest densitometry readings, with peak densitometry ranging from 73.3 – 95.1.  These values were much higher than pre-operative densitometry readings, which ranged from 21.8 – 27.2.  In two cases, the Pentacam densitometry map revealed progression of ingrowth towards the visual axis that was only faintly detectable or not detectable at all on corresponding slit lamp photographs. Corneal densitometry can be used as an objective measure of the severity and progression of epithelial ingrowth.

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# ABBREVIATIONS

BCL          Bandage Contact Lens

BCVA        Best Corrected Visual Acuity

BSS          Balanced Salt Solution

CTK          Central Toxic Keratopathy

DLK          Diffuse Lamellar Keratitis

EI             Epithelial Ingrowth

IOP          Intraocular Pressure

LASEK       Laser Epithelial Keratomileusis

LASIK       Laser in Situ Keratomileusis

Nd:YAG    neodymium:yytrium-aluminum-garnet

OD           Right eye

OS           Left eye

PISC         Pressure Induced Stromal Keratitis

PL           Plano (0 diopters of spherical power)

PRK          Photorefractive Keratotomy

Sph          Sphere (0 diopters of astigmatism)

UCVA        Uncorrected Visual Acuity

## INTRODUCTION

**Histology of the cornea**

The cornea makes up about 16% of the anterior portion of the eye. It has no color, no vasculature, and is completely transparent. Along with the lens, it is responsible for refraction of all light that will eventually reach the retina. Overall, the cornea is responsible for about 2/3 of the refractive power of the eye. It is made of 5 layers: the epithelium, Bowman's layer, stroma, Descemet's layer, and endothelium.

The epithelium of the cornea consists of about 5-6 layers of stratified squamous non-keratinized epithelial cells. These flattened-like squamous cells make up about $1/10^{th}$ of the thickness of the cornea. Since this is the first layer that will come into contact with the exterior environment, it has a very abundant set of sensory nerves. This innervation can trigger the blink reflex for protection against foreign bodies. The basal layers of the epithelium have many mitotic figures present, especially in the periphery of the cornea. These particular cells have a strong ability to renew themselves and repair damaged cornea. A tear film overlays the surface of the epithelial, produced by glands of the surrounding eyelids (Junqueira et al., 2010).

The next layer of the cornea is Bowman's layer. This is a very thick membrane (8-12 microns) that functions partially to protect the underlying stroma from infection. It may also function to bind growth factors and other substances

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signaling the proliferation of overlying epithelial stem cells (Junqueira et al., 2010).

The remaining 9/10 of the thickness of the cornea is a connective tissue layer called the stroma. The stroma consists of about 60 layers of parallel collagen bundles (Type I fibers). The orthogonal arrangement of these fibers permits minimal scattering of light throughout most of the stroma, contributing largely to the transparency of the cornea. The fibroblast-like cells of the stroma that are embedded in the connective tissue are called keratocytes. These cells produce a ground substance rich in proteoglycans that bathes the entire stroma. This ground substance assists in providing the intricate structural organization and spacing of the collagen fibers (Junqueira et al., 2010).

Underlying the stroma is another basement membrane called Descemet's membrane. This is also a very thick connective tissue border (~10 microns) that is the basement membrane of the underlying endothelium (Junqueira et al., 2010).

The endothelium is a single layer of simple squamous cells whose apical border faces the anterior chamber of the eye. These cells actively pump sodium ions via sodium/potassium ATP pumps into the aqueous humor of the anterior chamber. Subsequently, chloride and water follow this sodium movement from the stroma into the anterior chamber as well. This maintains the proper state of hydration that is needed in the cornea for full transparency and appropriate curvature for refraction of light. Since the stroma and epithelium are avascular,

nutrients need to diffuse through the endothelium first to reach and nourish the keratocytes and epithelial cells (Junqueira et al., 2010).

**Corneal Refractive Surgery**

Modern corneal refractive surgery utilizes an excimer laser to correct refractive error of the eye. There are two categories of refractive surgery that use an excimer laser for ablation: surface treatments and flap treatments (Shortt et al., 1996). Surface treatments, comprised of photorefractive keratotomy (PRK) and laser epithelial keratomileusis (LASEK), involve the mechanical removal of the epithelial layer via scraping or peeling to expose the stroma. The surface of the stroma is subsequently ablated by the excimer to alter the shape of the cornea and correct the refractive error of the eye. In PRK, the epithelial layer is left to heal on its own with the assistance of a bandage contact lens (BCL) placed over the cornea at the end of the procedure.  With LASEK, the removed epithelial layer is replaced on the cornea to promote faster healing (Shortt et al., 1996).

In contrast, laser in situ keratomileusis (LASIK) is a flap procedure that does not involve removal of the epithelial layer. This form of treatment involves the creation of a thin corneal flap that includes the epithelial layer along with a part of the stroma. The flap is created with either a microkeratome or a femtosecond laser, allowing the excimer to then ablate the underlying stroma and reshape the cornea (Shortt et al., 1996).

**Complications of LASIK**

Several possible complications can occur after LASIK.  A category of these complications includes those that occur within the flap interface. While the flap adheres to the stromal bed after surgery, there is a space created between the two that has potential for a number of pathologies (Randleman and Shah, 2012).

The most dangerous complication that can occur at the interface between the stromal bed and flap is infectious keratitis (Donnenfield et al., 2008). Despite its potential to damage visual acuity, an infection of the interface is a rare occurrence.  The most common cases for infectious keratitis presenting itself early in the post-operative period are due to staphylococcus and streptococcus species. In hospitals, the most common cases are due to methicillin-resistance staphylococcus aureus infections (Donnenfield et al., 2008). If the infection presents itself later in the post-operative period, the most common etiology is due to mycobacterium and fungi. Treatment of infectious keratitis for early onset cases involves lifting of the flap to take cultures, followed by irrigation of the interface with appropriate antibiotics.  In addition, the patients should be started on broad-based antibiotics.  Later onset cases of infectious keratitis are treated with amikacin for atypical mycobacteria (Donnenfield et al., 2008).

A more common complication that occurs at the interface is diffuse lamellar keratitis (DLK).  DLK is a white blood cell infiltrate that usually appears within the first five days after LASIK surgery.  Unlike infectious keratitis, this

complication occurs due to sterile causes (cultures are negative), although the exact etiology is unknown.  Treatment of DLK involves topical and oral steroid use in earlier stages.  Flap lift and irrigation may be necessary in worsening stages of the inflammation (Stulting et al., 2004).

Another complication that resembles later stages of DLK but presents in much earlier post-operative periods is Central Toxic Keratopathy (CTK).  CTK is a rare, non-inflammatory opacification of the central cornea.  It involves the loss of stromal tissue and a hyperopic shift in visual acuity.  Clinically, CTK can be distinguished from DLK because it is almost always painless, while DLK has a mild foreign body sensation.  Treatment is unnecessary because the complication is self-limiting and resolves on its own (Sonmez and Maloney, 2007).  The pathogenesis is not yet clear, but it is thought to be due to a toxic reaction of some substance that becomes photoactivated by the laser.

Another unique and potentially dangerous complication at the flap interface is Pressure-Induced Stromal Keratopathy (PISC).  PISC is an acute reaction to steroid use resulting in an increased intraocular pressure (IOP), and subsequent fluid accumulation between the flap and stromal bed.  In severe cases, a strip of fluid can be seen during slit lamp examination at the flap interface (Bellin et al., 2002).   Treatment consists of terminating steroid use (Hamilton et al., 2002) and beginning anti-glaucoma medication (Tourtas et al., 2011) until the IOP goes down. If not treated appropriately, optic nerve damage and visual field loss can occur (Hamilton et al., 2002).

**Epithelial Ingrowth**

Epithelial ingrowth (EI) is the least common of the complications that can occur at the flap interface (Randleman and Shah, 2012). The incidence of epithelial ingrowth occurring after primary LASIK varies in the literature. With the use of a microkeratome to make the flap, one study found an incidence of 0.92% out of 3786 eyes (Wang and Maloney, 2000), while another study found an incidence of 0.4% out of 783 cases (Walker and Wilson, 2000). Stulting et al. reported a much higher incidence of 9.1% among 1,062 cases reported by 14 different surgeons (Stulting et al., 1999). With femtosecond ablation to make the flap, a study found an incidence of 0.03% out of 6415 cases (Kamburoglu and Etran, 2008). The decreased incidence with the use of femtosecond ablation is possibly due to the reduced risk of epithelial defects during flap formation. The incidence of EI occurring after retreatment also varies quite a bit in the literature, with one study reporting 1.7% in 480 eyes (Wang and Maloney, 2000) and another reporting 1.8% in 108 cases (Kamburgolu and Etran, 2008).

The pathogenesis of epithelial ingrowth is not entirely understood. Currently, there are two theories as to how the complication develops.  The first theory states that the ingrowth arises from an insertion of surface epithelial cells into the flap interface while the flap is being created. With a microkeratome, such an incidence would occur if epithelial cells were tugged into the flap interface. With the femtosecond laser, there would be a back flow of cells within the suction

ring into the interface. (Wang and Maloney, 2000) Since these epithelial cells would have lost their connection to the surface layer, the question remains as to whether or not these cells would have mitotic potential. A recent study showed that an isolated colony of epithelial ingrowth cells had characteristics of stem cells (Nicolas et al, 2012).

The second theory holds that epithelial ingrowth results from a migration of surface epithelial cells between the edges of the flap into the flap interface. In this scenario, the ingrown cells would progressively move under the flap early in the post-operative stage until they reached some limit of extension. Facilitating this progression would be the formation of an epithelial fistula starting from the edge of the flap, which could be detected via a pooling of fluorescein. Next, a demarcation line develops due to moderate fibrosis at the leading edge of the ingrowth. Progressing even further, epithelial pearls become evident as a result of the entrapment of squamous cells between opposing sheets of progressing epithelium (Figure 1 and Figure 2). Over time, these trapped squamous cells can release enzymes that cause keratolysis near the flap edge (flap melt) (Wang and Maloney, 2000).

**Figure 1: Epithelial Ingrowth as seen on slit lamp examination**.
The short arrow points to the demarcation line, while the large
arrow points to the pearls. Taken from Wang and Maloney, 2000
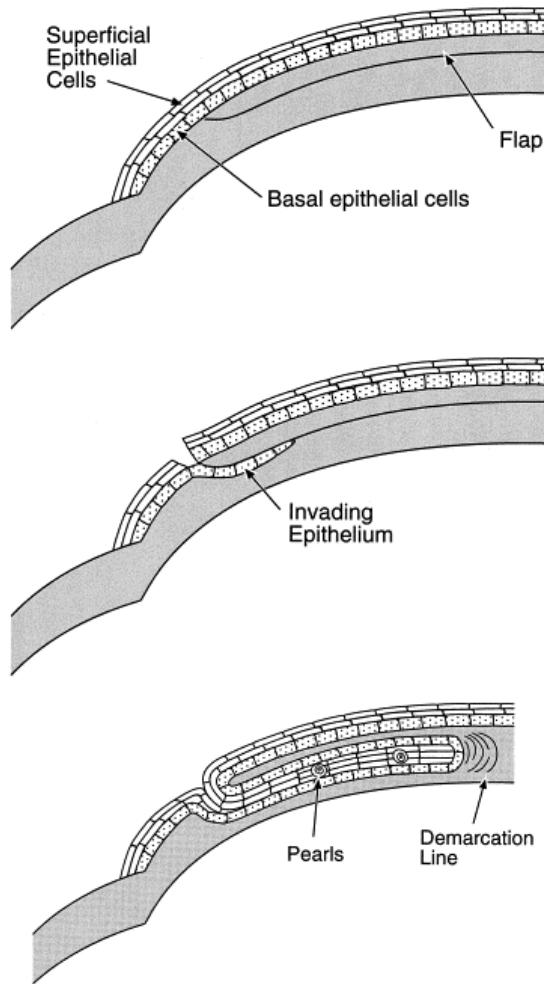
**Figure 2: Migration theory of pathogenesis of EI.** Poor flap adhesion allows surface epithelial cells to migrate between the flap edges into the interface. A fistula develops which allows further ingrowth to occur, leading to the formation of epithelial pearls. A demarcation line forms at the leading edge of the ingrowth. Taken from Wang and Maloney, 2000.

Multiple risk factors for epithelial ingrowth have been proposed. One major risk factor is poor attachment of the flap to the underlying stromal bed. (Wang and Maloney, 2000). One factor that could lead to poor flap adherence is an epithelial defect formed intraoperatively. Such a defect could allow tears to

move between the flap edges into the interface, leading to excessive hydration underneath the flap.  Other causes of poor flap attachment are corneal basement membrane dystrophy (WM), excessive hydration of the flap interface intraoperatively via excessive topical anesthetic use, and a buttonhole or thin flap (Domniz et al, 2001).

Another risk factor of epithelial ingrowth is hyperopic correction (Domniz et al., 2001).  Correction of hyperopia aims to make the cornea steeper for more convergence of light, and thus aims the ablation around the periphery of the cornea near the flap.  Ablation close to the flap periphery may cause poor flap attachment. Furthermore, hyperopes tend to be older and may be more prone to lose adhesive characteristics of their corneal epithelium. (Domiiz et al., 2001) Other risk factors include a history of corneal erosions and enhancements. Retreatment requires relifting of the flap, which may cause new epithelial defects near the flap edge (Chan and Boxer Wachler, 2007).

The major clinical findings for patients with significant epithelial ingrowth are photophobia, corneal haze, and foreign body sensation (Wang and Maloney, 2000).  Wang and Maloney proposed five criteria that could classify epithelial ingrowth as clinically significant: 1) the ingrowth has progressed into the visual axis and quality of vision has deteriorated, 2) the ingrowth has moved towards the edge of the pupil, causing nighttime glare, 3) the ingrowth has caused irregular astigmatism by raising the flap in an isolated area, 4) the ingrowth has resulted in keratolysis (flap melt), and 5) the ingrowth has causes an epithelial

defect with fluorescein staining at the flap edge (Wang and Maloney, 2000). If any of these criteria is met, the ingrowth may require surgical intervention.

Currently, the only classification scheme for the severity of EI is one proposed by Machat and Probst (Ayala et al., 2008). Under this system, Grade 1 describes ingrowth that is vaguely detectable on slit lamp examination, having not progressed more than 2 milimeters from the flap edge.  At this stage the ingrowth has a visible demarcation line at its leading edge, keratolysis has not occurred near the flap, and treatment is not required.  Grade 2 characterizes ingrowth that has clear pearls, or nests of trapped epithelial cells, having progressed at least 2 milimeters from the flap edge.  Demarcation lines are no longer evident, and the flap may be grey and thickened.  Treatment may be necessary depending on the extent of flap involvement. Grade 3 Ingrowth involves whitish nests of cells that have moved more than 2 milimeters from the flap edge.  The flap is thickened, rolled, and/or melted.  Immediate treatment is required to prevent further flap melt (Ayala et al., 2008).

One of the documented ways to treat epithelial ingrowth is to lift the flap and scrape off the ingrowth on both sides of the flap with a blade, spatula, or surgical sponge. After removal, the flap is repositioned and a bandage or BCL is placed over the cornea for tight adhesion of the flap. The issue with this method is that it has a high risk for regrowth of the ingrowth, as documented in one study that saw a 44% recurrence rate (Wang and Maloney, 2000).

A more improved version of this treatment is to lift the flap, remove the ingrowth mechanically, and then suture the flap (Rojas MC et al., 2004). The goal of suturing the flap is to ensure tight attachment and prevent regrowth. If the migration theory of pathogenesis of EI holds true, then a fistula that has formed at the flap edge would remain open even though cells have been scraped off, allowing ingrowth to recur if the flap was repositioned without tight adherence. Suturing would ensure that the fistula closes properly, preventing further progression of ingrowth cells into the flap interface to allow complete healing. One study showed that no regrowth occurred after scraping of ingrowth under the flap with sutures (Rojas MC et al., 2004). One problem with this technique is the induction of astigmatism (Narvaez et al., 2006). An alternative method of scraping and suturing with the application of fibrin glue has been found to reduce the induction of astigmatism (Narvaez et al., 2006). Ethanol and mitomycin treatments have also been proposed as methods to destroy epithelial ingrowth but are not as reliable due to their toxic effects (Wang and Maloney, 2000).

Another form of treatment that has been discussed in the literature is the neodymium:yttrium-aluminum-garnet (Nd:YAG).  The YAG is a laser than can fire short pulses of infrared light on a very small spot of tissue (about 8 microns). This ablation causes plasma formation, which results in the formation of small vacuoles that merge to form large vacuoles. In turn, this sets of an explosive wave that ionizes nearby tissue. When fired on epithelial ingrowth, the laser removes the unwanted tissue and leaves vacuoles that will eventually clear.

(Ayala et al., 2008) In a study by Ayala et al., 80% of epithelial ingrowth was removed by the procedure, and in 60% of cases vision improved by at least one line.

**Densitometry and the Scheimpflug principle**

Because epithelial ingrowth involves an opacification of the cornea, it calls for the need of corneal imaging techniques that could assess the loss of transparency where the ingrowth lies. The Scheimpflug principle allows undistorted photography of an obliquely shaped object, such as the cornea, with a wide depth of focus and a very high resolution. This principle allows the Oculus Pentacam (Oculus Inc., Wetzlar, Germany) to use a rotating camera to take up to 50 cross-sectional images of the anterior segment of the eye in less than 2 seconds. Thus, it can obtain valuable biometric data from the anterior surface of the cornea to the posterior surface of the lens (Wegener and Laser-Junga, 2009). Included in this data are corneal topography, corneal pachymetry (corneal thickness), and densitometry of the lens and cornea (Oculus, 2003).

Densitometry measures the amount of scattering of light through tissue. As discussed above, a large part of the cornea is transparent and would be expected to have a relatively low densitometry due to minimization of light scattering. It would thus be plausible that development of opacity in the cornea would increase the amount of light scattered through the cornea and increase the densitometry as measured by the Pentacam.

Densitometry is measured on a scale of 0-100. A completely transparent cornea would have a densitometry of 0, while a completely opaque cornea would have a value of 100 (Ori et al., 2012). For a healthy cornea, the highest points of light scattering should occur at the surface epithelium and the posterior endothelium, where the indexes of refraction would see the largest changes (Ori et al., 2012). Within the cornea, light scattering would be minimal compared to these interfaces, with the most light scattering occurring at Bowman's layer and Descemet's membrane (Oculus, 2003). As discussed above, the stroma maintains its transparency through precise orthogonal arrangement of collagen fibers and adequate ground substance to allow for spacing of fibers.

In the past, densitometry has been used as a tool to evaluate the degree of cataract opacification (Kirkwood et al., 2009). Recently, the densitometry function of the Pentacam has begun to be used to quantify corneal pathologies. Ori *et al* outlined the use of densitometry in objectively assessing bacterial keratitis, showing that densitometry values in the areas of infection were higher than average values of corneas in control groups (Ori et al., 2012). During the infection, inflammatory cells and microbes make their way into the flap interface, compromising the lattice orientation of the extracellular matrix with resulting light scatter (Ori et al., 2012). Furthermore, Elfein *et al* showed that densitometry could be used to objectively evaluate corneal haze in patients with mucopolysaccharidosis, and Greenstein *et al* used densitometry to quantify

collagen-crosslinking associated corneal haze (Elfein et al., 2013) (Greenstein et al., 2010).

**Purpose/Aims:**

The goal of this study was to quantify the severity and progression of epithelial ingrowth after LASIK using densitometry values given by the Oculus Pentacam.  Accurate tracking of EI progression can guide the surgeon in their decision to relift the flap for scraping. It also helps in determining the frequency at which the patient needs to be monitored. To our knowledge, there is no objective method to monitor epithelial ingrowth discussed in the literature.  The current method of assessment for EI is through slit lamp examination.  This method has several limitations, since slit lamp examination of the ingrowth is a subjective assessment.  One of the issues with monitoring via slit lamp is the difficulty of pinpointing the location of the demarcation line, or leading edge, of the ingrowth. This makes it difficult to track how far the epithelial ingrowth cells have moved towards the visual axis from the flap edge.  In addition, the degree of opacity due to the pearls of ingrowth cells is not always clear, which makes it difficult to tell whether the complication has improved or worsened between visits.  Different slit lamp photographs of the same ingrowth may lead to a different assessment depending on the amount and orientation of the incident lighting.

In this study, we investigated the correlation between the densitometry feature of the Pentacam and the severity of epithelial ingrowth, with the goal of developing an objective method of monitoring this complication.

## METHODS AND MATERIALS

We performed a retrospective study on three patients diagnosed with epithelial ingrowth after either primary treatment or retreatment. All patients had primary LASIK treatment, retreatment, and/or follow up treatment at Boston Eye Group, a private ophthalmology clinic in Brookline, Massachusetts. Patients who had developed or presented with an EI between mid-2010 and early 2014 were selected for this study. Slit lamp photographs were collected from the Reseevit™ (Eclyptic, Inc.) digital imaging software database. All data included in this study other than slit lamp photographs and Pentacam examinations was collected through Next Gen Healthcare Information Systems EHR (Horsham, PA).

For all LASIK treatments, a topical anesthetic was first used. For primary treatments, the operated eye was docked under the Intralase™ (Abbott Medical Optics, Inc.) for femtosecond ablation to create a large diameter corneal flap. The STAR S4 IR™ (Abbott Medical Optics, Inc.) was the excimer used for laser ablation for both primary treatments and retreatments. One drop of Vigamox 0.3%, Nevanac and Prednisolone acetate 1% were applied at the end of the procedure. For treatment of epithelial ingrowth in two of the discussed cases, the surgeon used a 15 mm blade and weck cell to scrape the ingrowth on both sides of the flap. A BCL (bandage contact lens) was placed over the eye after the scrape. For one patient in the study, a YAG laser was performed to treat the ingrowth. The laser was fired on 35 spots with a power of 0.6-1 mJ.

For all cases except one (Case 1), Pentacam pictures were taken once pre-operatively before treatment, and subsequently during post-operative periods upon discovery of the ingrowth. Each examiner ensured that pictures were obtained from each eye that met sufficient quality specifications. These included the appropriate analyzed area of the cornea, valid data (>95%), minimization of lost segments (<1%), and minimal 3D model deviation (<14%). In addition, appropriate fixation was necessary with minimal eye movement (<150) for usable data. For two of our analyzed Pentacam exams, a yellow warning indicated that our data be interpreted with caution (Post Op 3 for Case 2, and Post Op 1 for Case 1). For Case 2, the examination had unsteady fixation (208), while for Case 1, the examination had data gaps (90%). Since both of these values were near the borderline of the necessary quality specifications, we included these exams in our study as usable data.

For our study, we analyzed the densitometry maps on the Pentacam for separate visits for each patient. The map displays a color scaled representation of the maximum densitometry values measured by the Pentacam across the full thickness of the cornea (anterior to posterior). The color scale was selected as 1.7% Densitometry Absolute. The colors ranged from light blue (densitometry = 1) to black (densitometry = 100) (Figure 3).
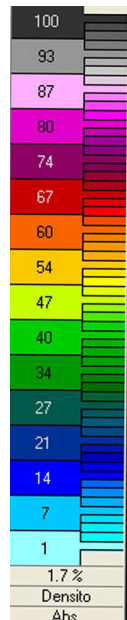
**Figure 3: Densitometry map color scale.** A densitometry of 100 (black) indicates complete opacity, while a densitometry of 1 (light blue) represents complete transparency.

By hovering the cursor over suspected areas of ingrowth on the map, we were able to view the exact maximum densitometry at a specific point on the cornea.  Each point has its own X and Y coordinate value.  Since the pupil center deviated slightly from the origin of the axis for each Pentacam picture, we adjusted the coordinates for each point in subsequent visits to match the exact point on the cornea.  Thus, we were able to look at a single point within an opacity of the cornea and compare densitometry values for that point between visits.

For each area of ingrowth, we picked four points to compare between visits.  One point was chosen at the densest region of the opacity, which we hypothesized to correlate to the dense pearls seen on slit lamp examinations.  We also picked three additional points at the outer edges of the opacity, which we think correlate to the leading edges of the ingrowth.  We recorded the

densitometry values for each of these four points for each patient's pre-operative

visit (excluding Case 1) and subsequent post-operative visits when ingrowth was

noted.  For each visit, all four of these points were added together to get the total

densitometry value, which could be compared as well between visits.

# RESULTS

**Case 1:**

      A 22-year-old female patient arrived to her first visit with us having had previous LASIK surgery OU one year ago at a different facility. She had developed epithelial ingrowth OD and had a scrape done 3 months after her primary treatment.  The previous surgeon did not fully lift the flap due to flap melt and fear of tear. She had an UCVA (uncorrected visual acuity) of 20/80 and a BCVA (best corrected visual acuity) of 20/20 (with a refraction of +5.00, -2.50, 136).  Slit lamp examination showed a large amount of ingrowth superiorly, temporally, and inferiorly.  Our surgeon was hesitant to lift the flap due to scarring inferio-temporally, but feared further melt and scheduled a scrape for her next visit.

      6 weeks later, the patient had Pentacam and slit lamp pictures taken before her scrape (Table 1).  The surgeon partially lifted the flap and removed the ingrowth on both sides of the flap.  The patient was administered topical antibiotics and corticosteroids.  One day after the scrape, the patient reported having swelling, tearing, and pain in her right eye, with a UCVA of 20/150.  Slit lamp examination showed a significant removal of ingrowth superiorly, temporally, and inferiorly, with only mild residual ingrowth.

      2 weeks after the scrape was done, the patient stated that her pain and swelling had subsided but had now developed photophobia.  She had an UCVA

of 20/50-.  Slit lamp examination showed mild epithelial ingrowth that had not progressed from the previous visit.

6 weeks after the scrape, a recurrence of epithelial ingrowth was noted superiorly in the 1 o'clock position.  7 weeks post-scrape, slit lamp examination showed that the new ingrowth was actively progressing.  The patient had an UCVA of 20/40.

10 weeks after the scrape, slit lamp examination showed that the density of the new ingrowth had progressed at the one o'clock position, and a decision was made to surgically intervene.  Due to fear of flap tear, the surgeon decided to ablate the new ingrowth with a YAG laser. 5 days after the YAG procedure, slit lamp examination showed improvement in the area of the YAG laser burns.

In the following months, the 1 o'clock ingrowth showed consistent improvement on slit lamp examinations.  9 months after the YAG procedure, the patient had no complaints about her vision, with a UCVA of 20/25 OD.  No active EI was noted on slit lamp exam, and no fistula was observed with fluorescein staining. Peripheral scarring was noted at the flap edge.
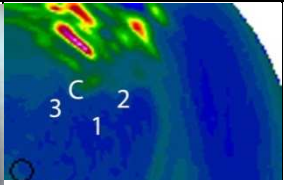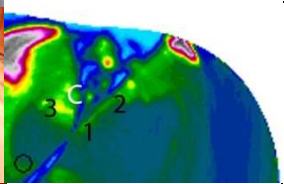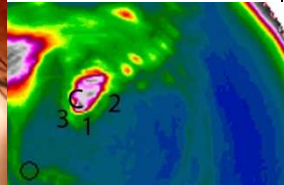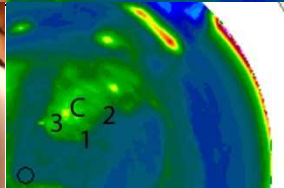
For our retrospective analysis, we isolated the regrowth that occurred at the 1 o'clock position on both Pentacam densitometry maps and slit lamp photographs (Table 1).  The original points were selected for the 7-week post-scrape visit (labeled post-op 2) since the regrowth was actively progressing and appeared high in density on slit lamp examination.  We then compared the maximum densitometry values for these points with the values selected for the

same points for the pre-scrape visit (same day), the 2 week post-scrape visit (post-op 1), and the 9 month post-YAG visit (post op 3) (Table 1). The table also compares the total densitometry (sum of points C, 1, 2, and 3) between visits.

The highest densitometry value for a single point occurred at point C for post-op 2 before the YAG procedure was performed (73.3). This correlates with the highest opacity observed in the slit lamp photo for the same visit. The lowest values for all four points occurred during the pre-scrape visit, before the regrowth had occurred in the selected area. These findings are also confirmed by the total densitometry, with the highest and lowest values occurring at post-op 2 and pre-scrape, respectively. Between the pre-YAG and post-YAG visits, the densitometry at point C fell significantly (-40%) (Table 2), correlating with the improvement observed between the visits in the slit lamp photographs.

**Table 1: Comparison of slit lamp photographs and Pentacam densitometry for Patient 1.** Maximum densitometry values are shown for pre-scrape and post-scrape visits.

| Visit | Slit Lamp Photo | Pentacam/Densito Map | Pt C | Pt 1 | Pt 2 | Pt 3 | Total |
|---|---|---|---|---|---|---|---|
| Pre-Scrape | | | 22.4 | 21.3 | 22.4 | 23.3 | 89.4 |
| Post-Op 1 (2 weeks post-scrape) | | | 41.8 | 27.3 | 31.1 | 44.5 | 144.7 |
| Post-Op 2 (pre-YAG, 7 weeks post-scrape) | | | 73.3 | 32 | 27.1 | 31.6 | 164 |
| Post-op 3 (1 year post-scrape/post-YAG) | | | 43.4 | 26.3 | 31.7 | 38.7 | 140.1 |
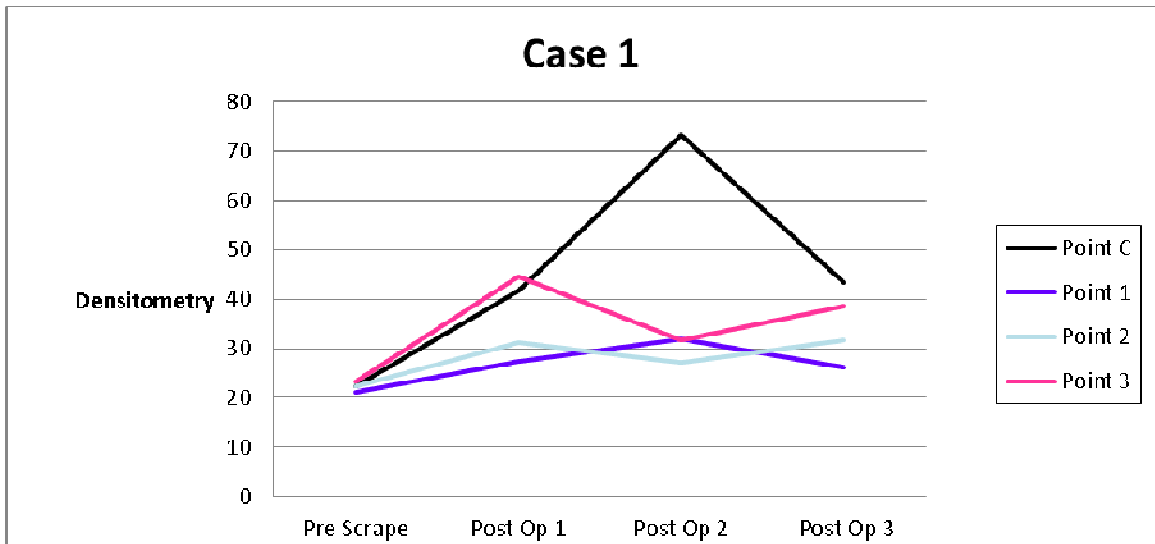
**Figure 4: Patient 1's plot of densitometry over time throughout four visits**

**Table 2: Degree of change in densitometry between visits for patient 1.** The percentage change between visits is shown for each point C, 1, 2, and 3.

| Percentage Change Between Visits | Point C | Point 1 | Point 2 | Point 3 |
|---|---|---|---|---|
| % Change Pre-Scape to Post-Op 1 | 86.6% | 28.2% | 38.8% | 91.0% |
| % change Post-Op 1 to Post-Op 2 | 75.4% | 17.2% | -12.9% | -29.0% |
| % Change Post-Op 2 to Post-Op 3 | -40.8% | -17.8% | 17.0% | 22.5% |
| % Change Pre-Scrape to Post-Op 2 | 227.2% | 50.2% | 21.0% | 35.6% |

**Case 2:**

A 51-year-old female patient had a retreatment after undergoing primary hyperopic LASIK two and a half years prior.  She had no complications after the primary procedure. For her retreatment, she had a pre-operative BCVA of 20/20 OU (OD: +0.50 -0.25 x 25, OS: +1.50 -0.50 x 110).  No flap or excimer events occurred during the procedure for either eye. The day after her procedure her UCVA was 20/20 in both eyes.

6 weeks later, epithelial ingrowth was noticed on slit lamp examination temporally in her left eye.  Her UCVA at this point was 20/25 OS, and her BCVA was 20/20 OS (+0.50 -0.50 x 180).  5 months after retreatment, ingrowth was seen nasally as well as temporally.  The patient had an UCVA of 20/40 OS and a BCVA of 20/20- (+0.50, Sph).  The surgeon elected not to surgically intervene at this point since the patient was doing well.

9 months post-operatively, the ingrowth appeared stable in both locations. The patient had an UCVA of 20/20-. 1 year and 18 months after retreatment, new ingrowth was noticed centrally upon slit lamp examination along with the temporal and nasal ingrowths.  The patient reported blurry vision, but was doing well overall.  Once again, the surgeon decided to monitor the ingrowth closely and elected not to intervene surgically.

We analyzed densitometry values in two isolated locations: the temporal ingrowth and the later-onset central ingrowth.  For the temporal ingrowth, the highest values for all points occurred on the last post-operative visit (Table 3). This correlates to the highest opacity observed on slit lamp examination.  The

lowest values for all points occurred pre-operatively, before any ingrowth was

present.  These findings are also affirmed by the total densitometry, with the

highest and lowest values occurring on the last post-operative visit and the pre-

operative visit respectively.

The central ingrowth appeared much more scattered than the more

contained temporal ingrowth with a clear pearl of high density.  Thus, we picked

a point C at one of the higher density opacities shown on the densitometry map

for the last post-op visit, and three other points at the edges of ingrowth area

superior to the pupil center (Table 5).  Once again, the lowest values for each

individual point and the total densitometry occurred during the pre-operative visit,

while the highest values for each point and total densitometry occurred during the

last post-operative visit.  Interestingly, while the density did not increase

significantly from the pre-op visit to the first post-up visit, there was a substantial

increase in all four points between the first post-op visit (6 weeks) and the

second post-up visit (9 months).

**Table 3: Comparison of slit lamp photographs and densitometry at 4 o'clock ingrowth for patient 2.**

| Visit | Slit Lamp Photo | Pentacam Densito Map | Pt C | Pt 1 | Pt 2 | Pt 3 | Total |
|---|---|---|---|---|---|---|---|
| Pre-Op | |  | 22.7 | 24.1 | 23.6 | 21.8 | 92.2 |
| Post-op 1- 6 weeks |  |  | 57.7 | 29.9 | 29.6 | 29.7 | 146.9 |
| Post-op 2- 9 months |  |  | 66 | 38.1 | 34.4 | 30.6 | 169.1 |
| Post-Op 3- 1 Year, 6 months |  |  | 95.1 | 39.6 | 43.9 | 40.3 | 218.9 |
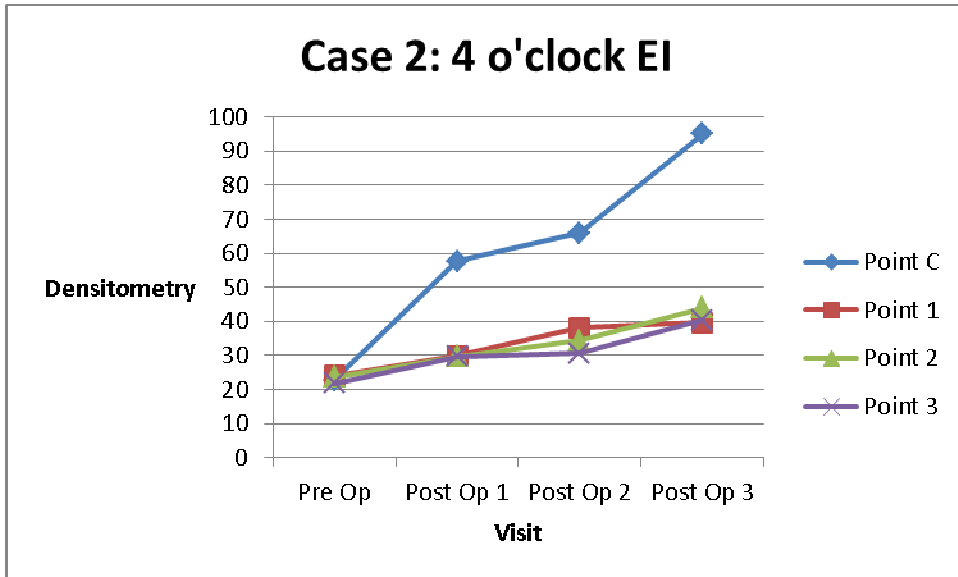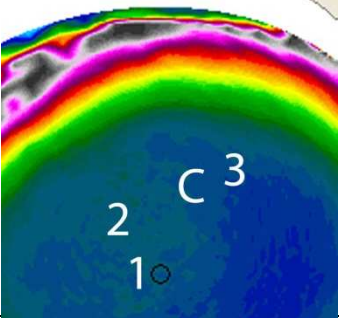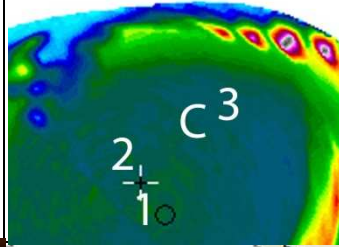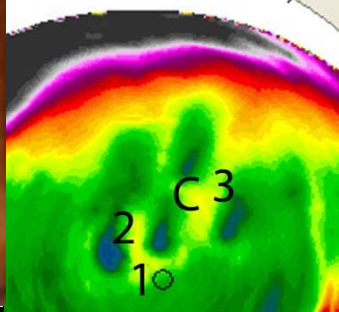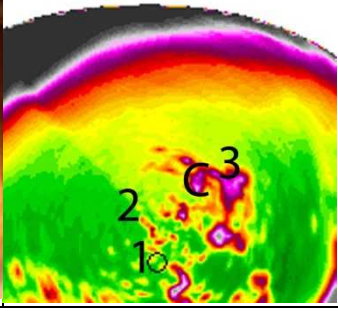
**Figure 5: Densitometry plotted against time for EI seen in 4 o'clock position for Patient 2.**

**Table 4: Degree of change between visits in 4 o'clock position for patient 2.** The percentage change between visits is shown for each point C, 1, 2, and 3.

| Percentage Change Between Visits | Point C | Point 1 | Point 2 | Point 3 |
|---|---|---|---|---|
| % Change Pre-Op to Post-Op 1 | 154.2% | 24.1% | 25.4% | 36.2% |
| % Change Post-Op 1 to Post-Op 2 | 14.4% | 27.4% | 16.2% | 3.0% |
| % Change Post-Op 2 to Post-Op 3 | 44.1% | 3.9% | 27.6% | 31.7% |
| % Change Post-Op 1 to Post-Op 3 | 64.8% | 32.4% | 32.4% | 35.7% |
| % Change Pre-Op to Post-Op 3 | 318.9% | 64.3% | 86.0% | 84.9% |

**Table 5: Comparison of slit lamp photographs and densitometry for central EI for patient 2**

| Visit | Slit Lamp Photo | Pentacam Densito Map | Pt C | Pt 1 | Pt 2 | Pt 3 | Total |
|---|---|---|---|---|---|---|---|
| Pre-OP | |  | 22.7 | 24.1 | 23.6 | 21.8 | 92.2 |
| Post-Op 1-6 weeks | |  | 26.9 | 28.2 | 27.3 | 26.8 | 109.2 |
| Post-Op 2-9 months |  |  | 44.8 | 44.5 | 38.7 | 43.6 | 171.6 |
| Post-op 3-1 year, 6 months |  |  | 83.8 | 52.9 | 44.6 | 51.2 | 232.5 |

**Table 6: Degree of change in densitometry between visits in central ingrowth position for patient 2.** The percentage change between visits is shown for each point C, 1, 2, and 3
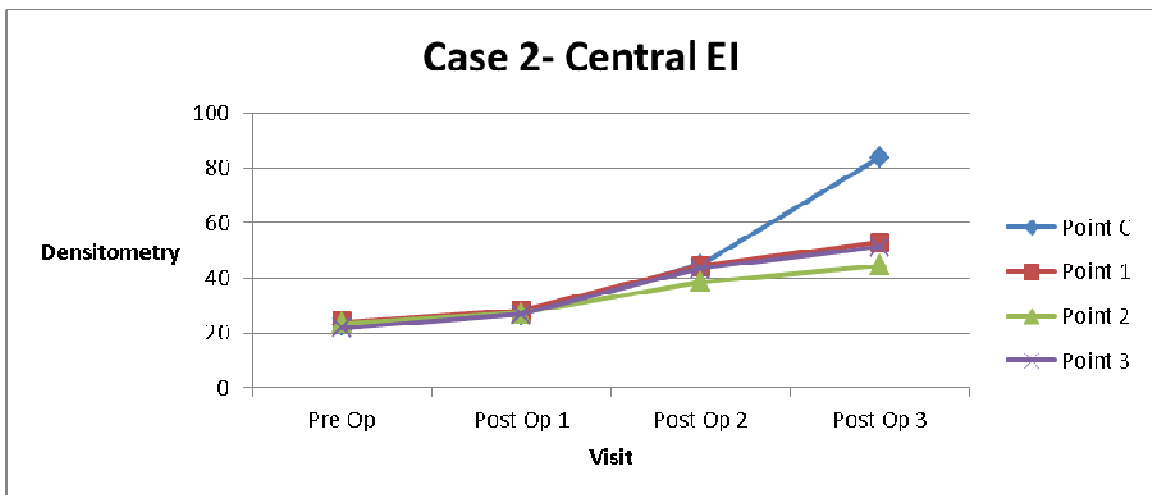
| Percentage Change Between Visits | Point C | Point 1 | Point 2 | Point 3 |
|---|---|---|---|---|
| % Change Pre-Op to Post-Op 1 | 18.5% | 17.0% | 15.7% | 22.9% |
| % Change Post-Op 1 to Post-Op 2 | 66.5% | 57.8% | 41.8% | 62.7% |
| % Change Post-Op 2 to Post-Op 3 | 87.1% | 18.9% | 15.2% | 17.4% |
| % Change Pre-Op to Post-Op 3 | 269.2% | 119.5% | 89.0% | 134.9% |



**Figure 6: Plot of densitometry vs. time for central ingrowth seen with patient 2**

**Case 3:**

A 49-year-old male patient had primary custom LASIK on both eyes. His pre-operative refraction was +0.50 -1.50 x 080 OD, and +0.50 -1.50 x 095 OS. During the procedure, an epithelial defect occurred 1 millimeter from the flap edge. Three months later the patient had an UCVA of 20/30- OD and 20/40 OS and BCVA of 20/20- OD (-0.50 -050 x 070) and 20/20- OS (-0.50 -0.50 x 070). The patient was unhappy with his vision and scheduled to have an enhancement in both eyes.

The enhancement was done on the patient's left eye first, with a pre-operative refraction of -0.50 -0.50 x 070. Four days after the retreatment, the patient had an UCVA of 20/15-, was happy with his vision and was ready for to have treatment on his right eye.

The pre-operative refraction for the patient's right eye was PL -0.50 x 055. 1 day after the retreatment, the patient had an UCVA of 20/25-. Slit lamp examination showed trace DLK inferiorly. Four days later, the DLK resolved, but the patient was very distressed over his cloudy vision. He had an UCVA of 20/60+ OD, and a BCVA of 20/25- OD (PL -0.75 x 180).

1 month after retreatment on the right eye, epithelial ingrowth was noticed on slit lamp examination OD. The patient's UCVA was 20/80-, and BCVA was 20/30- (+0.50 -0.50 x 070). 5 months post-enhancement OD, the patient had an UCVA of 20/20-, but still complained of blurry vision in his right eye. The patient was insistent on having more treatment done on his right eye. The ingrowth

looked stable on slit lamp examination, so the surgeon went ahead with the second enhancement OD.  The patient's pre-operative refraction was PL -0.75 x 175.

Six and a half months after the first retreatment on his right eye, the patient had an UCVA of 20/20-, but was still complaining of cloudy vision in his right eye. Ingrowth was noted at the 5 o'clock position.  Since the patient was very distressed about his vision and because the ingrowth had progressed towards the visual axis, the surgeon decided to lift the flap and mechanically remove the ingrowth.  The patient was warned that recurrence was possible. Five days after the scrape, the patient had no complaints about his vision and was doing well. Slit lamp examination showed no active ingrowth.

Seven and a half months after the first retreatment done on the right eye, the patient had an UCVA of 20/15- OD, but complained of blurry and blotchy vision in his right eye. The doctor explained to the patient that his visual acuity was good, but the patient complained of fogginess in his right eye that relieved after the previous scrape.  The doctor advised the patient that any intervention at this point would be risky and could worsen his complication, but the patient was adamant about intervention.  The surgeon went ahead and lifted the flap a second time, and scraped the epithelial ingrowth from the flap and stroma. The interface was then irrigated with balanced salt solution (BSS).  To prevent further regrowth, the surgeon decided to place five interrupted nylon sutures at the five o'clock position.
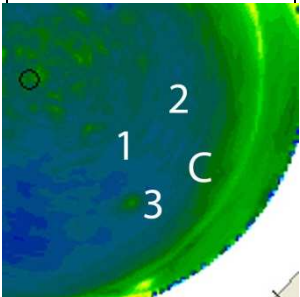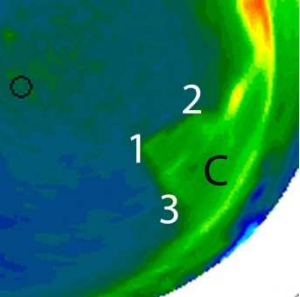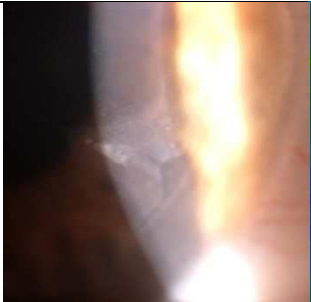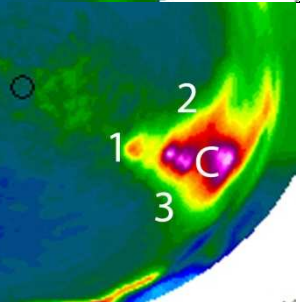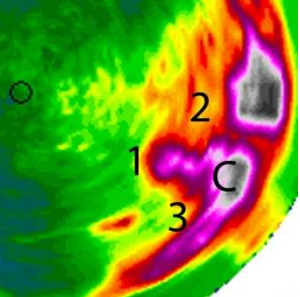
The following day, the patient complained of burning, pain, and extremely poor visual acuity in his right eye. Upon examination of his visual acuity, he was only able to count fingers from three feet away (CF3). No ingrowth was observed in the five o'clock position on slit lamp examination, but the patient had developed a large amount of astigmatism due to the sutures. Within the next month, the surgeon removed all but two sutures, and the patient's vision improved to 20/50- by the nine-month post-operative visit. Slit lamp examination showed that small ingrowth was now occurring at the 2 o'clock position.

A year and a half after the initial retreatment in his right eye, the patient had an UCVA of 20/20-. Upon slit lamp examination, the epithelial ingrowth looked much improved, and the area at the 5 o'clock position was now scarred. The 2 o'clock position only had small areas of ingrowth that looked stable. No further intervention was needed for this patient after this point.

Table 7 shows the densitometry values for points selected around the five o'clock ingrowth between four visits: the pre-operative visit (before the first retreatment), the 1 month post-operative visit (when ingrowth was first noted), the 8-month post-operative visit, and the 9-month post-operative visit. Point C was initially picked at x and y coordinates of +2.96, -1.59 on the last post-operative visit, where the central density appeared the highest. Points 1-3 were picked on the first post-operative visit to see how the leading edges progressed through future visits. A slit lamp photograph was only available for the 8-month post-operative visit.

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The highest maximum densitometry at a single point occurred at point C during the last post-operative visit, as did the highest total densitometry. The lowest values for all four points occurred during the pre-operative visit, as did the lowest total densitometry.

**Table 7: Comparison of slit lamp photographs and densitometry for patient 3**

| Visit | Slit Lamp Photo | Pentacam Densito Map | Pt C | Pt 1 | Pt 2 | Pt 3 | Total |
|---|---|---|---|---|---|---|---|
| Pre-op | |  | 27.2 | 25.7 | 26.4 | 25.7 | 105 |
| Post Op 1- 1 month | |  | 34.9 | 30.6 | 32 | 30.3 | 127.8 |
| Post-op 2- 8 month |  |  | 66.1 | 43 | 34 | 36.2 | 179.3 |
| Post-op 3- 9 month | |  | 81 | 54.7 | 55.5 | 53.7 | 244.9 |
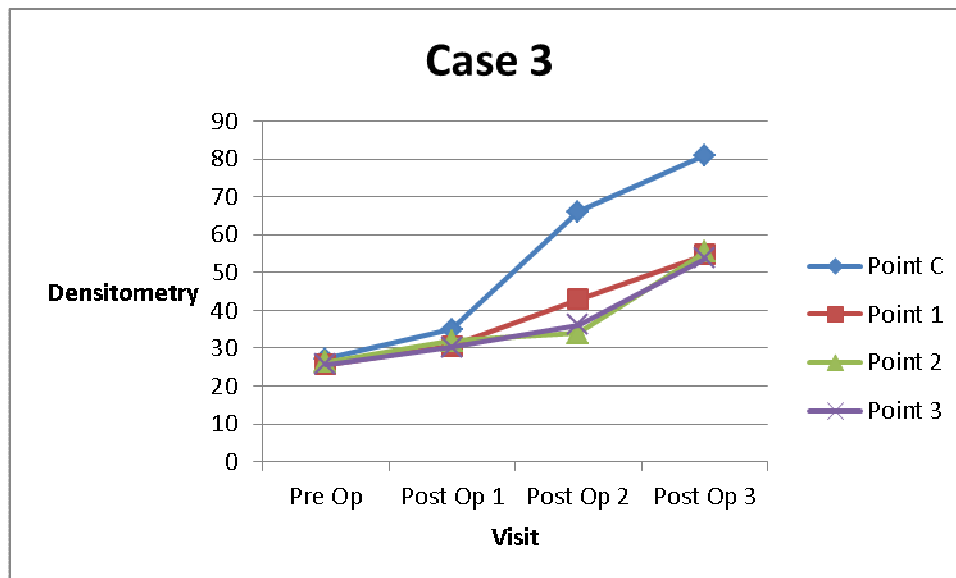
**Figure 7: Densitometry vs. time for patient 3.**

**Table 8: Degree of change in densitometry between visits for patient 3.**
The percentage change between visits is shown for each point C, 1, 2, and
3.

| % Change Between Visits | Point C | Point 1 | Point 2 | Point 3 |
|---|---|---|---|---|
| % Change Pre-op to Post-Op 1 | 28.3% | 19.1% | 21.2% | 17.9% |
| % Change Post-Op 1 to Post-Op 2 | 89.4% | 40.5% | 6.3% | 19.5% |
| % Change Post-Op 2 to Post-Op 3 | 22.5% | 27.2% | 63.2% | 48.3% |
| % Change Post-Op 1 to Post-Op 3 | 132.1% | 78.8% | 73.4% | 77.2% |
| % Change Pre-Op to Post-Op 3 | 197.8% | 112.8% | 110.2% | 108.9% |

## DISCUSSION

Our data shows that maximum densitometry values at points selected on suspected areas of epithelial ingrowth on the densitometry map of the Pentacam correlate with the degree of opacity observed on corresponding slit lamp photographs and exams.  For all cases in our study, the highest densitometry for a single point always occurred at point C during the visit that corresponded to highest opacity seen on a slit lamp photograph for that patient.  In addition, when the central pearls clearly increased in opacity between visits in the slit lamp photographs, there was a substantial increase in max densitometry at point C between those visits.  In case 1, there was a 75.4% increase for point C between post-op 1 and post-op 2, while in case 3 there was a 89.4% increase for point C between post-op 1 and post-op 2.  The opposite was also true for improvement of ingrowth, as was previously discussed for case 1.

The densitometry map is a color-scaled representation of the maximum densitometry throughout a 12-millimeter radius of the full thickness of the cornea. For our pre-operative maps, the majority of the cornea had a dark blue appearance, with the exception of the flap edge for patients who had primary treatments and the peripheral edges of the cornea.  For those exceptions, the flap edge was usually green, most likely having higher densitometry values due to minor fibrotic repair that occurs at the flap edge after primary treatment (Ivarsen et al., 2003).  A study by Ori *et al* found that healthy corneas have a maximum densitometry value of $19 \pm 4.4$, which fell close to our pre-operative

values that ranged from 21.8-27.2 (Ori et al., 2012).  The peripheral edges of the

cornea had spikes of very high densitometry (close to black), most likely due to

inclusion of the limbus in the image. At early stages, the ingrowth was visible as

a green to yellow isolated area superimposed onto the blue background (cite

figures).  As the ingrowth progressed and central pearls developed, the central

colors of the ingrowth shifted to orange and red.  At their peak density, the pearls

shifted to purple, grey, and sometimes black.  The color scheme of the central

pearls in the area of the ingrowth provides a better measure compared to the slit

lamp examination, which is limited to a subjective assessment of whitish-grey

opacities observed on an otherwise clear cornea.

Slit lamp examination is limited by the subjective bias of the viewer.  Our

study shows in two of our cases that the densitometry map reveals

characteristics of the ingrowth not obvious on slit lamp photographs. In case 1,

the ingrowth at the 1 o'clock position was not detected on slit lamp examination

at the 2-week post-scrape visit, while the densitometry map clearly shows an

area of opacity moving towards the visual axis (Table 1).  The slit lamp

photograph displayed shows only a faint demarcation of ingrowth in that area that

was especially hard to detect for this patient because she had a large amount of

surrounding scarring/other ingrowth that had been removed from underneath the

flap.  Similarly for case 2, the central ingrowth was not detected until the 18-

month post-op visit, but the densitometry map at the 9-month post-op visit

reveals a yellow-green area of opacity moving towards the visual axis from the

superior edge of the flap (Table 5). For this case, the slit lamp photograph we have corresponding to the 9-month visit fails to reveal any central opacity, suggesting that the Pentacam may have detected grade 1 ingrowth before it was clearly visible to the examiner.

In Ori *et al*'s study on bacterial keratitis, they found that densitometry values at points furthest away from the sight of infection were also higher than healthy control values (Ori et al., 2012). They suggested that the area of involvement for bacterial keratitis might be much greater than what is visible on slit lamp examination. Our study shows a similar finding, since in case 2 and case 3 the densitometry maps showed a shift from dark blue to light green (increased densitometry) in areas outside of where the ingrowth is evident on slit lamp examination.

There are some possible limitations that should be noted about our study. Certain factors may obscure measurements of areas of ingrowth. One of these is corneal scarring, which has been shown to significantly increase densitometry as well (Ori et al., 2012). This obstacle requires that the observer be adept at recognizing scarring as it may occur in areas of EI to in turn interpret the densitometry data cautiously. Patient 1 in our study developed several areas of scarring after her scrape, and the epithelial ingrowth that used to be active in those areas was not included in this study. Likewise, the placement of sutures in areas of ingrowth may also obscure the data by increasing densitometry readings. The densitometry maps in several visits showed evidence of possible

artifacts that may have been caused by several unknown factors.  The map for

patient 1's week 2 post-scrape visit shows a light blue strip (very low

densitometry) cutting through the area of green opacity (Table 1).  We interpreted

this artifact as an area of lost data for this visit, and did not select any points that

fell within it.  As discussed above, the Pentacam is limited by the quality of the

image that can be obtained, which can be influenced by excessive blinking or

loss of fixation by the patient.

In conclusion, we have shown that densitometry can be useful modality for

measuring and monitoring epithelial ingrowth after LASIK. It is a more objective

tool that can be used in conjunction with slit lamp examination and/or

photographs to guide the surgeon in his/her decision-making process.

Depending on the densitometry measurement, the surgeon can follow the rate of

progression and decide on the frequency of follow up exams or surgical

intervention.  Detecting focal increase in densitometry may prompt the surgeon to

further scrutinize the cornea allowing early detection of a condition that may lead

to flap melt, scaring, and irregular astigmatism, leading to loss of vision.

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## CURRICULUM VITAE

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## Education

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| September 2012- present | Boston University School of Medicine, M.A. in Medical Sciences Candidate |
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| September 2011- March 2012: | California State University, Los Angeles, Post-Baccalaureate |
| 2006- 2009:<br>Major: | University of California, Berkeley, B.S.<br>Molecular and Environmental Biology |

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|---|---|
| Neurophysiology, Fall 2011: | Research Project: Presented to the class about contemporary studies of Botulinum Neurotoxin A and its effects on the SNARE protein SNAP-25 |
| Neurodevelopment, Fall 2011: | Research Project: Presented to the class about contemporary studies of the role of Nogo-A, OMgp, and MAG in axonal regeneration after spinal cord injury |
| Neuroanatomy, Spring 2012: | Clinical correlation presentation: Anterograde Amnesia |

## Leadership Experience

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| 2008 | *Volunteer,* Think College Now Elementary School, Oakland, California<br>Organized play activities for kids during after school hours at a public elementary school focused on building strong academic foundations for students living in low income neighborhoods |
| 2007-2008 | *Member,* Formula SAE<br>Member of a student organization that designed and built a high-performance racecar for annual international competition attended by 80 universities. I worked with the management group to raise funds, allocate resources, and organize weekly work sessions. I helped guide the team through a period of rapid development, during which student involvement increased to 25 members and the annual budget increased by 150% |
| 2007 | *Volunteer,* ISA Experiential Learning Abroad Programs, Granada, Spain<br>Tutored English to Spanish speaking kids at their homes |

## Shadowing Experience

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| 2011 | *Internist*, Panorama City Kaiser Permanente Hospital<br>100 hours |
| 2010 | *Emergency Physician*, Glendale Adventist Medical Center<br>80 hours |

## Specialized Skills

Computer: Microsoft Word/Excel/PowerPoint
Languages: Fluent in Armenian, Conversant in Spanish