White Paper

Topography-Guided Laser Assisted In-Situ Keratomileusis vs Small-Incision Lenticule Extraction Refractive Surgery

A Summary of Clinical Outcomes

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Introduction

The global procedure volume for refractive surgery was approximately 3.8 million in 2016. Of those procedures, 840,000 were performed in the US market.[1] Modern refractive surgery has evolved significantly since the era of Radial Keratotomy, and with a projected growth of up to 4.9 million procedures globally in 2021,[1] it is important to provide a clinical perspective of the latest available refractive surgery modalities.

The main takeaways from this white paper are:

- Contoura® Vision outperforms small-incision lenticule extraction (SMILE*) with excellent visual outcomes that surpass "20/20 happy"
- The SMILE* procedure exhibits a lower incidence of dry eye symptoms in the early post-operative period
- Contoura® Vision improves quality of vision and results in an exceptionally high patient satisfaction

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Clinical Challenge: Maintaining the Natural Shape of the Cornea

Refractive Surgery is a permanent solution that reduces refractive error by reshaping the corneal surface. The ultimate goal of refractive surgery is to eliminate patient's dependency on glasses or contact lenses. Since refractive surgery is an elective surgery, there are many options for the surgeon to recommend and the patient to choose from, including, but not limited to, Photorefractive Keratectomy (PRK), Laser Assisted In-situ Keratomileusis (LASIK) or Small Incision Lenticule Extraction (SMILE*) to name a few. Ideally, these procedures should provide the patient with (1) excellent visual acuity and quality of vision within a short period after surgery, and (2) as little disturbance or impact on ocular health as possible.

This whitepaper describes two advanced technologies in refractive surgery in detail, namely topography-guided or –assisted LASIK and SMILE*. This paper will provide the reader with a comprehensive summary of clinical benefits of each approach.

Topography-guided LASIK and SMILE*

Both topography-guided LASIK and SMILE* are refractive procedures that remove corneal tissue to correct refractive error. However, there are fundamental differences between these two approaches, some of which are listed in Table 1. The indications for use in the United States are further detailed in Figure 1.

Table 1. Overview of topography-guided LASIK and SMILE* Procedures.

	Topography-guided LASIK	SMILE*
Procedural Technique	**3 Step Procedure (2 lasers):** 1. A thin hinged corneal flap is created using a femtosecond laser. The flap is opened to expose the underlying stroma. 2. An excimer laser is applied to reshape the stromal tissue, neutralizing irregularities of the corneal surface using the patient's manifest refraction and corneal topography data. 3. The corneal flap is repositioned.	**2 Step Procedure (1 laser):** 1. A femtosecond laser creates both an intrastromal lenticule that corresponds to the patient's spherical equivalent from the manifest refraction and a small site cut incision to allow for access to the lenticule. In low myopia, a refraction neutral corneal tissue base may be added to create a lenticule with a minimum thickness of 40 µm.[2] 2. After dissection of residual tissue bridges, the intrastromal lenticule is manually removed through the small incision.
Customization of the Treatment Profile	The treatment profile is customized based on the patient's specific corneal topography. A more uniform anterior corneal surface is created that corrects corneal irregularities causing HOAs.	The correction of HOAs and moderate to high amounts of astigmatism is not possible. Corneal topography data is **not** being used in the treatment.
Retreatments/ Enhancements	The corneal flap can be re-lifted and the residual refractive error corrected using an excimer laser.	No new lenticule can be created. The SMILE* procedure effectively needs to be converted into either of the 2 options below to correct residual refractive error with an excimer laser: 1. The pocket could be converted into corneal flap (if pocket parameters are known). 2. Convert into PRK to allow for surface ablation with an excimer laser.

Figure 1: Maximum indicated treatment ranges available for topography-guided LASIK and SMILE* Procedures in the United States.[5-7] LASIK: Laser Assisted In-situ Keratomileusis; SMILE*: Small Incision Lenticule Extraction; MRSE: Manifest Refraction Spherical Equivalent

Comparison of Topography-guided LASIK and SMILE* Outcomes

Important measures for the evaluation of a refractive surgery procedure include visual outcomes, refractive stability, patient reported post-operative dry eye symptoms, complications and safety. The following section aims to provide the reader with an overview of each of these measures.

Table 2 outlines the **visual outcomes** of available topography-guided LASIK and SMILE* procedures as described in the *Summary of Safety and Effectiveness Data Sheets* of US-approved devices. Overall, the visual acuity of each procedure is well within the required FDA efficacy criterion of 85% of eyes with 20/40 or better. A direct comparison of the data detailed in this table is not possible as these are three separate clinical trial datasets with differences in laser technology, laser indications, and/or patient populations. A comparative study by Kanellopoulos described significantly better visual performance in eyes that underwent topography-guided LASIK at 3 months[3] and 12 months[4] than in eyes that were treated with SMILE* (see Table 3).

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Table 2: Visual Outcomes for topography-guided LASIK and SMILE* Procedures at 12 months after surgery per the respective FDA Summary of Safety and Effectiveness Data (SSED) Sheet of three different clinical data sets.[5-7,**]

		Topography-guided LASIK		SMILE*
Percentage of eyes with		**Alcon Contoura® Vision** *(n = 230 eyes)*	**Nidek CATz Final Fit*** *(n = 111 eyes)*	**Zeiss VisuMax* SMILE*** *(n = 310 eyes)*
UCVA of 20/20 or better		92.6%	85.6%	88.1%
UCVA of 20/15 - 20/16 or better		64.8%	51.4%	63.9%
UCVA of 20/12.5 or better		34.4%	15.3%	NR
UCVA of 20/10 or better		15.7%	NR	NR
Attempted vs Achieved	MRSE ± 0.25 D	NR	NR	80.6%
	MRSE ± 0.50 D	94.8%	86.2%	93.9%
	MRSE ± 1.00 D	99.6%	100%	98.7%
	MRSE ± 2.00 D	100%	100%	100%
Post-op UCVA compared to pre-op BCVA	more than 2 lines better	3%	5.4%	1%
	2 lines better	8.3%	12.6%	4.2%
	1 line better	19.6%	27.9%	30%
	equal	58.3%	35.1%	38.4%
	1 line worse	7.8%	15.3%	18.4%
	2 line worse	1.3%	1.8%	5.8%
	more than 2 lines worse	1.7%	1.8%	2.3%

UCVA: uncorrected visual acuity; MRSE: manifest refraction spherical equivalent; BCVA: best corrected visual acuity; NR: not reported; NA: not applicable;A direct comparison of the data detailed in this table is not possible as these are three separate clinical trial datasets with differences in laser technology, laser indications, and/or patient populations.**

Table 3: Visual performance parameters at 3 months and 12 months after surgery in eyes undergoing myopic and myopic astigmatism treatment as described in a prospective, randomized contralateral study by Kanellopoulos.[3,4,**]

Percentage of eyes with	Post-op Time Point	Alcon Contoura® Vision *(n = 22 eyes)*	Zeiss VisuMax* SMILE* *(n = 22 eyes)*
UCVA of 20/20 or better	3 months	86.4%*	68.2%*
	12 months	NR	NR
UCVA of 20/16 or better	3 months	59.1%†	31.8%†
	12 months	71.4%††	38.1%††
MRSE ± 0.50 D (attempted vs. achieved)	3 months	95.5%‡	77.3%‡
	12 months	100%‡‡	66.7%‡‡

UCVA: uncorrected visual acuity; MRSE: manifest refraction spherical equivalent; NR: not reported
***, †, †† ,‡, ‡‡ significant difference between groups (p < 0.01); **A direct comparison of the data detailed in this table is not possible as these are three separate clinical trial datasets with differences in laser technology, laser indications, and/or patient populations.**

Refractive stability is a crucial factor when assessing options for refractive error correction. It may seem that eyes that underwent the SMILE* procedure would require a longer time to remodel and adjust to the removed intrastromal corneal tissue to achieve refractive stability after surgery. However, outcome analysis from the FDA clinical registration studies suggest otherwise. Similar to topography-guided LASIK, there are only minimal fluctuations in the manifest refractive spherical equivalent (MRSE) noted for SMILE* from 1 month to 12 months post-surgery.[5-8]

Other factors that may affect refractive stability have been considered as potential advantages of SMILE* procedures, including (1) reduced severance of corneal nerves and therefore a lower incidence of **patient reported** dry eye symptoms and (2) a greater biomechanical stability. The following paragraphs examine these potential advantages in comparison to general LASIK in more detail.

Any ocular surgery interferes with the delicate balance of the ocular surface system. In corneal refractive surgery, creating a corneal flap or an intrastromal lenticule severs the corneal nerves of the richly innervated cornea, thereby reducing corneal sensitivity in the short term. Long term, severed corneal nerve fibers regenerate. SMILE* procedures seem to be better at preserving the sub-basal nerve fiber density in the early post-operative period (up to 3 months) compared to Femtosecond LASIK (FS-LASIK) created flaps.[9] However, 6 months after surgery no differences between FS-LASIK and SMILE* created flaps were identified and the sub-basal nerve density recovered to similar levels in both groups.[9] A recent meta-analysis described significantly better corneal sensation, longer tear film break up times (TBUT) and patient reported Ocular Surface Disease Index (OSDI) scores in the early post-operative period in SMILE* treated eyes, which are likely linked to the greater extent of preservation of corneal nerve fibers.[10] Nevertheless, these differences did not translate into greater tear secretion in SMILE* compared to FS-LASIK.[10]

It has been hypothesized that the flapless nature of the SMILE* procedure may have less impact on the **biomechanical characteristics** of the cornea than femtosecond laser created flaps because the most anterior stromal lamellae remain intact during the SMILE* procedure. Clinical investigations into corneal refractive surgeries specifically studied corneal hysteresis and corneal resistance, parameters that assess the viscoelasticity of the cornea in ocular diseases such as glaucoma.[11] The majority of studies showed that the biomechanical strength between FS-LASIK and SMILE* was equivalent[12-15] or a very small difference in favor of SMILE*. [16] Another study conducted in an ex-vivo setting evaluated the corneal tensile strength of human donor corneas that were subjected to both surgical procedures and demonstrated that the level of myopic correction was the determining factor of post-procedure corneal tensile strength.[17] Both groups revealed similar tensile strength reductions for higher myopic corrections. [17] Contrary to previous findings, SMILE* showed a greater reduction in tensile strength in lower myopic corrections compared to LASIK.[17] The authors noted that SMILE* implements an additional refraction neutral corneal tissue base to maintain a minimum thickness of the lenticule, which may explain this finding.

FS-LASIK and SMILE*, because of their different approach to correct refractive errors, encounter procedure-specific complications. Table 4 lists unique intra- and post-operative complications that are flap or lenticule related for each procedure.

Table 4: FS-LASIK and SMILE* related intra- and post-operative complications.

Flap-related complications[18]	Lenticule-related complications[19]
• Buttonhole flaps as a result of vertical gas breakthrough for thin flap or conditions, such as previous radial keratotomy, corneal scars or microscopic breaks in the Bowman's membrane • Flap tears during lifting of the flap (a free flap may occur if the tear is at the hinge) • Interface debris • Dislocated flaps post-operatively	• Incisional abrasion due to excessive manipulation • Inadvertent dissection of the posterior plane with resulting cap-lenticule adhesion and very challenging to impossible extraction of the lenticule • Cap perforation/ incisional tear during plane dissection • Lenticule tear with lenticule remnants remaining in the interface (can generate topographic irregularities, irregular astigmatism and vision loss)

In terms of **safety**, both procedures have an acceptable safety profile based on loss of BCVA at 12 months (see Table 5). However, SMILE*-treated patients had a high number of eyes with a loss of best corrected visual acuity (BCVA) of 2 or more lines at scheduled and unscheduled visits throughout the study (no reports at 12 months). Alcon Contoura® Vision and Zeiss VisuMax* SMILE* studies allowed no retreatments, while one retreatment/secondary surgical intervention occurred in the Nidek CATz* study (a result of a small hemorrhage under the flap and a traumatic injury with diffuse lamellar keratitis). The occurrence of loss of BCVA of 2 or more lines in each registration study during the 12 month was as follows:

- Alcon Contoura® Vision had 5 eyes/occurrences with the vision loss described as transient and unrelated to the treatment;
- Nidek CATz* had 2 eyes with transient vision loss attributed to punctate epithelial keratitis and Meibomian gland disease;
- Zeiss VisuMax* SMILE* had 27 eyes/occurrences with causes for the loss of vision not clearly described but appearing to include treatment decentration and irregular astigmatism. At 12 months, none of these eyes had a BCVA loss of 2 or more lines.

Table 5: Visual Outcomes for topography-guided LASIK and SMILE* Procedures at 12 months after surgery per the respective FDA Summary of Safety and Effectiveness Data (SSED) Sheet of three different clinical data sets.[5-7,**]

	Topography-guided LASIK		SMILE*
Percentage of eyes with	**Alcon Contoura® Vision** *(n = 230 eyes)*	**Nidek CATz** *(n = 103 eyes)*	**Zeiss VisuMax* SMILE*** *(n = 310 eyes)*
Loss of more than 2 lines BCVA	0%	0%	0%
Loss of 2 lines BCVA	0.4%	0%	0%
Loss of 1 line BCVA	2.2%	8.7%	[2.6]%
Equal BCVA	57%	36.9%	72%
Gain of 1 line BCVA	27%	33%	22.8%
Gain of 2 lines BCVA	10.4%	14.6%	1%
Gain of more than 2 lines BCVA	3%	6.8%	1.6%
BCVA worse than 20/40	0%	0%	0%

BCVA: best corrected visual acuity. **A direct comparison of the data detailed in this table is not possible as these are three separate clinical trial datasets with differences in laser technology, laser indications, and/or patient populations.

In summary, the topography-guided LASIK and SMILE* platforms provide acceptable effectiveness and safety profiles. The Alcon Contoura® Vision topography-guided LASIK platform outperforms the SMILE* procedure in visual performance as demonstrated by the comparative study conducted by Kanellopoulos.[3-4] SMILE* demonstrated benefits of reduced incidence of dry eye symptoms in the early post-operative period but did not better preserve the biomechanical characteristics as compared to FS-LASIK. Both platforms have unique intraoperative and post-operative complications that surgeons should consider.

Contoura® Vision

Contoura® Vision topography-guided refractive surgery on the WaveLight® platform became available in the United States in 2015. Contoura® Vision uses the individual corneal topography of the patient to customize the ablation profile. Adjusted laser pulse placement also neutralizes corneal surface irregularities and preserves the aspheric shape of the cornea.

The WaveLight® Topolyzer® VARIO system measures up to 22,000 unique elevation data points to capture the distinct characteristics of the patient's anterior cornea and creates a complete topography map (Figure 2). The Contoura® Vision treatment planning software uses this information to guide the EX500 excimer laser and applies a smoothening ablation profile that flattens elevations and steepens flatter areas by ablating around them. The treatment is centered on the corneal apex and as opposed to the pupil center, thereby minimizing concerns related to the effect of angle Kappa in a pupil centered ablation treatment. In addition, planning refractive surgery using corneal topography is more consistent as it is less affected by pupil size, pupil centroid shift, accommodation and internal ocular pathologies associated with aging.[20]

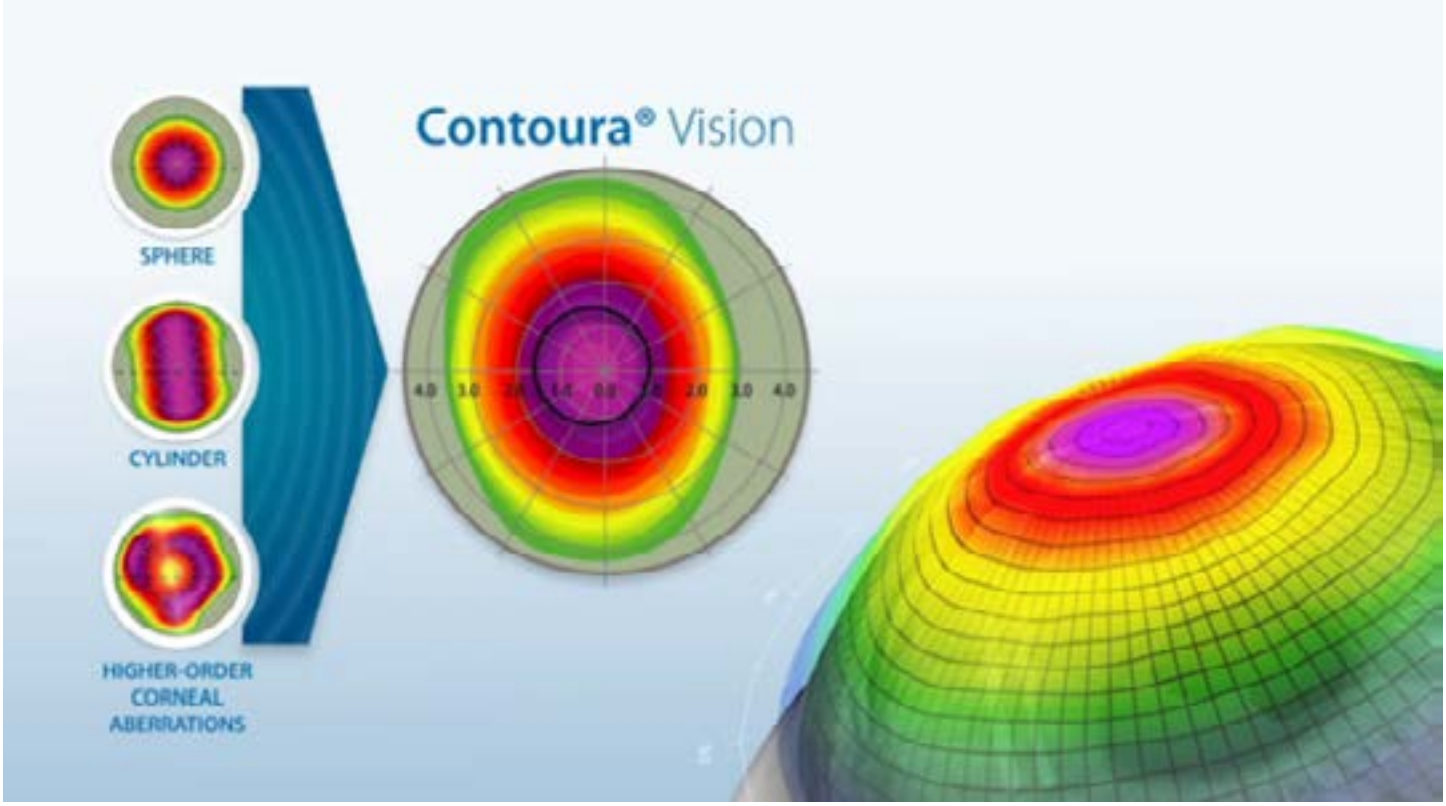

Figure 2: Contoura® Vision incorporates the elevation map from the WaveLight® Topolyzer® VARIO system to individualize the ablation profile.

Contoura® Vision builds on Wavefront Optimized® fundamentals. The ablation profile compensates for the cosine effect by fine-tuning the energy delivery profile in the periphery of the treatment zone, which preserves the aspheric shape of the cornea (see Figure 3). Without such compensation, the energy per unit area would be lower in the periphery and the effectiveness of the laser would be reduced. Reasons for the cosine effect are: 1) the shape of the laser beam ovalizes towards the periphery of the treatment resulting in a larger energy distribution for the same amount of energy; 2) the angle of incidence between the laser beam relative to the cornea is increased which subsequently increases beam reflectivity; 3) the likelihood of beam interference is increased by the plume created from earlier tissue ablation due to the longer path length. Overall, the compensation for the cosine effect helps to minimize the induction of spherical aberrations.[21]

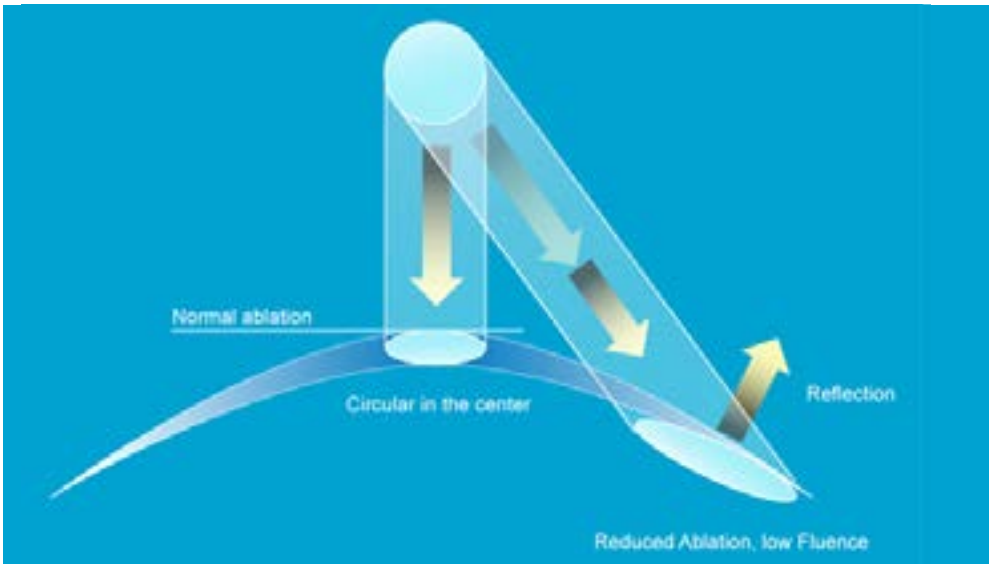

Figure 3: Contoura® Vision compensates for the cosine effect by applying additional laser pulses in the periphery of the treatment zone.

The cornea accounts for almost 70% of the overall refracting power of the eye. A uniform shape of the cornea is therefore a prerequisite to good vision and the Contoura® Vision system excels in providing uniform corneal shape by removing corneal irregularities. Stulting et al.[20] described excellent visual outcomes of eyes treated with Contoura® Vision, with 92.6% of eyes achieving 20/20 or better (see Figure 4). Other authors have also reported excellent visual acuity outcomes with 94% to 100% of eyes treated achieving 20/20 or better.[21-23] A recent post-hoc analysis of the Contoura® Vision FDA clinical trial data also showed improvement of vision over time. At 12 months post-operatively, the number of eyes achieving uncorrected distance visual acuity (UCVA) of 20/10 was 2.2 times greater compared to 3 months post-operatively.[24] Furthermore, smoothening of the corneal surface improved vision and studies have shown that 7% to 55.6% of eyes gain 1 line or more of BVCA. [20,21,23,25]

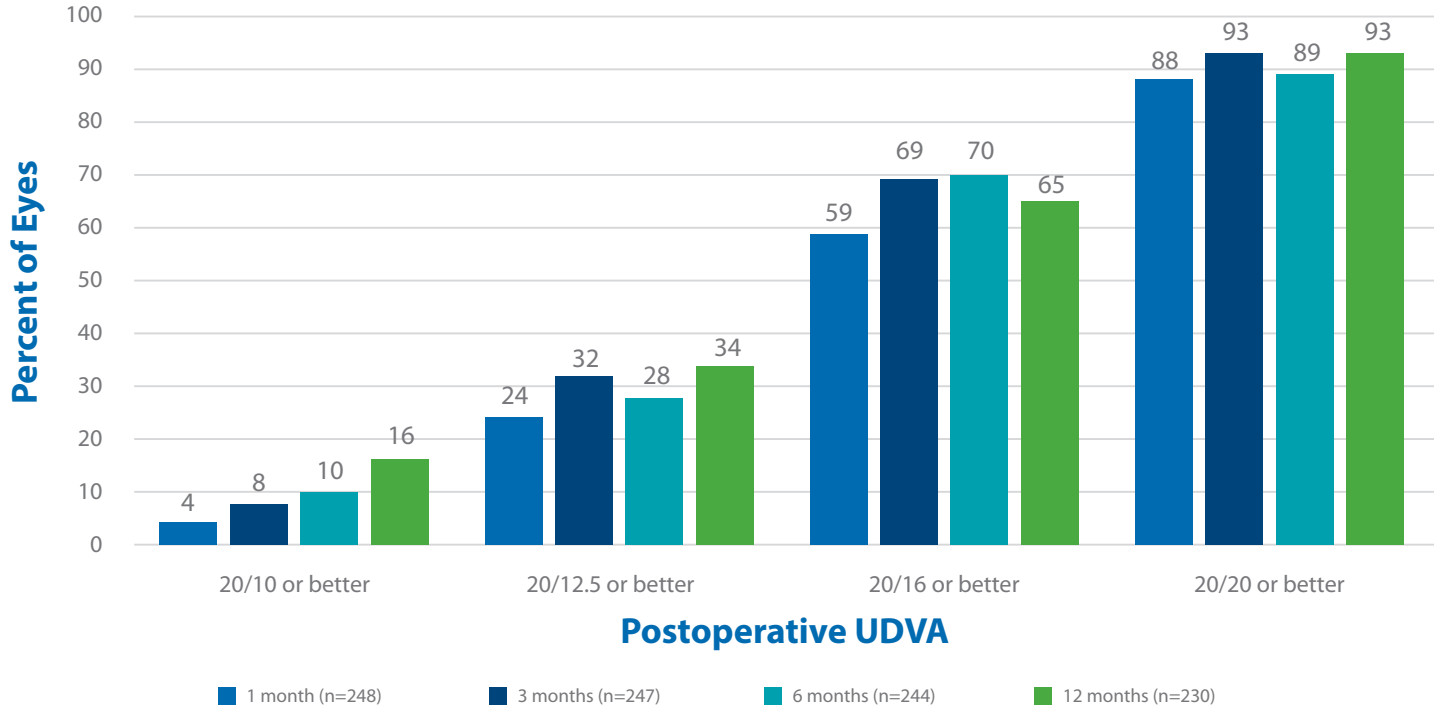

Figure 4: Uncorrected distance visual acuity (UDVA) at each post-operative visit following Contoura® Vision treatment.[20]

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A more uniform corneal shape improves the quality of vision. Contoura® Vision showed reduced induction of higher and lower order aberrations[21,23] as well as better mesopic contrast sensitivity post-operatively[8,23] in comparison to traditional LASIK procedures. In addition, patients that underwent Contoura® Vision surgery were happier and had fewer visual complaints. Patient satisfaction with Contoura® Vision is exceptionally high, with 98.4% of 124 patients willing to undergo the procedure again.[20] The severity of patient reported visual symptoms, such as light sensitivity, difficulty driving at night, reading difficulty, problems with glare and halos, were significantly reduced (Table 6).[20] In 30% of patients, visual acuity improvement surpassed the vision they had with their glasses or contact lenses before surgery.[20]

In conclusion, Contoura® Vision offers patients a personalized treatment plan that improves the quantity and quality of vision and surpasses the vision they had known with glasses and contact lenses.

Table 6: Patient reported outcomes prior to and 12 months after surgery with Contoura® Vision.[20]

	Prior Surgery (n=249 eyes)		12 months after surgery (n=230 eyes)		
Patient reported outcome	**% of eyes with no to moderate symptoms**	**% of eyes with marked to severe symptoms**	**% of eyes with none to moderate symptoms**	**% of eyes with marked to severe symptoms**	**Difference prior surgery to 12 months after surgery (in marked to severe)**
Light sensitivity	94.8	5.2	100	0	p<0.0005*
Difficulty driving at night	91.6	8.4	99.6	0.4	p<0.0001*
Reading difficulty	90.0	10.0	98.7	1.3	p<0.0001*
Glare	95.2	4.8	100	0	p<0.001*
Halos	96.8	3.2	100	0	p<0.01*
Starbursts	96.8	3.2	99.6	0.4	p<0.03*

*** Significantly different**

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