Chris Steele BSc (Hons), FCOptom, DipCLP, DipOC

Wavefront assisted LASIK
“For perfect visual outcomes?”

Wavefront-guided Laser-in-situ-keratomileusis (LASIK) is an emerging technique that offers the potential to correct refractive errors, to improve visual acuity and to increase the quality of vision, especially under mesopic conditions.

There are, however, a number of, as yet, poorly understood variables that will significantly affect the success of these customised laser ablations. In particular, these include concerns around the altered biomechanics of the cornea[1] post treatment and our still limited understanding of the corneal wound healing response. There are also the intra-operative and post-operative complications associated with the LASIK technique and the fact that higher order aberrations are not constant[6] and vary with, for example, increasing age[2], accommodation[3,4] and the use of certain mydriatic drugs[5]. If these “ideal” corrections do lead to better vision, how much better will it really be? Is it appropriate to correct all higher order aberrations, as some may actually be beneficial in terms of improving vision?

In this article, the principles upon which this emerging technology is based will be discussed and some of the key limiting factors that could potentially thwart its success are reviewed.

Wavefront analysis

Refractive corneal laser surgery currently focuses on the correction of sphero-cylindrical errors as the most apparent and disturbing optical aberrations of the human eye. Unfortunately, these corrections are accompanied by a significant increase in higher-order optical aberrations, such as coma and spherical aberration[6]. Several workers have reported a notable increase in higher-order optical aberrations after corneal laser surgery which is correlated with a significant decrease in quality of vision, especially under mesopic and scotopic conditions[7,8,9,10,11].

One of the exciting new research areas in laser refractive surgery is the development of sophisticated devices to measure the wavefront of the optical system of the entire eye. The ability to objectively measure performance of the eye and refraction, as opposed to simple corneal shape, is critical to “customising” ablation algorithms and generating an overall improvement of visual outcomes after laser refractive surgery.

Anterior corneal surface topography cannot alone take into account optically important contributions from other optical structures, such as the posterior corneal surface and crystalline lens. If a laser was programmed strictly with anterior topography data the correction would be at best incomplete, at worst, simply wrong. Wavefront analysis is clearly important, particularly if the ultimate goal is to correct higher-order aberrations along with sphere and cylinder. An important question is: Will wavefront analysis alone be sufficient to fully predict visual outcomes? Will it replace corneal topography in the quest for the “perfect aberration-free” guided procedure, or will the two procedures complement one another?

Measurement of wavefront aberrations

The basic concept of wavefront-guided LASIK involves measurement of the wavefront aberrations with a wavefront analyser, such as the Tscherning or a Hartmann-Shack aberrometer.

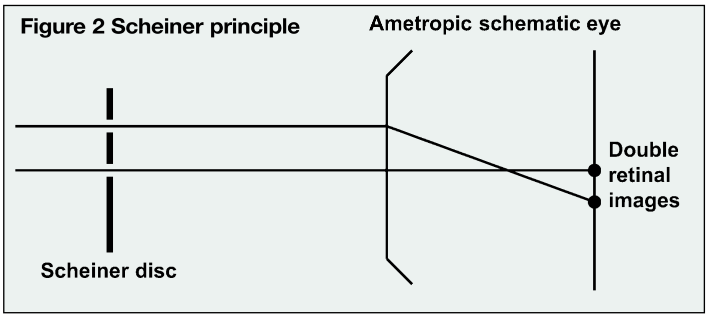
The Zywave™ aberrometer system (**Figure 1**) is based on the Hartmann-Shack aberrometer. It is marketed by Bausch & Lomb and is the only commercially available wavefront aberrometer which can be integrated with Orbscan’ II corneal topography results in conjunction with the Technolas® 217 scanning-spot excimer laser.

Figure 1
The Bausch and Lomb Zywave aberrometer in use

This laser can be upgraded to optimise it for the detailed ablation patterns needed to correct higher order aberrations. For example, the Technolas 217 is designed to accept a quartz card that will add a 1.0mm truncated Gaussian spot to the current 2.0mm “top hat” spot. A 1.0mm Gaussian spot will correct up to 5th and 6th order aberrations and so is still quite limited. The custom ablations use a combination of 1 and 2mm pulses which can be delivered anywhere on the cornea. The combination of spot sizes enables the laser to work quickly with great precision. The Technolas laser is capable of treating up to 12.0mm diameter treatment zones. The laser uses a 120Hz eye tracker which is vitally important to accurately placing each laser pulse exactly where required on the cornea - otherwise, the whole concept of customised ablation falls apart. To achieve precise tracking of eye movements requires a quick reaction time (10 milliseconds or less) in terms of moving the laser’s mirrors to adjust for eye movements. Overall reaction time of the laser is crucial rather than simply how quickly the eye tracker works. For example a fast tracker with slow reaction time is no use at all. As well as tracking x and y movements, the eye tracker must also be able to detect torsion. Eye trackers still have some way to go before perfection is achieved.

The combination of the Orbscan II corneal thickness and elevation data with the spatial refraction data from the Zywave aberrometer is achieved by a software

Figure 2 Scheiner principle



program called Zylink. The combined data is used to design a customised ablation suitable for one human eye which corrects for higher-order aberrations wherever they are in the eye.

The privately operated refractive surgery centre, "site-for-eyes" based within Sunderland Eye Infirmary, is only the second centre in the UK to have this combined instrumentation installed by Bausch & Lomb.

Hartmann-Shack aberrometry

The operating principle of the Hartmann-Shack aberrometer[12] is very simple and is partly based on the Scheiner disc (**Figure 2**).

If an ametropic eye views a distant point of light through a disc with two pin holes two retinal images will be formed. When the distant object is then viewed through an appropriately powered spectacle lens the two images can be made to coincide. For other optical aberrations, a simple lens will not bring the two images into coincidence. In such cases, a more general method is needed for quantifying the refractive imperfections of the eye in each pupil location. This can be achieved by using a fixed light source for the central reference pinhole and a moveable light source for the outer pinhole. By adjusting the moveable light source horizontally and vertically, the isolated ray of light is re-directed until it intersects the fixed reference ray at the retina and the person will then report a single point of light. The adjustment of δx and δy are measures of the ray aberration of the eye at the given point (**Figure 3**). This subjective aberrometer was first described by Smirnov[12] and has been used in visual optics research for many years.

To convert this Scheiner-Smirnov subjective technique into an objective aberrometer, the direction of the light propogation is reversed, by placing a spot of light on the retina. This spot then becomes a point source which radiates light back out of the eye. When additional holes are drilled in a Scheiner's disc, a Hartmann screen is the result[12]. Each aperture in the Hartmann screen isolates a narrow pencil of rays of emerging light through a different part of the pupil. These emerging rays intersect a video sensor to register the δx and δy displacements of each ray from the corresponding, non aberrated, reference position. The resulting instrument is a Hartmann aberrometer for objective measurement of ray aberrations (**Figure 4**). This becomes known as a Hartmann-Shack aberrometer once a small lens (lenslet) is placed at every aperture on the Hartmann screen as described by Shack and Platt[13] (**Figure 5**). The above is a ray optics description, but equally the device can be described in wave optics terms as well.

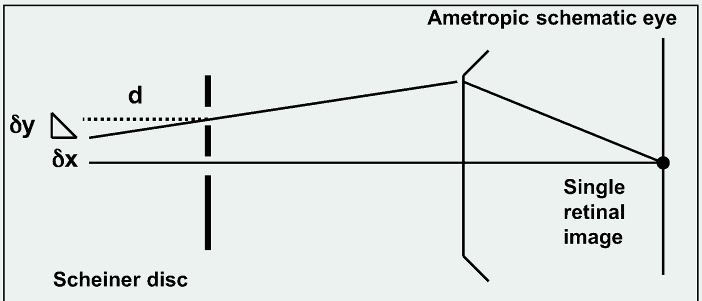


Figure 3 Scheiner optometer

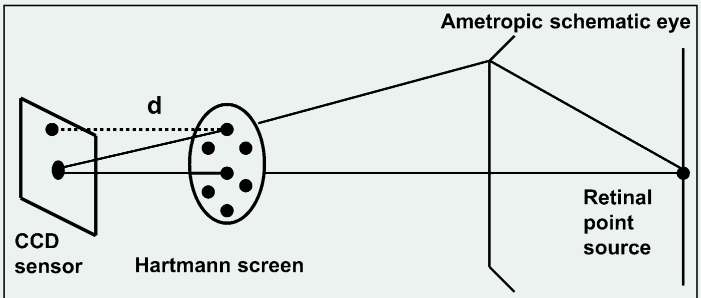


Figure 4 Objective scheiner/ Hartmann aberrometer

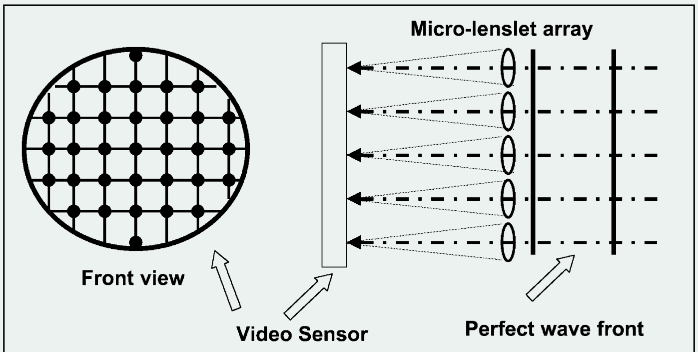


Figure 5 Microlenslet array subdivides wave front into multiple beams

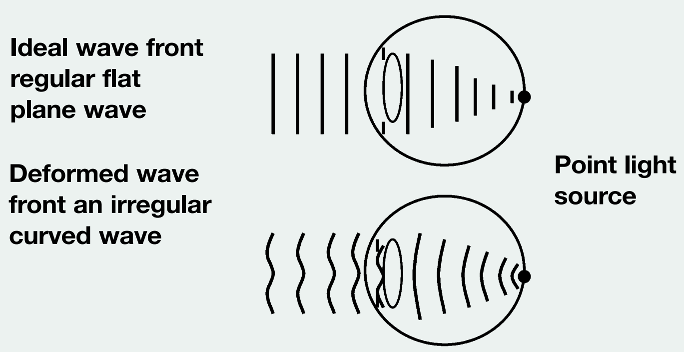


Figure 6 Wavefront aberrations

In wave optics terminology, the purpose of the Hartmann-Shack aberrometer is to measure the wave aberration function of the eye's optical system. That is, it measures the shape of the wavefront of light which is reflected out of the eye from a point source on the retina (**Figure 6**). The objective lens of a Hartmann-Shack aberrometer is constructed from an array of small lenses rather like the compound eye of an insect. In this way, multiple images from each retinal spot of light can be produced.

In a perfect eye, the reflected wavefront plane, which is perpendicular to the light rays with no deviations, would be focused into a perfect lattice of point images, with each image falling on the optical axis of the corresponding lens. The wavefront will be

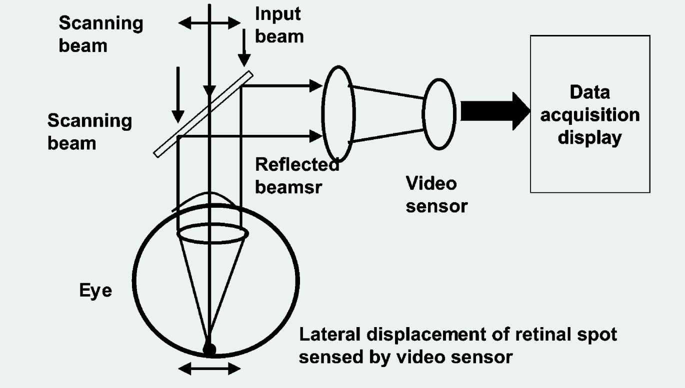


Figure 7a Optical principle of wavefront device

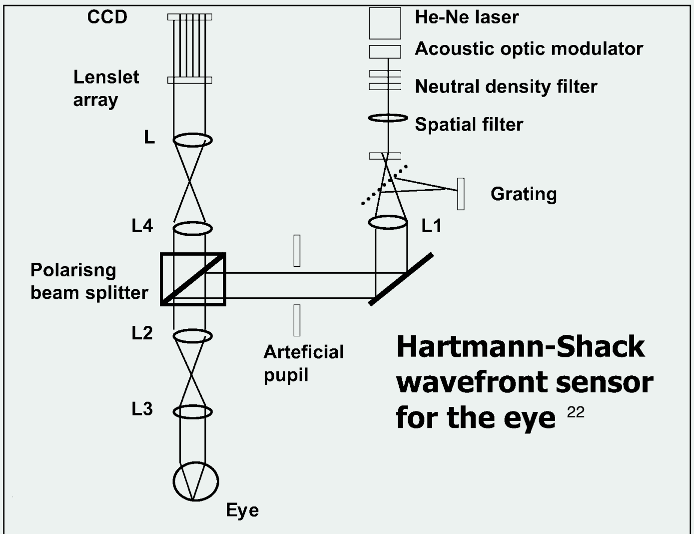


Figure 7b Hartmann-Shack wavefront aberrometer – Light from the He-Ne laser produces compact point source on retina. If aberrations are present the wavefront of the reflected light from the retina is distorted at the pupil plane. The reflected wavefront is recreated by lenses L2 and L3 and then by L4 and L5 in plane of the lenslet array. Focus spots from the distorted wave front plane are picked up by the CCD sensor.

distorted where aberrations do exist (**Figure 6**). The local slope of the wavefront will be different for each lenslet and therefore, the wavefront will be focused into a disordered collection of spot images. By measuring the displacement of each spot from its corresponding lens axis, the slope of the aberrated wavefront can be deducted where it entered the corresponding lens. Mathematical integration of this slope information yields the shape of the aberrated wavefront. The shape of the aberrated wavefront is a fundamental description of the optical quality of the eye called the "wavefront aberration function". This function allows us to calculate the retinal image of the object, assess the quality of that retinal image quantitatively and ultimately to predict human performance on visual tasks. To apply this optical theory, the wavefront is analysed as it passes through the pupil. This is achieved by using a pair of relay lenses which focus the lens array onto the pupil of the eye. Then the array appears optically to reside in the plane of the pupil where it can sub-divide the reflected wavefront immediately as it emerges from the pupil. This forms the configuration that is used in the Zywave (Hartmann-Shack) aberrometer (**Figures 7a and 7b**).

Current and future ablation algorithms

Munnerlyn et al[14] first described the "shape subtraction model" of refractive surgery, which was based on geometric equations for altering the surface curvature of the cornea making the assumption it is initially a sphere. To illustrate this model, a myopic corrective procedure would be achieved by superimposing a sphere of lesser curvature on the original sphere of greater curvature. The apex is displaced by an amount determined by the selected ablation diameter. The intervening tissue is then removed by the laser ablation. The assumption is that the original sphere will be sculpted to its new shape without any response to its structure imposed by the ablative procedure.

Since their first implementation, the Munnerlyn formulae have been empirically modified, based on statistical analyses of large numbers of treated patients. Current ablation algorithms are optimised to the mean population response.

Customised ablations, however, require prediction of individual rather than mean corneal response. Outcomes are currently analysed in terms of sphere and cylinder, which is a measure of central corneal performance. Higher order aberrations, on the other hand, are produced by a larger region of the cornea. Therefore, aberration reducing ablation algorithms must target a very specific corneal shape over that broader region.

To achieve a specific "perfect" corneal shape over the entire ablation zone, a much deeper understanding of corneal response than currently exists is going to be essential.

Certainly the correction of optical aberrations of the eye with large optical zones (>/= 6.5mm in diameter) might require deeper keratectomies than those of standard sphero-cylindrical ablations. This may adversely affect the biomechanics of the cornea.

Corneal biomechanics and excimer laser surgery

Prior to surgery the cornea is a layered structure consisting of many lamellae that stretch from limbus to limbus, with a loading force produced by the intraocular pressure. The inter-lamellar spacing is defined by the tension carried in an individual lamella. After surgery, a defined series of lamellae are circumferentially and permanently severed. This reduces the tension in the remaining peripheral segments, allowing expansion of the peripheral layers. This expansion generates a radial force outwards, which is transmitted to the lower layers via cross-linking. The peripheral radial pull causes the central cornea to flatten, independent of the ablation profile cut on the cornea (**Figure 8**). Therefore, the biomechanics involved cause an extra flattening in a myopic procedure resulting in over-correction. In hypermetropia, the increased flattening will cause a relative under-correction. Higher order aberrations increase where the peripheral cornea is relatively steep compared to the central area post excimer treatment.

Further clinical evidence is therefore required before accurate correction factors can be built into customised ablation zone algorithms to allow for these biomechanical effects of larger ablation zones.

It is quite likely that a single, linear correction factor may not be sufficient to account for all the biomechanical effects in large diameter ablations. Thus, in some cases it may not be possible to fully correct the optical aberrations without affecting the mechanical integrity of the cornea, especially where customised ablations for higher corrections are concerned.

Corneal topography offers a mechanism to measure the actual shape changes produced. With knowledge of the ablation algorithms, the biomechanical response can be separated from the shape change produced by the ablation profile.

Topographic changes can be also linked to the measured wavefront to more fully characterise both corneal shape and functional response. Ideally, the ultimate customised "guided" procedure involves a combination of wavefront and corneal topographic analysis to provide a complete picture of corneal response and visual outcome. The Zywave, for example, combines its wavefront data with that from the Orbscan II topography system.

Predicting this complete response on an individual basis is going to be one of the major challenges to the future of customised, aberration reducing ablative procedures. Correction of higher order aberrations will also require deeper ablations towards the edges of the ablation zone.

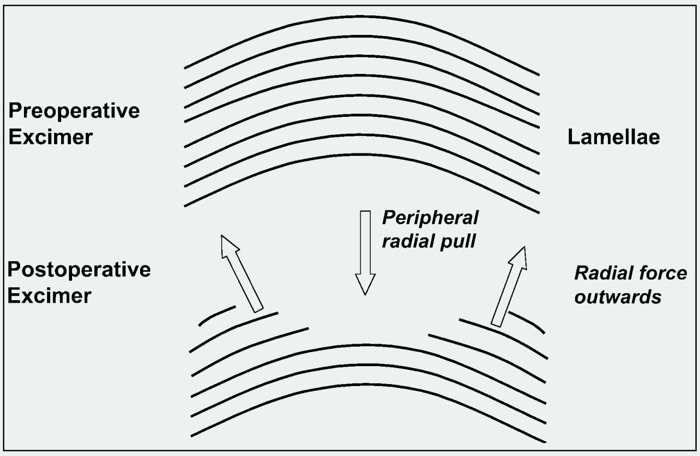


Figure 8
Biomechanical model of corneal response to excimer laser surgery

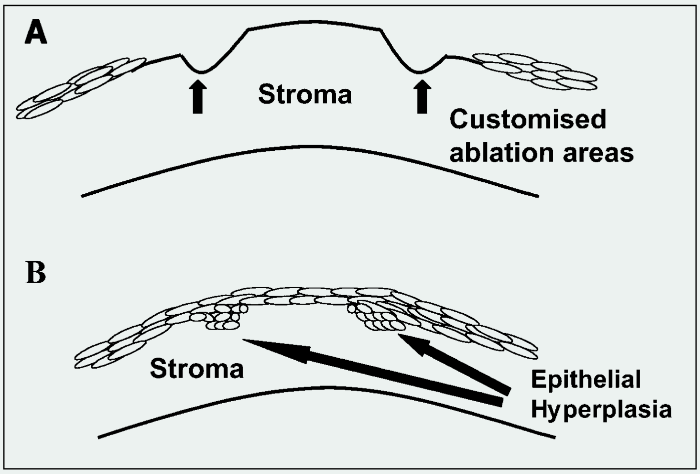


Figure 9
Potential effects of corneal wound-healing post customised laser ablations

The wound-healing response after LASIK and PRK

The corneal wound-healing response is extremely complex[15] and a greater understanding is critical to the success of topography and wavefront linked laser ablations. This is because of the importance of retaining subtle features of custom ablations and the tendency of epithelial hyperplasia and stromal re-modelling to obscure these features following either LASIK or PRK (**Figure 9**).

During the past five years, there have been tremendous advances in our understanding of the complex events which occur in corneal epithelium and stroma in response to injury or surgery. These contributions are slowly bringing us closer to being able to manipulate corneal wound healing to clinical advantage.

Dohlmann et a[16] were the first to observe the disappearance of superficial keratocytes following corneal epithelial scrape injury as long ago as 1968. During the decades that followed, this observation was independently made a further three times in a variety of species[16,17]. Investigators speculated that the disappearance was due to artefact, corneal hydration changes, exposure to atmosphere or other factors. Wilson et al[18] in 1996, were the first, however, to suggest that the disappearance of the keratocytes was mediated by apoptosis.

Apoptosis is a controlled, relatively gentle form of cell death in which the cells are dismantled and eliminated with minimal release of intracellular components that could seriously damage surrounding cells and tissues.

Since that time, there have been a number of other observations of manipulations such as PRK and LASIK triggering specific patterns of keratocyte apoptosis. This has been observed to lead to subsequently localised wound-healing events which occur in the epithelium and stroma.

The keratocyte apoptosis response occurs immediately beneath the healing epithelium in PRK. Subsequent events in wound healing are also localised immediately beneath the epithelium. Studies have demonstrated that epithelial hyperplasia is an important factor in regression following PRK[19,20]

In contrast, LASIK keratocyte apoptosis and subsequent cascades occur at the level of the interface and are further removed from the overlying epithelium. Therefore the epithelial hyperplasia response tends to be more attenuated compared with PRK. Recent studies have, however, demonstrated that epithelial hyperplasia can occur after LASIK[20]. This correlates well with the clinical observation that eyes with identical levels of myopia require less ablation when LASIK is performed compared with PRK. Eyes with LASIK are also likely to show less regression.

Variability in flap thickness could also be an important factor in variation of wound-healing and achieved correction between different eyes that have undergone LASIK. The closer the wound-healing response to the overlying epithelium, the more likely epithelial hyperplasia will be stimulated by growth factors released from keratocytes or myofibroblasts.

Since epithelial-derived cytokines seem to be inducers of keratocyte apoptosis, the operating surgeon should do everything possible to limit the introduction of epithelial tissue into the interface. Thus LASIK should always be performed with sharp blades which perforate the epithelium with minimal trauma rather than blunt blades which will tend to tear through the epithelium releasing relatively more unwanted cytokines.

Strategies such as limited irrigation with balanced salt solution and use of an aspirating eyelid speculum may also be useful in controlling the LASIK-associated wound-healing response.

Control of wound healing

The ultimate goal is to develop pharmacological agents which could be applied to the cornea prior to surgery to limit or normalise the subsequent wound healing response.

If we could even normalise the wound-healing response between different eyes and different patients so that it is consistent, it would be relatively straightforward to adjust laser algorithms to compensate.

Much work is being carried out into various ways of controlling initial keratocyte apoptosis which would help attenuate the cascade of events in wound-healing.

How can keratocyte apoptosis be controlled? Apoptosis is mediated by a series of defined steps much like glycolysis or the Kreb's cycle[21]. Enzymes called capases which mediate the apoptosis response are one target. Alternatively, gene therapy has been suggested. The cornea is uniquely accessible for gene transfer and it may be possible in the future to block apoptosis through the introduction of inhibitory genes.

It may only be necessary to transiently control keratocyte apoptosis to produce the desired effect over corneal wound-healing.

It is quite likely that frustrations with customised ablations will raise the profile of wound-healing research.

Wavefront-guided LASIK results to date

Recently Mrochen et al[6] published their clinical data of wavefront guided-LASIK three months post surgery results. At three months, 68.0% of eyes were within ±0.5D of emmetropia and 93.5% were within ±1.00D. Uncorrected visual acuity was 6/6 or better in 93.5% of eyes. No eye lost more than one line of low contrast, glare and best spectacle corrected visual acuity (BSCVA). "Supernormal" vision (6/3) or better was achieved in 16% of eyes. The correction of higher-order aberrations (spherical aberration and coma) was insufficient, with an increase factor of the overall root-mean-square wavefront error of 1.44±0.74 (pupil diameter 5.0mm). Coma aberration was better corrected than spherical.

Although these results were disappointing and far from expected, the increase factor was nearly one order of magnitude smaller than the factor in standard corneal laser surgery.

Potentially how much better will vision be?

Visual acuity is limited by receptor diameter in the retina, receptor packing and biological variation between individuals. For most people the upper limit of visual acuity correction is realistically likely to be 6/3. Improving the optics of the eye by removing aberrations increases contrast and spatial detail of the retinal image. These effects are however pupil size dependent, which varies throughout the day.

Eliminating a patient's sphero-cylindrical error and reducing the higher-order aberrations will, in most cases, improve contrast and produce crisper borders to images. Whether a person actually benefits from having their higher-order aberrations corrected depends, to a certain extent, on how much these were degrading their retinal image in the first place. For example a patient with 6/9 vision whose acuity is reduced because of optical aberrations in an otherwise normal eye, will benefit more than a patient with 6/4 visual acuity initially, where correcting higher order aberrations may not greatly improve contrast but perhaps only perceived contrast.

Conclusions

Wavefront-guided LASIK is a promising technique which still needs research and refinement. Presently nobody really knows to what degree it will be possible to optimise patients' vision. Although early results appear reasonably encouraging and indicate that higher order aberrations can be treated to some degree, there is unlikely to be immediate success. Prospective controlled clinical trials must clarify the major benefits of wavefront guided LASIK. A prospective case control study is currently underway at the Refractive Surgery Centre "site-for eyes", within Sunderland Eye Infirmary and preliminary results should be available in the coming few months.

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About the author

Chris Steele is Head of Optometry Services at Sunderland Eye Infirmary