COMMERCIALIZATION OF SOFTWARE FOR THE PREDICTION OF
STRUCTURAL AND OPTICAL CONSEQUENCES RESULTING FROM
CORNEAL CORRECTIVE TREATMENTS

by

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<td>AK</td>
<td>Astigmatic Keratotomy</td>
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<tr>
<td>LASIK</td>
<td>Laser Assisted In-situ Keratomileusis</td>
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<tr>
<td>PRK</td>
<td>Photorefractive Keratotomy</td>
</tr>
<tr>
<td>ReLEx</td>
<td>Refractive Lenticular Extraction</td>
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<tr>
<td>CXL</td>
<td>Corneal Crosslinking</td>
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<tr>
<td>ICRS</td>
<td>Intrastromal Corneal Ring Segments</td>
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<tr>
<td>PMA</td>
<td>Premarket Approval</td>
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<tr>
<td>Pre-sub</td>
<td>FDA Pre-submission Package</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>HDE</td>
<td>Humanitarian Device Exemption</td>
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<tr>
<td>BAD</td>
<td>Belin/Ambrosio Enhanced Ectasia Display</td>
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<tr>
<td>D</td>
<td>Diopter</td>
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<tr>
<td>3-D</td>
<td>Three Dimensional</td>
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<tr>
<td>cGMP</td>
<td>Cyclic Guanosine 3’-5’ Monophosphate</td>
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<tr>
<td>PKP</td>
<td>Penetrating Keratoplasty</td>
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Commercialization of Software for the Prediction of Structural and Optical Consequences Resulting from Corneal Corrective Treatments

Abstract

By

JOSHUA LLOYD

Biomechanical prediction of refractive surgery outcomes is a relatively new field in ophthalmology. OptoQuest is the first company in the field based on using finite element analysis to predict refractive surgery outcomes on a patient-specific basis. Getting this technology to market requires the understanding of the human ocular system, refractive error prevalence, incidence, prevention, and treatment as well as regulatory barriers between research and marketing approval. After analyzing these crucial areas, it is understood that the scientific support and marketing need for this technology is both adequate and sufficient to conclude that OptoQuest has a marketable technology.
Introduction

Vision problems cost Americans up to $7.2 billion every year\(^1\). This figure represents a large opportunity for businesses and researchers to help better lives and make a profit while doing so. OptoQuest is one company pursuing that opportunity. Founded inside the Cleveland Clinic, OptoQuest aims to improve the outcome of refractive procedures using predictive and diagnostic technologies.

Refractive procedures are surgical and non-surgical medical treatments that aim to correct refractive errors and include treatments such as laser assisted in situ keratectomy (LASIK), photorefractive keratectomy (PRK), refractive lenticular extraction (ReLEx), intrastromal corneal ring segment implantation (ICRS), astigmatic keratotomy (AK), and corneal crosslinking (CXL). These surgeries are performed by ophthalmologists.

LASIK is the most popular elective surgery performed in the United States with more than 428,000 surgeries expected to be performed in 2015\(^2\). The Food and Drug Administration (FDA) approved LASIK in 1996 and Market Scope reported that the market grew to as many as 1.6 million procedures being performed per year during the mid-2000’s. The market took a steep dive during the recession of 2008 and only recently has begun to make a slow recovery.

LASIK is used to correct mild to moderate cases of refractive error including myopia, hyperopia, and astigmatism. The procedure involves using a manual microkeratome or femtosecond laser to create a flap out of the epithelium and anterior stroma of the cornea, lifting the flap, and then using an excimer laser to ablate patterns
in the stroma that will alter the shape and focusing properties of the cornea after the flap is replaced. The success rate is generally considered very high, with 96% of patients indicating that they are satisfied with their outcomes\(^3\). PRK and ReLEx are different procedures that are less commonly used to correct many of the same forms of refractive error.

AK is a procedure for correcting astigmatism and can be performed using femtosecond lasers or surgical knives. ICRS and CXL are both used to reduce the progression of keratoconus. ICRS involves the implantation of ring segments into the corneal stroma while CXL is a non-surgical approach that involves chemically inducing structural changes in the collagen fibers of the cornea. CXL is also currently being investigated as an alternative method of treating refractive error.

For laser refractive surgery (LASIK, PRK and ReLEx), built-in laser algorithms translate an attempted refractive correction specified by the surgeon to a laser treatment profile. Because there is some case-to-case variability in refractive outcomes, surgeon intuition, combined with some third-party statistical tools to help refine the modifiable treatment parameters, is often used to modify standard algorithms. Results are less predictable in secondary treatments and higher refractive errors. Predictive algorithms for ICRS and AK are more complex, less formal, and less reliable. As a result, outcomes for these procedures are less predictable.

Additional challenges relate to treatment of patients exhibiting “risky” corneal attributes. These attributes may include things such as high myopia, hyperopia, and/or
astigmatism; or asymmetric corneal topographies or abnormally thin corneas among other things.

Other factors that contribute to the risk profile of any treatment is the familiarity the physician has with that type of treatment as well as any devices they use. For example, a physician who primarily performs cataract surgery will not necessarily be comfortable planning and performing refractive surgery procedures. Physicians tend to foster areas of expertise over time. These “newness” factors are increasingly important over time as the rate of innovation in ophthalmology increases and physicians are confronted with new devices and procedures more frequently.

ICRS and CXL are commonly described as having low predictability for improving visual acuity\(^4\text{,}^5\). Either procedure will most commonly improve a patient’s vision by 1 to 2 lines on an eye chart; however, not infrequently will a patient see no increase or even a decrease in visual acuity. AK, although used frequently for astigmatism, is also considered to have low predictability\(^6\) particularly in corneas with higher astigmatism that have had prior surgical intervention. As a result, AK is commonly paired with other interventions such as glasses, contacts, toric intraocular lenses, etc. in order to achieve target visual acuity. Case-to-case variability in refractive and visual acuity outcomes is the rule among these procedures and has hampered efforts to produce reliable surgical formulae.
LASIK, PRK and ReLEx procedures, on the other hand, have the benefit of being much more predictable and outcomes, by a vast majority, tend to be favorable\textsuperscript{7,8,3,9,10,11,12,13,14,15}. However, retreatments are required in 6\% to 14\% of cases\textsuperscript{11,16}. See Table 1 for a limited summary of reported outcomes. When lasers for refractive surgeries are first investigated in clinical trials, outcomes data are often less impressive until empirical modifications to treatment algorithms are made by device manufacturers. In addition, physicians observe, learn and share best practices in post-market use; therefore, Table 1 focuses on studies performed since 2004.

<table>
<thead>
<tr>
<th></th>
<th>% Achieving 20/20 or Better</th>
<th>% Within 0.5 D of Emmetropia</th>
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<tr>
<td></td>
<td>Lower Limit</td>
<td>Upper Limit</td>
</tr>
<tr>
<td>LASIK</td>
<td>84.1%</td>
<td>98%</td>
</tr>
<tr>
<td>PRK</td>
<td>54%</td>
<td>96%</td>
</tr>
<tr>
<td>ReLEx</td>
<td>83.5%</td>
<td>100%</td>
</tr>
<tr>
<td>Refractive Retreatments (primarily LASIK)</td>
<td>58%</td>
<td>82%</td>
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Abbreviations: (D) Diopter; (LASIK) Laser Assisted In-situ Keratomileusis; (PRK) Photorefractive Keratotomy; (ReLEx) Refractive Lenticular Extraction.

In order to reliably produce positive outcomes in less certain or riskier situations, physicians have to go beyond the “educated guessing” they do in simpler, more familiar cases. This is where modeling technologies stand to help a physician the most. It can draw on the collective outcomes of many physicians to provide quantitative guidance to physicians who are newer in the field. Modeling technologies can also add a structural analysis component to predictive tools that has hitherto been absent from tools in the field.
The use of finite element analysis as a predictive tool in the field of ophthalmology is a relatively new idea. Finite element analysis in ophthalmology is a mathematically based modeling solution used to create a virtual, three dimensional (3-D) cornea and simulate the effects of medical treatments on the shape, thickness, and biomechanical features of that virtual cornea. OptoQuest, a Cleveland Clinic spinoff company, is a pioneer in this field\textsuperscript{17,18,19,20,21} and what follows is an assessment of the benefits of the technology and the pathways that will lead to its success in the marketplace.

**Human Vision**

In order to correct vision and understand opportunities within the field of ophthalmology, a correct understanding of how human vision operates is essential. Vision begins with light entering through the cornea or front (anterior) part of the eye and ends with signals, representing those photons of light, being translated into an image within the brain. Although the process takes less than a second, the ocular system is a complex mixture of processes involving physics, biomechanics, chemistry, and neuroscience.

First, light enters through the cornea of the eye. The cornea is transparent tissue made up primarily of collagen fibers, a protein-rich matrix, and water. The convex shape of the cornea helps to refract the light through the pupil and subsequently through the lens of the eye. The lens is also made of transparent material but its shape is dynamic and controlled by the ciliary muscles that attach to the periphery of the lens. The lens
further refracts the light to the point where it actually inverts the image and focuses it on the retina, or back surface of the eye. This is where the neuroscience begins.

**Constructing the Visual Image**

From “Principles of Neural Science” we learn many things about the neuroscience perspective of human vision. The retina consists of several types of neural cells – photoreceptors, bipolar cells, and ganglion cells – that sequentially transmit the visual signals further down the visual pathway. The axons of those ganglions cells exit the retina, form the optic nerve, and transmit the signal to the lateral geniculate nucleus, which resides in the thalamus of the brain. The signals then go to the visual or striate cortex located at the back of the brain. The signals will continue even further till they end in the extrastriate areas that coordinate the higher order functions of vision. The process is very orderly and yet complex. Portions of the visual field are projected in bundles, simultaneously and then get pieced together and interpreted in one final visual image.

Human vision is primarily a system of pattern recognition. Two of the main components for these pattern identifications lie in object recognition (contours, colors, etc.) and spatial recognition (distance, motion, etc.). While incredibly powerful and helpful, the pattern recognition base upon which vision rests can often play tricks on us.

Object recognition has proven to be the primary responsibility of the temporal cortex, while spatial recognition is the responsibility of parietal cortex. These areas of the brain are the final resting place of the neural pathway. If anything along the way
gets disrupted, or if anything in those areas is out of place, the ability to recognize spatial patterns or objects becomes deficient. While we see a fairly large area in our surrounding, our visual attention seems to only be able to recognize patterns based on what our vision is focused on; meaning that what you get through the course of the visual neural pathway is a funneling of visual signals down to the most important information receiving the greatest amount of neural processing and interpretation.

All of this information is conveyed through at least two major pathways beginning with two different types of ganglion cells in the retina, but ending in separate parts of the brain. Thus, within each eye there are two pathways through which all of the relevant information is conveyed. The P pathway, so named for the transmission through the parvocellular layers of the lateral geniculate nucleus, start with smaller retinal cells and ends up in the temporal lobe. The P pathway runs parallel, though in separate layers, with the M pathway, so named for the transmission through the magnocellular layers of the lateral geniculate nucleus. When both pathways reach the posterior part of the brain they separate ways and the M pathway goes to the parietal cortex.

Visual Processing by the Retina

When light has passed through the vitreous humor of the eye and reaches the retina, it will encounter one of two structures – photoreceptors or the pigment epithelium. If it hits the pigment epithelium, the light will be absorbed so it does not
reflect off the back of the eye and cause interference with other photons entering into the eye and destined to be sampled by photoreceptors.

There are two types of photoreceptors – rods and cones. If light hits a cone with sufficient intensity, it gets turned into a color image by the eye (contributing to so-called “day” vision). If less light enters the eye (< 300 cd/m²) and hits the rods it gets turned into a black and white image (night vision).

The main differences between rods and cones, beside the differences in the types of images they produce, are their structure, the pigments they contain, and how they synapse onto axons. Both types of photoreceptors have an outer segment, inner segment, and synaptic terminal. Rods have more expansive outer segments primarily to capture what little light is available during the night. By contrast, cones’ outer segments are more compact since they typically deal with lots of light. The outer segment of rods contain rhodopsin with the retinal portion of the protein being the primary light absorption agent. Retinal light absorption triggers a cascade of events ending in a decrease of concentration in cyclic guanosine 3’-5’ monophosphate (cGMP) which in turn controls gated ion channels which perpetuate the signal through the synapse. Cones on the other hand use different forms of opsin that resemble rhodopsin in many ways. Both photoreceptors use cGMP to mediate signal communication. Rods will often bundle together to have multiple rods synapse onto one interneuron. Cones, on the other hand, operate much closer to a one-to-one configuration though sometimes synapse onto multiple interneuron cells at the same time. This facilitates higher spatial
sampling of an image and higher resolution for fine visual perception tasks such as reading.

Sudden changes in light intensity are managed by the flow of Ca\textsuperscript{2+} ions across the photoreceptor membrane. When the sudden flash of light occurs, the membrane potential goes to about -70 mV by closing all of the cGMP-gated channels. As long as the intense light continues, the cell will eventually depolarize closer to -40 mV as ions re-equilibrate themselves across the membrane. This depolarization accounts for the time required for humans to adjust to sudden changes in light intensity.

Ganglion cells can be broken into several overlapping classes. All classes have to do with how ganglion cells react to their receptive fields (the proximally situated regions of photoreceptors near the end of the ganglion cell). Two contrasting classes are the P and M classes. M class ganglion cells have large receptive fields and tend to focus on receiving signals about large objects and following rapid changes in the stimulus. Hence, the motion and distance related processing that goes on in the parietal region of the brain. The P class of ganglion cells tend to be focused on transmitting signals relating to small items and specific wavelengths. Hence the more detailed, color processing that happens in the temporal cortex. There are also more P cells than there are M cells.

Another classification scheme ganglion cells fall into is their on-center/off-center response. In this classification you can think of the receptive fields as two concentric rings with an inner circle (the center) and an outer circle (the surround). Ganglion cells are always active; however, the rapidity of their activity depends on whether they are
excited by the signals of photoreceptors. Their activity also depends on whether they respond to light that is on-center or off-center. This system of on-center/off-center information relay is thought to indicate a focus on contrasts in visual image.

Between photoreceptors and ganglion cells are the interneurons, which transmit the information from photoreceptors as well as modulate it and give the final signal to the ganglion cells. There are three types of interneurons – bipolar, horizontal, and amacrine cells. Bipolar cells are the only cells of the three types that act as a direct bridge between photoreceptors and ganglion cells. Horizontal cells mainly lie in the outer layer of interneuron network and typically relay information from the surround of the receptive field to the target bipolar cell and subsequent ganglion cell. Hence, bipolar cells have the same on-center/off-center classification scheme as ganglion cells have. Amacrine cells lie mainly within the inner layer of the interneuron network. In some cases, these amacrine cells behave like horizontal cells, in other cases, they seem to play a part in shaping receptive field properties of some ganglion cells. All three types of interneurons operate on a graded potential basis like the photoreceptors as opposed to the action potential mechanism used by the ganglion cells.

Central Visual Pathways

The visual image is inverted by the cornea and lens when it enters the eye such that the image that hits the image is the inverse of what we see it as. The fovea is the place at the center of the retina where the center of the visual image is focused. The middle section of the visual field (the binocular zone) is the part of the visual field that
both eyes can see. There are zones to the left and right edges of the visual field that only the left and right eyes can see respectively. In addition, it is important to note that the place where the ganglion cells gather together to begin the optic nerve is located both inferiorly and nasally compared to the fovea and is called the optic disc. There are no photoreceptors in this area of the retina and thus represent a blind spot in human vision.

The retinal ganglions project through the optic nerve to the optic chiasm where the axons carrying contralateral information crosses over and bundles with the information from the opposite eye but the same respective hemisphere of the visual image. In other words, the right half of the retinal image for each eye projects to the right side of the brain and, likewise, for the left half of the retinal image. In the end, the left side of the visual field is processed by the right side of the brain and vice versa.

From the optic chiasm, the optic tract for each eye projects to three subcortical targets: the pretectum, the superior colliculus, and the lateral geniculate nucleus. 90% of the axons go to the lateral geniculate nucleus which will be discussed in a moment. The rest of the axons project to one of the other targets. Cells and/or signals that project to the superior colliculus will often be combined with signals from other sensory systems and are generally considered to control saccadic eye movements that allow our eyes to track to the source of a sound. The signals that propagate to the pretectum are used to activate the pupillary response – the dilation and constriction of the pupil in response to light intensity.
The retinal axons that terminate in the lateral geniculate nucleus get divided into 6 different layers according to the eye they came from and type of cell (P or M). The layers of the lateral geniculate nucleus are numbered one through six, ventrally to dorsally. Layers one and two bundle together synapses for M cells and layers three through six hold the P cells. These two bundles project in parallel to the primary visual cortex where the rest of the processing occurs. These lateral geniculate neurons also have similar receptive fields to their retinal ganglion counterparts; that is, their excited states depend on the on-center/off-center stimulation patterns.

By interrupting the signals at this point for the P and M pathways, researchers were able to determine the finding that the P pathway is mostly used to process color and spatial information while the M pathway is primarily responsible for processing luminary contrasts and temporal changes in the visual field\(^2\). It is interesting to note that only 10% to 20% of the presynaptic connections in the lateral geniculate nucleus come from the retina. The rest of the connections seem to be mostly feedback inputs going to and from the brain stem and visual cortex.

From the lateral geniculate cortex, the neurons project to the primary visual cortex. On each side of the brain the primary visual cortex is divided into six regions. The two largest regions focus on the upper and lower half of the respective side of the visual field, indicating that most of the processing power seems to be dedicated to the center of our field of vision. The four remaining regions process information relating to the
middle and outer concentric rings of our field of vision with the smallest regions dedicated to peripheral vision.

The primary visual cortex comprises of six layers, the fourth layer being broken down into sub layers. Most of the P and M lateral geniculate neurons terminate within one of the four sublayers of layer four. Cells from the intralaminar regions of the lateral geniculate nucleus terminate in the blob regions of layers two and three. There are many pyramidal and non-pyramidal cells that inhabit only the primary visual cortex and tend to connect the layers together.

All layers besides layer 4C and the blob regions seem to respond in a different way to visual stimuli. Whereas, all the cells analyzed up to this point seem to respond to on-center/off-center stimuli, these other regions contain simple and complex cells that respond differently. They still have on/off receptive fields by they are not made up of concentric circles. Instead, most simple cells have smaller, linear on-areas; everything in the receptive field is an off area. Complex cells respond similarly to the simple cells, but their receptive fields are much larger. Thus we have the beginnings of visual abstraction. These cells, together, help the brain process the contour of the objects in the visual field. Multiple simple cells converge onto one complex cell and combine their inputs, so that this convergence of information creates hierarchies and pieces together larger contours from the smaller contours perceived by individual simple cells. Those simple cells receive their input from P and M lateral geniculate neurons which got their signals from P and M retinal ganglion cells.
The primary visual cortex is structurally organized into what are called orientation columns. Each column contains cells that pertain to portions of the retinal image and, therefore, certain receptive fields. These columns are about 2 mm deep and 30 to 100 µm wide. They contain simple and complex cells that are interconnected with each other. Also within some of these columns are the blobs that come from the intralaminar cells that terminate in layers 2 and 3 of the primary visual cortex. These blobs are responsible for the color processing that corresponds to that column’s portion of the visual field.

Alternating orientation columns are organized into ocular dominance columns meaning that these larger groupings of columns correspond to one eye as opposed to the other. Put these all together in larger groupings and you have hypercolumns that designate areas that are responsible for entire binocular sections of the visual field.

Axons of some pyramidal cells stretch horizontally within each hypercolumn providing interconnection between orientation columns. These horizontal connections are thought to contribute to the contextual processing or recognition of objects in our field of vision.

**Refractive Errors**

As can be seen from the foregoing review of human vision, there are many places in the ocular system where problems can arise and cause problems. The most common problem affecting the quality of visual input to the retina is refractive error. It is estimated that half of the American population suffers from vision problems\textsuperscript{25} and far
more than half of those individuals suffer because of refractive errors\textsuperscript{26}. Refractive error is the result of several ocular components (axial eye length, corneal tomography, lens shape, etc.) interacting in ways that do not focus the optical image on the fovea of the eye. The vast majority of refractive error is manifest through lower-order aberrations such as myopia, hyperopia, and astigmatism. Some form of refractive error affects over half the European population\textsuperscript{27}, and the numbers are likely the same for the US population\textsuperscript{28}. Higher-order aberrations include irregular astigmatism, which is often caused by keratoconus or corneal treatments in irregular eyes. Presbyopia is another condition relative to OptoQuest’s technology and is a condition associated with age.

Refractive Errors are diagnosed using a combination of visual acuity tests. However, for treatment purposes ophthalmologists use imaging modalities such as Schiempflug cameras and optical coherence tomography to help discover the irregularities at a more finite level through corneal tomography, topography, pachymetry, etc. Commonly used devices include the Pentacam, Galilei, Orbscan, Ocular Response Analyzer, RTVue and others.

**Myopia**

Myopia can also be called nearsightedness, which means that objects close to the observer appear better focused than distance objects. Myopia is the result of light focusing at a point that is in front of the retina as opposed to right on the retina.

The magnitude of refractive error is measured in diopters (D), which is a unit of measure used for indicating the vergence or focusing power of a curved lens. The
measurement of a patient’s myopia is determined as the amount of refractive change necessary to focus the light onto the retina where it should be. Positive diopter values indicate a move away from the cornea in the direction of the retina and negative diopter values indicate the opposite. A common clinical threshold for establishing the presence of myopia is refractive error greater than -0.25 or -0.5 diopters\textsuperscript{29}. Myopia is best measured in the absence of lens accommodation.

\textit{Incidence & Prevalence}

Prevalence rates for myopia vary widely based on many variables. In highly agricultural and warmer climate countries, rates as low as 0.8\% have been reported\textsuperscript{30}. In Asian populations sometimes rates can be seen as high as 75\%\textsuperscript{31}. In the US, it was once reported to be roughly 25\% of individuals from age 12-54\textsuperscript{32}; however, more recent estimates claim that it is now almost double that\textsuperscript{33}. In fact, other comparative studies have found that myopia prevalence is increasing throughout the world\textsuperscript{34,\ 35}. Many confounding variables exist in these reports due to inconsistency in measuring methods and the diverse array of populations measured\textsuperscript{29}. Most myopia will occur before children enter adulthood with most being diagnosed between the ages of 6 and 14 years\textsuperscript{29}.

\textit{Prognosis}

Trends show that myopia stops increasing in females sooner than males at 14 to 15 years of age and 15 to 16 years of age respectively. Also, the earlier the age at which a diagnosis happens tends to be associated with higher rates of progression.
Risk Factors

Axial eye length, or distance from the cornea to the retina, is a primary cause of myopia\textsuperscript{29}. If the axial eye length increases as a child grows and the refractive power of the cornea and lens does not grow in proportion, then myopia is the result. Although decent amounts of animal model studies have been conducted to test this hypothesis\textsuperscript{36,37} we still lack conclusive proof of what induces the overgrowth of eye length relative to refractive power of the cornea and lens.

Environmental and genetic risk factors play a part in myopia. The longstanding belief that “close-up work,” (reading books, writing, etc.) may play a part in the development of myopia is held up in some twin studies\textsuperscript{38}. Part of the theory posits that the consistent accommodation, eye muscle action to change the shape and therefore refraction power of the lens, required by reading, computer work, etc. can induce the eye to actually grow longer than it would otherwise. The more accommodation your eyes perform early in life, the more inducement for axial eye length growth there is. However, enough conflicting evidence has been reported that no conclusive determination has been made for close-up work causing myopia. Other plausible and tested ideas include premature births and low birth weight although this clearly does not account for all cases of myopia\textsuperscript{39,40,41}.

Family history of myopia is a strong predictor of myopia\textsuperscript{42,43}. Inheritance through genetics seems to play a role particularly with higher myopes, but genetics is not able to account for all of the manifestations of myopia.
Treatment & Prevention

Although several methods for the prevention of myopia progression have been tested, scientific evidence for the efficacy of any of them is either mixed or not well established. Among the methods are bifocal glasses, contact lenses (of various types), atropine drops, and beta-blocking agents for their intraocular pressure lowering effects. An interesting, though fairly orphan suggestion includes the alternative of increasing children’s exposure to sunlight throughout childhood, but it is unclear whether sunlight exposure just correlates with a reduction on “close work”.

Apart from improving the prognosis of disease, treatment types abound. Common treatments include spectacles (both bifocals and non-bifocals), LASIK, PRK, and contact lenses in all their varieties.

Hyperopia

Hyperopia is the inverse of myopia. It can also be called farsightedness, which means that objects far away from the observer are better focused than closer objects. Hyperopia is the result of light focusing at a point that is beyond the retina as opposed to right on the retina.

The definition and measurement of hyperopia is almost the inverse of myopia as well. The cutoff point is typically non-accommodative spherical equivalent refraction of +0.50 D. Anything above +2.0 D is considered to be moderate hyperopia. Severe hyperopia is defined differently for most studies.
Incidence & Prevalence

For adults, prevalence was reported as 25.2% in European adults\textsuperscript{27}. In the US, 10% is the reported prevalence\textsuperscript{46}. In children, prevalence rates of moderate hyperopia (spherical equivalent of the prescription $> 2.0$ D) have been reported at a wide range of geographies between 0.6% and 26%\textsuperscript{45}; however, consistency among studies limits the accuracy of these findings. In most populations, the prevalence rates do not increase above single digits for children.

Incidence rates for hyperopia are less frequently reported but the rates generally follow the age related factors described in the following section.

Prognosis

Most full-term infants have a mild amount of hyperopia\textsuperscript{47}. Premature infants tend to have less hyperopia than healthy infants\textsuperscript{48}. In most cases, infants seem to “grow out” of this by age 5\textsuperscript{49}. The trends show that as children get older myopia tends to be more prevalent than hyperopia with older children being less likely to exhibit hyperopia than young children\textsuperscript{50, 51}. In the older ages, hyperopia increases again in prevalence due to associations with presbyopia and ciliary muscle failure and crystalline lens changes. If not corrected early in life, hyperopia can lead to the development of strabismus (crossed eyes)\textsuperscript{46} and amblyopia.

Patient Variables & Clinical Components

The main causative factor of hyperopia is generally considered to be a shorter axial eye length. Gender does not seem to be a factor in the prevalence of hyperopia.
Family history, as for myopia, is a main risk factor\textsuperscript{52}. The ethnicities of Native Americans, African Americans, and Pacific Islanders are the ones at greatest risk for developing hyperopia\textsuperscript{53}.

\textit{Treatment & Prevention}

The most common form of hyperopia treatment includes glasses, contacts and refractive surgery depending on the age of the patient and other symptoms. Mild hyperopia typically does not undergo treatment early in life, but presents problems to patients as they develop presbyopia and the crystalline lens no longer readily accommodates to focus on near objects. Corneal Crosslinking is a newer treatment method that has been shown to reduce hyperopic regression after LASIK for hyperopia\textsuperscript{54}, and crosslinking has implications for the treatment of primary hyperopia as well as myopia\textsuperscript{55}.

\textbf{Presbyopia}

Presbyopia is the farsightedness that occurs because of losing accommodative power with age. There are several different theories for why this happens, some claim mechanical changes in the lens are the cause, and others claim that some form of extra-lenticular change makes accommodation difficult \textsuperscript{56}. Helmholtz’s theory of accommodation is the most broadly accepted, but modern imaging techniques continue to enhance understanding of accommodate mechanisms and age-related changes.

Visual acuity tests can often catch presbyopia which begins to manifest itself through blurry near vision. The accommodative power differs dramatically with age.
Children and teenagers up to the age of 20 typically can accommodate around 11.5 D. However, by age 50 this power drops dramatically to an average of 2.0 diopters\textsuperscript{57} (See Figure 1 \textsuperscript{58}).

![Figure 1 - Accommodative Power Change as a Function of Age.](image)

Upper (dark blue) and lower (light blue) limits for normal cases are provided at each age.

**Incidence & Prevalence**

Presbyopia affects everyone if they get old enough. Understandably, incidence rates rise with age. Some reports have claimed that 83\% of adults above the age of 45 in the US have presbyopia\textsuperscript{33}. 

---

\textsuperscript{57} Source: [Reference 57]

\textsuperscript{58} Source: [Reference 58]

\textsuperscript{33} Source: [Reference 33]
**Prognosis**

Once an individual develops presbyopia, the condition progresses until all accommodative ability is lost, typically by the 7\textsuperscript{th} decade. No current treatments can stop its progression.

**Patient Variables & Clinical Components**

The most obvious risk factor is age. Other factors that can reduce the age of onset include hyperopia, the close-work demands of the person’s occupation, sex (females tend to show an earlier onset), other ocular diseases, poor nutrition, and proximity to the equator – thought to be due to higher average temperatures and more UV light exposure \textsuperscript{59}.

**Treatment & Prevention**

No prevention for presbyopia exists\textsuperscript{59}. The most common treatment for presbyopia is reading glasses, bifocals or alternative forms of contact lenses. Refractive surgeries cannot directly reverse the effects of presbyopia by restoring accommodation. If patients wish to remain free of glasses and contacts they may opt for refractive surgeries that target monovision\textsuperscript{60}. Monovision is the correction of one eye for long distance and the correction of the other eye for near vision. A trial of monovision in a trial glasses frame or contact lenses is often recommended before opting for a monovision outcome to assess the subjective response both in terms of gains in spectacle independence at distance and near and tolerance for interocular blur.
Other experimental techniques are currently in development that involve altering the anterior sclera to increase the distance from the ciliary body to the lens and thus adding tension to the system\textsuperscript{61}. OptoQuest’s technology has the potential to model the effects of these experimental types of surgeries.

**Astigmatism**

Astigmatism occurs when the light refracting through the eye has multiple foci anterior and/or posterior to the retina causing blurring vision. Although myopia and hyperopia are primarily caused by an optical mismatch between corneal curvature and distance to the retina (eye length), astigmatism can be superimposed on these refractive errors and results from rotational asymmetry in the shape of the cornea. It is manifest in 13% of the population but is often co-morbid with other types of refractive error\textsuperscript{62}. Astigmatism most often manifests itself in the cornea through a football shape. This can most simply be described by defining two different meridians, sometimes perpendicular to each other, that represent the steepest and the flattest meridians.

This asymmetry gives rise to at least two, possibly more, focal points near the retina. The combination of where the focal points fall and the degree of difference between the two meridians determines the type of astigmatism that one has. For example:

- **Myopic astigmatism** is defined as astigmatism where all of the focal points lie in front of the retina.
• Hyperopic astigmatism is defined as astigmatism where all of the focal points lie behind the retina.

• Mixed astigmatism is defined as astigmatism where one or more focal points lie in front and one or more focal points lie behind the retina.

• Regular astigmatism is defined as astigmatism where the 2 primary corneal meridians exist perpendicular to or at 90 degrees from each other.

• Irregular astigmatism is defined as astigmatism where the two primary corneal meridians exist at some angle other than 90 degrees from each other.

• With-the-rule (WTR) astigmatism is a regular type of astigmatism where the vertical meridian is the steepest.

• Against-the-rule (ATR) astigmatism is a regular type of astigmatism where the horizontal meridian is the steepest.

Like other forms of refractive error, astigmatism is measured using diopters. However, it is important to note that there are additional considerations in identifying the amount of refractive change necessary to correct the error. Toric lenses are used to correct for astigmatism and toric lenses have two components and an axis associated with its measurement. The spherical and cylindrical components refer to the correction along the two most different axes. If the spherical component is a dioptric value associated with the most convergent meridian then the cylindrical component is a certain dioptric value more divergent than the spherical value. This gives rise to
notations such as -4.00 -0.75 x 90 indicating a spherical correction of 4.00 D in the horizontal meridian and -4.75 D in the vertical meridian. Anything above 1 diopter is considered to be a “high” amount of astigmatism. Astigmatism magnitudes above 4 diopters are more often observed in pathological conditions such as keratoconus, corneal scar, after corneal transplant, or with post-refractive surgery corneal ectasia.

**Incidence & Prevalence**

One study found that early aged school children do not show a high prevalence of astigmatism. Only 4.8% of children showed astigmatism greater than 1 diopter. In adults, 18 years of age to 40 years of age, astigmatism is actually fairly common, except it is either not measurable or does not noticeably affect an individual’s vision. For example, one study discovered that 63% of their subjects exhibited astigmatism higher than 0.25 D, but the vast majority of them showed less than 1 D. Astigmatism seems to noticeably affect around 5% of adults. Ethnically, astigmatism is more prevalent among Native Americans, Asians, and Hispanics, as well as other smaller nationalities.

Cataract surgery incisions generate a mild astigmatic change in the cornea that can either enhance or interfere with the refractive target of the surgery. More than 3 million cataract surgeries occur in the US alone, making it the most commonly performed surgery. These numbers are due to increase as more and more baby boomers come of age. Since roughly 75% or more of adults older than 65 get cataracts and there is an increasing interest in optimizing refractive outcomes, there will be a high
demand for refractive optimization of cataract surgery outcomes as the population ages.

Prognosis

The common manifestations of astigmatism change through a person’s lifetime. At early ages, it is common to have steep corneas showing against-the-rule astigmatism. By age 4, the astigmatism begins to decrease in magnitude. Corneas get flatter and with-the-rule astigmatism begins to be more prevalent. From the ages of 18 to 40 astigmatism tends to stabilize without any significant changes but will begin to worsen after the ages of 40. After that age, against-the-rule astigmatism becomes more common again. These changes are generally of low magnitude and are not a major confounder of refractive surgery outcomes.

Patient Variables & Clinical Components

Although the exact causes of astigmatism remain unidentified, putative causes include genetics, extraocular mechanisms such as eyelid movement on the cornea, and eye rubbing.

Treatment & Prevention

There is no known prevention for astigmatism or its progression. However, normal refractive treatments are all used to mitigate its effects. One additional surgical procedure – outside of LASIK, PRK and ReLEx – includes AK which involves making one or two arc shaped incisions in the cornea that typically penetrate to a depth of 75-80% of the corneal tissue. Astigmatic keratotomy is often performed with cataract surgery to
address pre-existing astigmatism\textsuperscript{71} and reduce the dependence of the patient on distance spectacle correction. Such combination approaches are gaining in popularity now that femtosecond laser-assisted cataract surgery allows precise programming of the AK treatments as part of the treatment. Another incentive is the importance of minimizing postoperative astigmatism when premium multifocal intraocular lenses are placed during cataract surgery since even low levels of residual astigmatism can interfere greatly with ability to resolve both distance and near objects. Patients who pay premium upcharges for such specialty lenses increasingly require post-cataract surgery refractive surgery to treat residual astigmatism, and the cost is often assumed by the surgery center.

**Keratoconus**

Keratoconus is a rare progressive disorder that can severely reduce vision and, in some cases, require corneal transplantation for visual rehabilitation. It is characterized by a progressive thinning and protrusion or steeping of the cornea. Keratoconus is the most common form of corneal ectasia. Ectasia can arise from or be exacerbated by refractive surgery and, if the physician is found negligent, can be as disastrous to a physician’s practice as it is to a patient’s vision.

The diagnosis of keratoconus is usually determined by looking for particular clinical signs. Some of these early signs include: high and progressive astigmatism, corneal thinning especially on the inferior part of the cornea, irregularities in shape and topography. Other later signs might include scarring and breaks in the Bowman’s layer.
of the cornea as well as other more severe signs. In all cases, vision correction with spectacles is typically inadequate due to high or irregular forms of astigmatism.

**Incidence & Prevalence**

The reports regarding the prevalence of keratoconus vary widely according to geography or ethnicity. Some of the most common reports put it around 1 in 2000 people (0.05%) in the general population. Incidence has been reported as between 5 and 23 per 10,000 people (0.05-0.23%) \(^{72, 73}\). In Asian populations, the prevalence has been reported up to 7.5 times what it is amongst the Caucasian population \(^{74}\). It is generally agreed upon that these estimates are low because they are based on epidemiological studies that were performed before more sensitive topographic measurement systems were widely available to aid diagnosis.

The occurrence of corneal ectasia following refractive surgeries is difficult to determine since most physicians may not be comfortable sharing the rates they see in their practices, but incidence rates of 0.04\(^{75}\) to 0.6\(^{76}\) were reported more than a decade ago. This means that 1/2500 to 1/166 eyes that underwent LASIK developed ectasia following treatment; however, screening criteria are generally more refined than they were when these cohorts were reported. Surgeons are less likely to treat the very high magnitudes of myopia that were treated in the first years after LASIK was introduced, and incidence is suspected to be somewhat lower now. There are still wide discrepancies in screening standards, however, and the problem of detecting patients
who may be prone to postoperative instability or ectasia remains one of the most heavily represented topics at professional society meetings from year to year.

Prognosis

Most commonly, keratoconus manifests itself during the teenage years\textsuperscript{72} and can progress over time, most commonly ending its progression during a person’s thirties\textsuperscript{73}. The vast majority of cases do not require corneal transplants to correct the disease\textsuperscript{77}. It is possible that with better technologies in corneal imaging entering the market, identification of keratoconus or other forms of ectasia could occur earlier and more frequently.

Patient Variables & Clinical Myopic Components

Genetics does seem to play a major role in prediction of keratoconus occurrence\textsuperscript{78}. Linkage studies have produced several loci as candidates but conflicting studies have made it difficult to ascribe astigmatism to any one or few loci\textsuperscript{79}. Some people tend to believe that eye rubbing, especially in early stages of life, might exacerbate or cause the disorder\textsuperscript{80}. As with many other refractive errors, keratoconus is more common among individuals with Down Syndrome\textsuperscript{81}.

Risk factors for development of post-LASIK ectasia include young age, asymmetrical topography patterns, low residual stromal bed thickness after surgery, and low preoperative corneal thickness among others\textsuperscript{82,83}. OptoQuest’s approach to the problem is to simultaneously consider all these geometric derivatives and surgical parameters through a whole-structure computational analysis that can predict stresses,
strains and optical outcomes on a simulated operative eye. There is early evidence that this approach should provide a more direct and personalized method for estimating ectasia risk.

_Treatment & Prevention_

No medical prevention is available for keratoconus, but various treatments help reduce the visual effects of disease progression. Spectacles are typically not effective for very long as keratoconus progresses. Contact lenses, especially gas permeable types, significantly delay the need for surgery in 99% of cases, but contact lens wear can become difficult or impossible with highly irregular corneas.

The most common surgery performed for the correction of keratoconus is penetrating keratoplasty (PKP); however, keratoconus seems to rarely develop to the point were it is needed (less than 20% of cases). PKP is performed by removing the entire thickness of the cornea and replacing it with a normal donor cornea, and many patients experience high levels of refractive error after transplantation that require additional procedures or contact lenses to address. Another treatment for keratoconus is the implantation of intrastromal ring segments. However, it can only be performed on mild to moderate forms of keratoconus and outcomes are highly variable. Yet another treatment option is corneal crosslinking, which has been shown to reduce cone progression and improve best corrected visual acuity. Selective spatial corneal crosslinking is being investigated as a method for more precisely manipulating the shape change of keratoconic and normal corneas to achieve reductions in refractive errors.
(OptoQuest has worked closely with Avedro, Inc. in simulating procedures to support development of this approach). Crosslinking can be combined with other procedures such as PRK and ICRS to facilitate both optical correction and stabilization. Predictive surgical guidance tools are currently lacking altogether for these applications.

While post-refractive surgery ectasia can be prevented by avoiding refractive surgery in at-risk patients, it is the identification and quantification of this risk that presents a significant, persistent unmet need in the field. For that reason, many groups have attempted to identify screening criteria and technologies that better identify patients who may be at risk for developing ectasia following surgery.

Market Need

All of this data together indicates that there is a large need for vision correction services and for improving the technologies and procedures currently used for detection, prevention, and treatment of refractive errors. OptoQuest has technologies tailored to enhance technologies and procedures in each of those functions.

Technology

SpecifEye is software for use by physicians, though they may elect for their technicians to deal with data entry. It is intended to aid the physician in predicting the outcome of refractive procedures. SpecifEye provides a physician feedback about the expected outcomes of their treatment plan before the treatment takes place allowing them to optimize their treatment plan accordingly. In effect, this should reduce the
margin of error physicians see in the various treatment types and provide patients more consistent visual outcomes.

The workflow of the software is relatively straight-forward and flows easily with most clinics’ diagnostic workflows. In most cases, after a user logs into the software they will open a new job submission form. They will begin by importing the target patient’s tomography file (e.g., Pentacam’s U12 file, etc.) from their clinic’s database or electronic medical record. They will then continue to fill out relevant patient data in that form. Then a separate form will be filled out where the user can input the parameters of the surgery they wish to perform on the eye/s of that patient. Once all of the surgical parameters are entered the user can submit the simulation job.

This job, with all of its patient and surgical plan information, is securely uploaded to SpecifEye’s central web-based simulation engine where it enters a queue and is processed in the order in which it was received. The software will create a virtual 3-D mesh that represents the patient’s eye and then the simulation of the planned surgery will commence. Any cuts, ablations, chemical changes or implants are simulated and the structural effects of changes are calculated using finite element analysis. What results is a new mesh that represents the eye of the patient after the surgery is performed and healing has occurred.

This new mesh is visualized and quantified through numerous clinical maps and variables and collated into a report that is sent back to the client and/or email box of the user who submitted the job. This information is then used by the physician to either
proceed with the surgery as planned (with greater confidence in the likely outcome) or alter some of the planned parameters in order to optimize the outcomes. See Figure 2 for a graphical representation of this process.

Abbreviations: (LASIK) Laser Assisted In-situ Keratomileusis; (PRK) photorefractive Keratotomy; (AK) Astigmatic Keratotomy; (CXL) Corneal Crosslinking; (ReLEx) Refractive Lenticular Extraction; (ICRS) Intrastromal Corneal Ring Segments.

**Figure 2 – Engineering Diagram Depicting SpecifEye’s Workflow.**

**Regulatory Pathway**

One of the largest hurdles for medical devices in the United States is getting marketing clearance from the Food and Drug Administration (FDA). The major risk is not the likelihood of failure (like it is for drugs), but because it takes a non-trivial amount of
time and expertise. For this reason, it is imperative that new medical device developers identify the correct regulatory pathway through the FDA from a very early stage.

The FDA provides a Pre-Submission Program (pre-sub) that allows a device manufacturer to ask questions and receive specific feedback from the FDA on various aspects of a device’s marketing approval pathway and application. The program can and should be used to elucidate the specific pathway for which a medical device is best suited. OptoQuest is embarking on the pre-submission process for SpecifEye.

There are five marketing application programs that the FDA has provided for a device to receive FDA’s approval for its introduction into the US market: simple registration, 510(k), de novo, Humanitarian Device Exemption (HDE), and premarket approval (PMA). A device’s program eligibility is determined by the risk it poses to patients and the controls necessary to prove the device’s safety and efficacy. There are three classes of risk a device can fall into. Class I devices pose the lowest risk to patient health and require only general controls (as defined by the FDA) to establish its safety and efficacy. Class II devices are more risky and require special controls to ensure their safety and efficacy. Class III devices pose the greatest risk to patient health and require general and special controls as well as considerable amounts of performance data collected through a rigorous clinical trial.

Class I medical devices either do not require an application submission at all or only a simple registration with the FDA before it can be marketed. Class II devices, depending on the level of risk and the existence of a similar (predicate) device, can go
through the registration, 510(k), or de novo programs. Class III devices must go through the PMA program unless the disease it treats or diagnoses is a very rare disease in which case it would go through the HDE program.

Risk Classification

SpecifEye should be reclassified as a class II medical device because general controls and special controls are sufficient to provide reasonable assurance of SpecifEye’s safety and efficacy. Table 2 explains the risks and mitigations that should be proposed to the FDA for acceptance as justification for the Class II classification.

<table>
<thead>
<tr>
<th>Identified Risk</th>
<th>Recommended Mitigation Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improperly predicting target cornea as low probability for negative response to treatment leading to high-risk treatment.</td>
<td>- Software Verification, Validation, and Hazard Analysis</td>
</tr>
<tr>
<td></td>
<td>- Non-clinical Performance Testing</td>
</tr>
<tr>
<td></td>
<td>- Labeling</td>
</tr>
<tr>
<td>Improperly predicting target cornea as high probability for negative response to treatment leading to incorrect patient management.</td>
<td></td>
</tr>
</tbody>
</table>

Because of SpecifEye’s use as a prediction aid, we believe it is necessary to validate its results with clinical data. Labeling will help ensure that the device is used appropriately according to its intended use. Otherwise, we do not believe the risks of using SpecifEye require further mitigations.

The only real risks to patients are if SpecifEye predicts something that would not reflect reality if the procedure was performed in the specified way and the physician
decides to perform their plan in accordance with SpecifEye’s prediction. Even in these cases, the worst thing that could happen is the patient would receive a sub-optimal treatment (e.g., achieving 20/25 uncorrected visual acuity instead of 20/20, etc.). In these cases, the patient can opt for a retreatment or use vision aids (spectacles or contacts). A physician should easily detect any grossly incorrect predictions made by SpecifEye. Due to current clinical workflows and best practices, sub-optimal treatments are more likely to come from human error (not attributable to SpecifEye) or treatment device error than they are to come from SpecifEye directly. For example, a technician is more likely to input the wrong treatment parameters into a laser device than a poor prediction is to pass a surgeon’s review, convince a physician to modify the already planned treatment, get communicated to a technician, and pass the laser device’s data input controls.

A physician may choose to use SpecifEye’s prediction to help screen patients. In this case, two worst-case scenarios could result: a patient does not get treated that should get treated, and vice versa. SpecifEye’s indications for use do not include any life-threatening indications; therefore, any delay in treatment caused by SpecifEye’s predictions would not increase risk to a patient since they already function at adequate levels with spectacles or contacts. On the other hand, the worst thing that could happen is that a patient that shouldn’t be treated gets treated. If this happens, the worst thing that could result (albeit extremely rare) is that the patient develops ectasia from the surgery and would then require a corneal transplant in order to restore function to the
cornea. This particular risk also provides the rationale for identifying SpecifEye’s Software Level of Concern as Major.

SpecifEye stratifies patients according to the risk their corneas display in undergoing refractive treatments. There is no hard and fast “Yes” or “No” coming from SpecifEye. The physician will have to make a judgment call using SpecifEye’s standard clinical eye maps and probabilistic variables as their justification. There are many factors that a physician must take into account when determining a patient’s candidacy for treatment. SpecifEye does not make a comprehensive analysis or decision. It provides useful additional validation of the physician’s mental predictions. Therefore, the previously identified “worst case scenario” would never be fully attributable to the use of SpecifEye.

Other potential risks have not be recorded here because they were deemed either completely unlikely to occur, or the severity of the risk was low enough to consider the risk as acceptable.

Program Selection

Given this risk classification, SpecifEye is eligible for the 510(k) or de novo programs. The correct pathway is selected according to the existence of a predicate device. A predicate device is used for comparison purposes. In a 510(k) application, the manufacturer must prove that the subject device is equally as safe and effective or more safe and effective compared to its predicate. The subject device is allowed to differ in its features and technological characteristics only so long as the new features or
characteristics do not raise new questions of safety and efficacy that were not evaluated as part of the marketing application of the predicate device. From a business perspective, this allows a manufacturer to differentiate its product while lowering the regulatory burden from the FDA. In some cases, from a business perspective the subject device may represent a completely new class of product, but from an FDA or technical standpoint the two devices are argued to be substantially equivalent. However, if the new features and characteristics of the subject device raise new questions of safety or efficacy, the manufacturer must apply for marketing approval through the de novo program. See Appendix 1 for a more complete representation of the 510(k) analytical process.

**Predicate Identification**

There is software that can be arguably considered similar to SpecifEye; however, the new technological features of SpecifEye make it difficult to justify their use as a predicate device. These similar devices include: Surgivision’s DataLink, Zubisoft’s IBRA, and Oculus’ Belin/Ambrosio Enhanced Ectasia Display.

Both DataLink and IBRA are similar refractive surgery outcomes analysis software. Both collect data on the surgical parameters and clinical outcomes of an ophthalmologist’s previous surgeries. This data is then statistically analyzed in such a way to suggest surgeon-specific adjustments in the programmed treatment that will optimize the target surgery. This type of software is often referred to by surgeons as nomogram software and is standard, if not critical, in most refractive surgery clinics in
the US. The resulting recommendations take the form of a treatment offset that the surgeon can specify in the laser interface, for example reducing the myopic correction from -6.25 diopters to -5.75 to avoid a historical trend toward overcorrection. These trends are developed from regression analyses of past results for patients undergoing similar levels of treatment in the past with similar laser systems, and recommended adjustments come either from aggregated outcomes data from multiple users or from the users own historical performance data if adequate personal history exists.

Although there are differences between the two technologies (Nomograms, standard statistics; SpecifEye, structural simulation and historical statistical data) the problem with using nomogram software as a predicate is the fact that they are not listed in FDA’s archives. Additionally, there is probably enough discrepancy between the technologies that they would not be ruled as substantially equivalent—the ruling needed to clear a device for marketing through the premarket submission or 510(k) program.

A similar issue arises in attempting to use the Belin/Ambrosio Enhanced Ectasia Display (BAD) associated with Oculus’ Pentacam imaging system. The BAD is similar to OptoQuest’s ectasia risk analysis feature in that it computes a patient’s risk for developing surgery induced ectasia based on a variety of factors including a normative database of comparative eyes. It does not suggest new surgical approaches as SpecifEye’s main feature do, but provides a risk based score for each patient eye. The Pentacam has been cleared through the FDA and is classified as a Class II device;
however, the BAD does not have its own clearance. It is unclear whether or not it is considered a feature of the Pentacam and therefore falls under the Pentacam’s clearance. In either case, the conclusion is still the same as with the nomograms—it cannot be used as a predicate.

In addition to the products and devices mentioned above, a variety of search terms were used to identify devices, regulations, or product codes that would match the subject device. Table 3 shows the device classifications that come closest to describing SpecifEye.

Terms Used

- Calculator
- Decision
- Decision Support
- Predictive
- Software
- Accessory
- Image
- Computational
- Model
- Planning
Table 3 - Table of Similar Device Classifications

<table>
<thead>
<tr>
<th>Prod. Code</th>
<th>Device Definition</th>
<th>Definition</th>
<th>Reg. Number</th>
<th>Device Class</th>
<th>Submission Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQB</td>
<td>Medical Computers And Software For Ophthalmic Use</td>
<td>-</td>
<td>None</td>
<td>3</td>
<td>Contact ODE</td>
</tr>
<tr>
<td>LNX</td>
<td>Medical Computers And Software</td>
<td>-</td>
<td>None</td>
<td>Unclassified</td>
<td>510(k)</td>
</tr>
<tr>
<td>NFF</td>
<td>Device, Storage, Images, Ophthalmic</td>
<td>A medical image storage device is a device that provides electronic storage and retrieval functions for medical images. Examples include devices employing magnetic and optical discs, magnetic tape, and digital memory.</td>
<td>892.2010</td>
<td>1</td>
<td>510(k) Exempt</td>
</tr>
<tr>
<td>NFG</td>
<td>Device, Communications, Images, Ophthalmic</td>
<td>A medical image communications device provides electronic transfer of medical image data between medical devices. It may include a physical communications medium, modems, interfaces, and a communications protocol.</td>
<td>892.2020</td>
<td>1</td>
<td>510(k) Exempt</td>
</tr>
<tr>
<td>NFJ</td>
<td>System, Image Management, Ophthalmic</td>
<td>A picture archiving and communications system is a device that provides one or more capabilities relating to the acceptance, transfer, display, storage, and digital processing of medical images. Its hardware components may include workstations, digitizers, communications devices, computers, video monitors, magnetic, optical disk, or other digital data storage devices, and hardcopy devices. The software components may provide functions for performing operations related to image manipulation, enhancement, compression or quantification.</td>
<td>892.2050</td>
<td>2</td>
<td>510(k)</td>
</tr>
<tr>
<td>OUG</td>
<td>Medical Device Data System</td>
<td>(1) A medical device data system is a device that is intended to provide one or more of the following uses, without controlling or altering the functions or parameters of any connected medical devices: (i) the electronic transfer of medical device data; (ii) the electronic storage of medical device data; (iii) the electronic conversion of medical device data from one format to another format in accordance with a preset specification; or (iv) the electronic display of medical device data. (2) A medical device data system may include software, electronic or electrical hardware such as a physical communications medium (including wireless hardware), modems, interfaces, and a communications protocol. This identification does not include devices intended to be used in connection with active patient monitoring.</td>
<td>880.6310</td>
<td>1</td>
<td>510(k) Exempt</td>
</tr>
<tr>
<td>MXK</td>
<td>AC-powered slitlamp biomicroscope.</td>
<td>An AC-powered slitlamp biomicroscope is an AC-powered device that is a microscope intended for use in eye examination that projects into a patient’s eye through a control diaphragm a thin, intense beam of light.</td>
<td>886.1850</td>
<td>2</td>
<td>510(k)</td>
</tr>
</tbody>
</table>
Rationale for De Novo

It is recommended that OptoQuest submit a de novo application to receive approval to market SpecifEye. The subject device does not fit neatly within any one of the regulations or product codes in Table 1 because different components of SpecifEye fall within more than one of them. Additionally, the product codes that come closest to describing SpecifEye do not contain a cleared device that can be claimed as a predicate.

SpecifEye contains an image storage system (NFF) and an image communication component (NFG). Additionally, SpecifEye takes those images, creates a 3-D finite element mesh and then processes the mesh by passing it through an algorithm that simulates the surgery and generates surgical outcome data. This processing component can arguably be used to classify SpecifEye as an “Ophthalmic Image Management System” (NFJ), but two contradictions are seen: 1) The regulation (892.2050) fails to capture the predictive/analytical purpose of SpecifEye even though it claims the “software components may provide functions for performing operations related to image manipulation [or]... quantification.” In other words, SpecifEye’s primary purpose is not to manage images. SpecifEye would best be described as ophthalmic treatment decision support software and an accessory to corneal imagers. 2) There are no cleared medical devices with the NFJ product code that have either the same intended use or indications for use that SpecifEye has.

Further complicating the issue, SpecifEye can logically be seen as an accessory to either of two devices: the imagers and topographers (e.g., Pentacam) or the laser
systems that are used to perform the actual treatments that SpecifEye simulates. From informal feedback given to OptoQuest by FDA personnel and regulatory consultants, we know the tendency is to associate SpecifEye with the treatment devices for which they simulate procedures even though SpecifEye is not designed to have direct contact with those devices. The problem with this is that accessories are automatically classified equivalently to the parent device – in SpecifEye’s case, that could elevate its class to III for some indications. If SpecifEye were classified as a Class III device rather than as an accessory or as a clinical decision support tool, this would require a PMA, the most rigorous and expensive FDA marketing application.

It is also important to note that feedback from consultants and FDA personnel suggested that SpecifEye’s indications for use (LASIK, PRK, CXL, AK, ICRS, ReLEx) should not be submitted in a single application, but rather as separate or strategically bundled pre-subs. They also indicated that applications should not be submitted for indications that do not yet have FDA approval in the US (namely CXL). Therefore, the most advisable pathway would be to submit a marketing application for LASIK, PRK indications first with ectasia risk analysis incorporated since it overlaps significantly with LASIK and PRK, followed by AK, then ICRS. If or when CXL and ReLEx are approved in the US, then applications for those indications can be submitted.

**FDA Interaction**

Prior to the *de novo* application it is advised to receive feedback from the FDA through the pre-sub program regarding SpecifEye’s categorization as an accessory to
topographers and corneal imaging devices as opposed to laser systems because they have a lower classification. SpecifEye’s technology is far more similar to the software associated with the BAD and other ectasia probability algorithms that use corneal structure to assign a relative risk than the laser systems themselves. SpecifEye is also much more similar to un-regulated surgical nomogram tools than to the treatment systems themselves, and still uses patient data and abstracted structural data from the eye to yield a predicted refractive outcome and assist the surgeon in adjusting the plan accordingly if they wish. The risk profiles between imaging devices and SpecifEye are also far more similar. In addition, the fact that there is no direct/automatic input into the laser system represents an entirely different level of risk than automated modification of treatment plans by SpecifEye. Any additional justifications for this logic should be included in the pre-sub.

Having determined the classification and mitigations for the proposed risks is only part of the de novo process that should be elucidated in the feedback during the pre-sub meeting. Because, by definition, there are no standards for testing and validating a device going through a de novo, another important discussion item for the pre-sub is what performance testing is required to provide reasonable assurance of the device’s safety and efficacy.

There is a section of the pre-sub dedicated to proposed validation studies. In this section, OptoQuest should provide its best, reasonably tough testing criteria through which it can assess SpecifEye’s safety and efficacy. The current methods for testing a
predictive algorithm’s accuracy should be sufficient to prove both. In other words, retrospective comparisons of the algorithm’s prediction versus the actual results of a surgery should be sufficient proof that SpecifEye is safe to use. Recruiting new patients for a study would not produce different results than a study that blinded OptoQuest to retrospective results.

The pre-sub is an opportunity to ask additional questions regarding the development and/or performance testing process regarding a device. It is advised that OptoQuest consider any unclear points of SpecifEye’s development and ask appropriate questions. This practice will avoid any unexpected feedback from the FDA after the submission of a de novo application.

The structure for pre-sub questions to the FDA should be guided. Questions that invite open ended responses typically allow the FDA to set expectations that may not be in the manufacturers best interest. Questions such as, “Does the FDA agree that the above stated risks correctly capture the risk profile of the subject device?” is better than a question that says, “What does the FDA think the risks associated with the subject device include?” The first question, allows the manufacturer to make an argument and defend it, whereas, the second question invites the FDA to conjure up risks that may surprise the manufacturer and cause it extra work during the submission process.

Once the FDA has responded to the content of a pre-sub, the manufacturer can continue to develop the device in accordance with the counsel of the FDA. Continued interaction may be required and is even encouraged between the FDA and the
manufacturer during this time. Ideally, the time spent getting FDA opinion during the
pre-sub process should reduce the amount of time the FDA spends reviewing a *de novo*
application. The FDA claims that it is required to respond to a *de novo* application with
120 days of its submittal\(^\text{90}\). In reality, the average time from an application’s submission
to market clearance for a device going through the *de novo* pathway has been almost a
year in recent cases\(^\text{91}\).

It is important to note that marketing cannot take place on SpecifEye until the
FDA has approved the *de novo* submission. Afterward, there is an annual fee to maintain
any marketing clearance. Regardless of SpecifEye’s classification it is necessary to follow
the regulations given in Part 21 CFR 820 regarding the controls on the design and
manufacture of medical devices. Such control systems must be maintained at least for
the duration of the life of the device.

Given each of SpecifEye’s separate indications, it is possible that the FDA will
require a separate *de novo* application for each indication. This can be a costly and time
consuming process. However, the process might be streamlined somewhat by
submitting multiple applications at the same time and having the FDA consider them
altogether. Guidance on this aspect of SpecifEye’s pathway would be a crucial point to
get feedback on during the pre-sub process.

**Conclusion**

OptoQuest has invented and developed a novel medical device or software for the
prediction of refractive surgeries called SpecifEye. Within the context of the entire vision
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system, SpecifEye optimizes the performance of the refractive portion of the human vision system, but provides a nonetheless important component to improving human well-being. SpecifEye works well to guide a physician through the difficult decision making process of diagnosing and treating the various refractive errors that can occur in human vision—a decision making process that, if correctly performed can halt progression of refractive error or suggest approaches to treat it more effectively. Special attention must be given to the regulatory barriers that stand between OptoQuest and the commercial success of SpecifEye.
Appendix 1

FDA 510(k) Program Decision Flowchart.

Identify the new device and the predicate device.

Decision 1: Is the predicate device legally marketed?

Review all labeling and assure that it is consistent with IFU statements.

Decision 2: Do the devices have the same intended use?

Review design, materials, energy source and other features of the devices.

Decision 3: Do the devices have the same technological characteristics?

Evaluate performance data.

Decision 4: Decide 1. Are the methods acceptable?

Decision 5a: Do the different technological characteristics of the devices raise different questions of safety and effectiveness?

Review the proposed scientific methods for evaluating new/different characteristics' effects on safety and effectiveness.

Decision 5b: Do the data demonstrate substantial equivalence?

Determine what questions of safety and effectiveness the different technological characteristics raise.

Refer to Sections IV. E (Technological Characteristics) and IV. F (Requests for Performance Data) and 21 CFR 807.100(h)(2)(ii)(B).

NSE = “Not Substantially Equivalent”
SE = “Substantially Equivalent”
IFU = “Indications For Use”


From conversation with consultant Regulatory & Quality Solutions.