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OFTALMOLOG

Extending what is humanly possible

Exploring the limits and moving beyond

Dear Colleagues,

Tor P. Utheim

This special Christmas edition explores the edge of the human capacity of sight and technology beyond previous comprehension. We begin by congratulating Mehrdad Rafat, Neil Lagali, and their co-authors for their extraordinary scientific achievements originating from Linköping University in Sweden, which culminated in a recent paper in Nature Biotechnology. The authors discuss highlights of their amazing journey in the article "Bioengineered Corneal Tissue." Also in this issue, Atle Østern, Oslo University Hospital, tackles the foundational question – What is the absolute maximal vision? Journey with him as he ventures to the limits of human sight and explores how it compares with other animals.

In "How to Work Smarter, Not Harder," Professor David S. Friedman, Co-Director of the Glaucoma Center of Excellence at the Department of Ophthalmology, Harvard Medical School and his co-author Matthew C. Johnson address another fundamental question. Their work focuses on anterior chamber angle assessment and the use of the latest in artificial intelligence to improve diagnostics and expand the capabilities of eye doctors.

The Editorial Board wishes all our readers a *Merry Christmas* and a *Happy New Year.*

Tor Paaske Utheim
Editor-in-Chief

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A CHRISTMAS GIVEAWAY:
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We will draw 3 winners:
One person who signs up for the newsletter, one who connects on LinkedIn, and one who follows us on Facebook between December 1, 2022, and January 1, 2023, will be randomly selected to receive a gift. The winners will be announced on our social media pages in the new year!

COVER:

This festive, Christmas cover was created by MidJourney, a text-to-image AI program. After being given the command to /imagine "happy Christmas outdoor in the winter, lots of gifts," no human input was given on the image-creation process beyond a handful of "variation" commands and two "upscale" commands. As the topic of the current issue is the exploration of the limits of human capabilities and illuminating what lies beyond, we thought it befit to ask one of the most advanced image-generating programs available to help us find the happy, holiday spirit. And we believe it has.

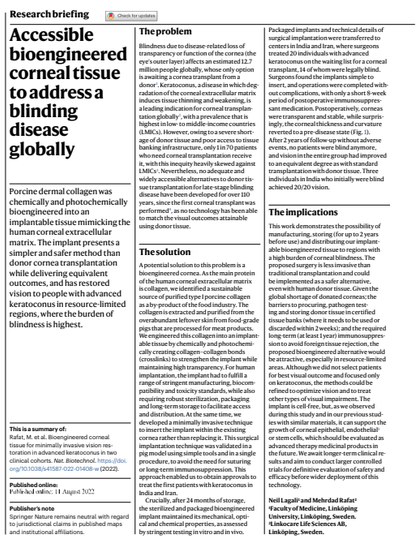
To explore the full catalog of our AI-generated, Christmas-themed art, please check out the special gallery at oftalmolog.com

A Nordic Research Team Addressing Global Challenges

How the work of researchers in Sweden can bring sight to those most in need around the world

The Editorial Board in *Oftalmolog* extends our congratulations to the authors of the article entitled "Bioengineered corneal tissue for minimally invasive vision restoration in advanced keratoconus in two clinical cohorts" published in *Nature Biotechnology* on August 11, 2022. The Editorial Team of *Nature Biotechnology* summarized this amazing achievement as follows: "This study is remarkably expansive, going from laboratory development of a collagen material for use as a synthetic cornea, to thorough safety testing in small and large animals, to clinical-grade manufacturing, to a pilot study in 20 patients with keratoconus in two countries. Encouraging clinical results after 2 years of follow-up suggest that the approach could benefit patients in low- to middle-income countries who do not have access to alternative therapies such as corneal transplantation."

Photo: Thor Balkhed / Linköpings universitet



Research briefing Check for updates

Accessible bioengineered corneal tissue to address a blinding disease globally

Porcine dermal collagen was chemically and photochemically bioengineered into an implantable tissue mimicking the human corneal extracellular matrix. The implant presents a simpler and safer method than donor cornea transplantation while delivering equivalent outcomes, and has restored vision to people with advanced keratoconus in resource-limited regions, where the burden of blindness is highest.

The problem

Blindness due to disease-related loss of transparency or function of the cornea (the eye's outer layer) affects an estimated 12.7 million people globally, whose only option is awaiting a cornea transplant from a donor[1]. Keratoconus, a disease in which degradation of the corneal extracellular matrix induces tissue thinning and weakening, is a leading indication for corneal transplantation globally[2], with a prevalence that is highest in low- to middle-income countries (LMICs). However, owing to a severe shortage of donor tissue and poor access to tissue banking infrastructure, only 1 in 70 patients who need corneal transplantation receive it, with this inequity heavily skewed against LMICs[3]. Nevertheless, no adequate and widely accessible alternatives to donor tissue transplantation for late-stage blinding disease have been developed for over 110 years, since the first corneal transplant was performed[4], as no technology has been able to match the visual outcomes attainable using donor tissue.

The solution

A potential solution to this problem is a bioengineered cornea. As the main protein of the human corneal extracellular matrix is collagen, we identified a sustainable source of purified type I porcine collagen as a by-product of the food industry. The collagen is extracted and purified from the overabundant leftover skin from food-grade pigs that are processed for meat products. We engineered this collagen into an implantable tissue by chemically and photochemically creating collagen–collagen bonds (crosslinks) to strengthen the implant while maintaining high transparency. For human implantation, the implant had to fulfill a range of stringent manufacturing, biocompatibility and toxicity standards, while also requiring robust sterilization, packaging and long-term storage to facilitate access and distribution. At the same time, we developed a minimally invasive technique to insert the implant within the existing cornea rather than replacing it. This surgical implantation technique was validated in a pig model using simple tools and in a single procedure, to avoid the need for suturing or long-term immunosuppression. This approach enabled us to obtain approvals to treat the first patients with keratoconus in India and Iran.

Crucially, after 24 months of storage, the sterilized and packaged bioengineered implant maintained its mechanical, optical and chemical properties, as assessed by stringent testing in vitro and in vivo.

Packaged implants and technical details of surgical implantation were transferred to centers in India and Iran, where surgeons treated 20 individuals with advanced keratoconus on the waiting list for a corneal transplant, 14 of whom were legally blind. Surgeons found the implants simple to insert, and operations were completed without complications, with only a short 8-week period of postoperative immunosuppressant medication. Postoperatively, corneas were transparent and stable, while surprisingly, the corneal thickness and curvature reverted to a pre-disease state (Fig. 1). After 2 years of follow-up without adverse events, no patients were blind anymore, and vision in the entire group had improved to an equivalent degree as with standard transplantation with donor tissue. Three individuals in India who initially were blind achieved 20/20 vision.

The implications

This work demonstrates the possibility of manufacturing, storing (for up to 2 years before use) and distributing our implantable bioengineered tissue to regions with a high burden of corneal blindness. The proposed surgery is less invasive than traditional transplantation and could be implemented as a safer alternative, even with human donor tissue. Given the global shortage of donated corneas; the barriers to procuring, pathogen testing and storing donor tissue in certified tissue banks (where it needs to be used or discarded within 2 weeks); and the required long-term (at least 1 year) immunosuppression to avoid foreign tissue rejection, the proposed bioengineered alternative would be attractive, especially in resource-limited areas. Although we did not select patients for best visual outcome and focused only on keratoconus, the methods could be refined to optimize vision and to treat other types of visual impairment. The implant is cell-free, but, as we observed during this study and in our previous studies with similar materials, it can support the growth of corneal epithelial, endothelial or stem cells, which should be evaluated as advanced therapy medicinal products in the future. We await longer-term clinical results and aim to conduct larger controlled trials for definitive evaluation of safety and efficacy before wider deployment of this technology.

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Bioengineered corneal tissue for minimally invasive vision restoration in advanced keratoconus in two clinical cohorts

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Visual impairment from corneal stromal disease affects millions worldwide. We describe a cell-free engineered corneal tissue, bioengineered porcine construct, double crosslinked (DPCDX) and a minimally invasive surgical method for its implantation. In a pilot feasibility study in India and Iran (clinicaltrials.gov no. NCT04653922), we implanted DPCDX in 20 advanced keratoconus subjects to reshape the native corneal stroma without removing existing tissue or using sutures. During 24 months of follow-up, no adverse event was observed. We document improvements in corneal thickness (mean increase of 209 ± 18 μm in India, 285 ± 99 μm in Iran), maximum keratometry (mean decrease of 13.9 ± 7.9 D in India and 11.2 ± 8.9 D in Iran) and visual acuity (to a mean contact-lens-corrected acuity of 20/26 in India and spectacle-corrected acuity of 20/58 in Iran). Fourteen of 14 initially blind subjects had a final mean best-corrected vision (spectacle or contact lens) of 20/36 and restored tolerance to contact lens wear. This work demonstrates restoration of vision using an approach that is potentially equally effective, safer, simpler and more broadly available than donor cornea transplantation.

Loss of corneal transparency and poor refractive function are among the leading causes of blindness globally[1–3]. Although corneal blindness can be treatable by transplantation, an estimated 12.7 million people await a donor cornea, with one cornea available for every 70 needed[1]. With an incidence of over 1 million new cases of corneal blindness annually[1], the severe shortage of donor corneas presents an unequal burden of blindness heavily skewed towards low- and middle-income countries (LMICs) in Asia, Africa and the Middle East[1,2]. Over half of the world's population does not have access to corneal transplantation owing to a lack of infrastructure for tissue donation, harvesting, testing and eye banking in LMICs[1,2]. The access problem is complex, involving economic, cultural, technological, political and ethical barriers[1,2]. Additionally, infectious diseases and pandemics bring donor tissue procurement and use to a virtual standstill, necessitating further measures to ensure donor tissue safety[1,2].

For these reasons, intense research effort has focused on bioengineering tissue for corneal transplantation[1–12]. To date, however, no biotechnological advance has been able to address the burden of corneal blindness or improve access to transplantable corneal tissue. In many parts of the world including Europe and Australia, keratoconus—a corneal disease characterized by stromal thinning, weakening and scarring[13]—is the leading indication for corneal transplantation[1,2]. Keratoconus affects both men and women and all ethnic groups, with highest prevalence reported in China (0.9%, or 12.5 million)[14], India (2.3%, or 30 million)[15] and Iran (4% of the rural population, or 3.4 million)[15].

Keratoconus is progressive, but with a complex etiology that is not well understood. With proper screening and access to specialist care, keratoconus progression can be detected and halted in its early stages while vision is still good; however, if not addressed early and in LMICs where keratoconus is highly prevalent and access to healthcare is limited, the disease often progresses. In advanced stages, it requires transplantation to prevent blindness, using techniques such as penetrating keratoplasty (PK) or deep anterior lamellar keratoplasty (DALK)[16–18]. These techniques, however, are subject to the limited supply of donor corneas, risk of graft rejection, post-operative complications associated with sutures and wound healing, risk of corneal neovascularization and/or infection, high astigmatism after suture removal, need for long-term immunosuppression and necessity for long-term patient follow-up[19]. To partially address these issues, newer and less invasive techniques such as stromal lenticule addition keratoplasty[20] and Bowman layer transplantation[21] have been introduced. While promising and still developing, these techniques stabilize the condition but offer only marginal vision improvement[16,22], and rely on availability of donor corneas and tissue banking infrastructure and are thus inapplicable in many regions of the world.

To address these limitations, we bioengineered a cell-free implantable medical device as a substitute for human corneal stromal tissue. As a raw material we used natural type I collagen, the main protein in the human cornea[23]. For an abundant yet sustainable and cost-effective supply of collagen, we used medical-grade collagen sourced from porcine skin, a purified byproduct from the food industry already used in FDA-approved medical devices for

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(source: Altimetric)

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The absolute maximal vision

How well can humans see?

Atle Einar Østern, MD,
Oslo University Hospital HF (Ullevål)

Good vision is important. For some, such as pilots, it is a vital requirement. I have examined air force pilots for many years. In some instances, I have recorded uncorrected monocular visual acuity of 20/10, even with a refractive error. Consequently, I have wondered what the maximum limit of human vision is and how it compares to animals. In this article, I attempt to answer such questions.

A starting point is then to determine what we mean by visual acuity. As shown in **Table 1**, there are several categories of visual acuity. We often label 20/20 as "normal" or "standard" vision, which is the ability to see an ortotype on the Snellen chart that subtends an angle of 5 arc minutes (5') at 6 meters or 20 feet (**Figure 1**).

Table 1. Classification of visual acuity

Type of acuity	Description	Degrees
Minimum resolvable acuity	The resolution of two close objects	0.017
Minimum recognizable acuity	The angular size of the smallest identifying feature	0.017
Minimum visible acuity	The smallest detectable object	0.00014
Minimum discriminable acuity	The angular size of the smallest change in a feature	0.00024

The minimum resolvable acuity is a fundamental boundary of spatial vision (the perception of the relationships of objects in space). This is the finest level of detail where a visual system can still discern two separate points. The prerequisite is that three cones on the row are involved. Under ideal contrast and luminance, two photoreceptors must be excited while the gap between the observed points falls on the intermediate cone. The distance between the centers of side-by-side cones in the fovea is 0.5 arc minutes (0.008 degrees or 30 arc seconds). Thus, the lower limit of minimum resolvable acuity must be twice that, which is one arc minute (0.017 degrees). More light is sampled if the photoreceptors are closely packed. The average peak density of photoreceptors in the foveola is 160,000 cones/mm^2, with considerable variation between individuals (ranging 100,000 to 324,000 cones/mm^2), corresponding to theoretical visual acuities of 20/10.5 and 20/7.1.[1] Resolution diminishes dramatically with eccentricity from the fovea. If not, we would have needed eyes and associated brain regions larger than our heads.[2]

However, on a bright day, humans can spot a wire against the background, which spans only 0.5 arc seconds (0.00014 degrees). That is less than described above. How is that possible? This remarkable minimum visible acuity is best explained by the imperfection of the eye's optics. The optics spread and distribute the image of the thin line, making it much broader on the retina. In this situation, the outfall is beneficial, but otherwise not. In fact, your camera might have superior optical quality compared to your eye. Thus, the visual potential of the eye is worse than retinal anatomy might alone imply. One limitation in this respect is that visual acuity depends on pupil size. Optical aberrations decrease visual acuity when the pupil is large (around 8 mm). However, with a small pupil (1–2 mm), diffraction occurs with the bending and scattering of the light waves after passing through the aperture, causing a reduction of image sharpness. The

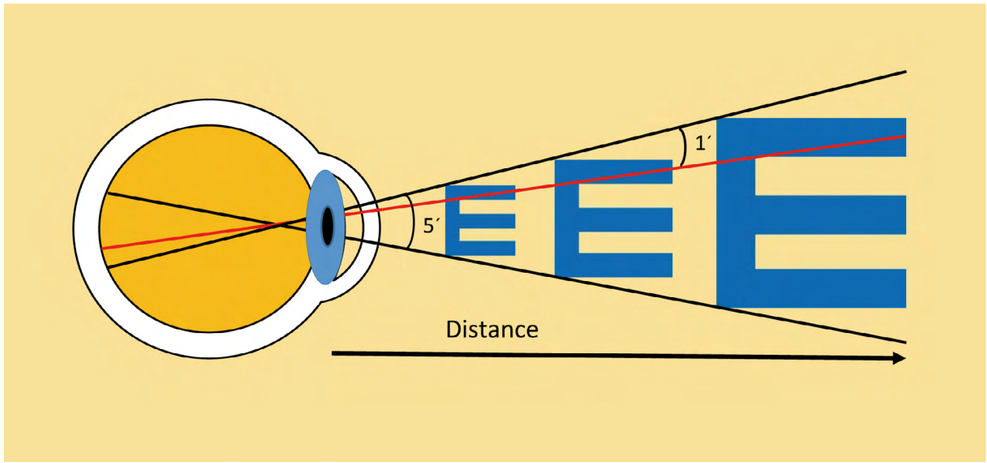

Figure 1. Schematic representation of the visual angle and the Snellen letter E: The visual angle is formed by the imaginary rays from the eye's nodal point to the top and bottom of an object. Arc minute is a unit of angular measure equal to 1/60 of a degree = 0.017 degrees = 1/21600 of a complete circle = 60 arc seconds. Illustration: Atle Østern.

visual acuity is best with a pupil diameter of around 3–4 mm. A measure of the optical performance is the modulation transfer function by testing patterns of sinusoidal gratings (**Figure 2**). The ratio between the contrast of the detected image and the original object defines the quality of the optical system.[2] Contrast sensitivity is hugely important for our visual function. Even when vision is 20/20, poor contrast sensitivity leads to problems in low-light situations, such as driving in darkness or fog.

There is more to vision. Humans have the amazing ability to discriminate a tiny misalignment of two lines that far surpasses the eye's minimum spatial resolution. Consider this: According to Guinness World Records 2005, Dr. Levi, in 1984, "repeatedly identified the relative position of a thin, bright green line within 0.8 seconds of arc (0.00024 deg), which is much less than the smallest foveal cones [and] equivalent to a displacement of some 0.25 inches (6 mm) at a distance of 1 mile (1.6 km)."[2] This fascinating phenomenon is called Vernier acuity, a form of hyperacuity. Hyperacuity refers to the ability of the visual system to recognize the relative location and offset of stimuli (**Figure 3**). The underlying mechanism is not yet fully understood but is an indicator of cortical visual function. Other visual examples include the detection of curvature, line orientation discrimination, and stereoscopic binocular vision.[3]

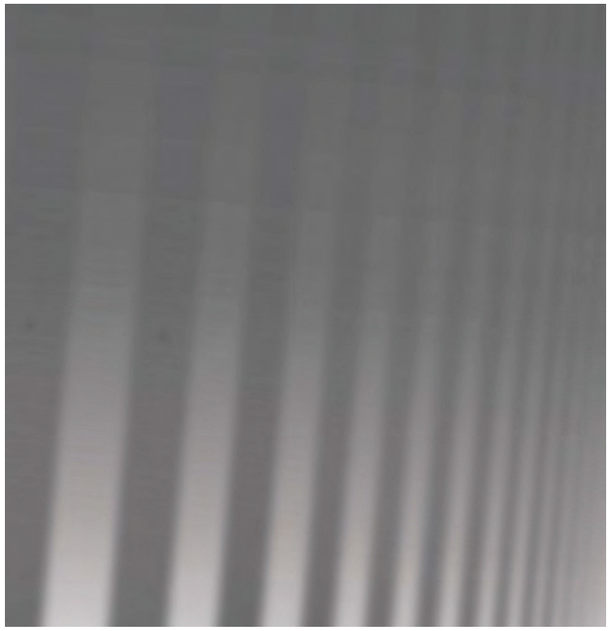

Figure 2. Contrast sensitivity: An image where the luminance varies gradually as a sine wave is called a sinusoidal grating, which can be used to test the optical system concerning the spatial frequency (number of bars, usually specified in cycles per degree), contrast (intensity difference between the dark and light bars), orientation (tilt), and spatial phase (the relative position of a grating). Humans are most sensitive to frequencies of 2–6 cycles per degree. Illustration: Atle Østern.

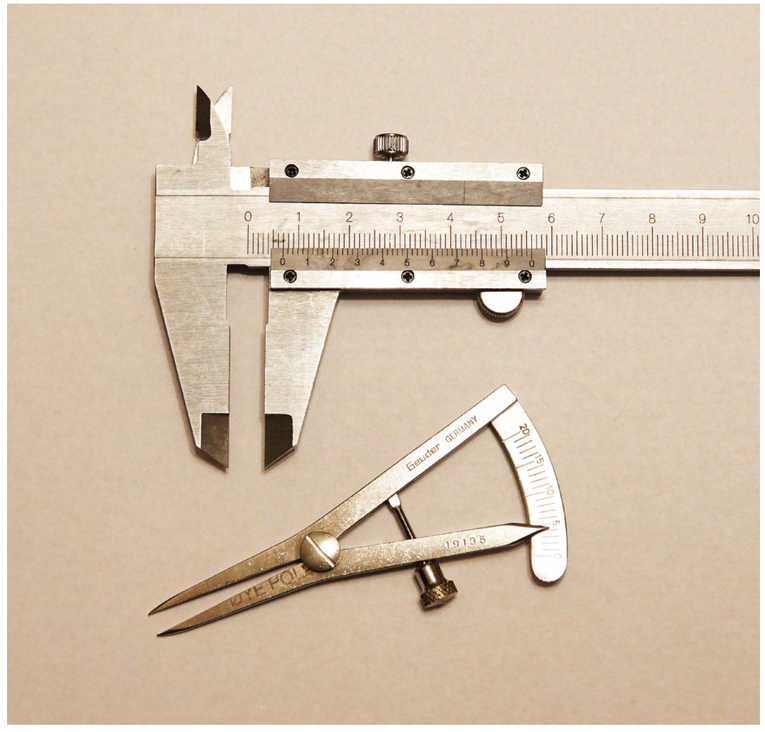

Figure 3. Vernier acuity is applied when detecting the slight misalignments of vertical lines between two adjacent scales, allowing for highly accurate measurements. That is the principle behind calipers. Calipers have long been used in many areas when high precision is needed, such as hand tools and in ophthalmology. Photo: Atle Østern

It gets more complex. As pointed out, the quality of the human optical apparatus and retinal anatomy is crucial for resolution acuity. However, recently published research suggests new compelling aspects of how visual signals are modulated beyond that. For example, scientists have demonstrated that the power-producing mitochondria in the photoreceptors can function like optical microlenses that channel light to the outer segments.[4] Furthermore, continuous unnoticeable microsaccades, accompanied by simultaneously brief periods of blindness, are critical contributors to normal visual acuity. They allow people to read at least two more lines on the Snellen chart compared to an immobilized gaze, which is essential knowledge when evaluating vision in patients with eye motion disturbances such as dyslexia and Parkinson's disease.[5,6] Moreover, how well people see relatively can be predicted based on unique individual differences in the extent of V1 surface area in the visual cortex, generating variable contrast sensitivity among people.[7]

To summarize, the best-corrected vision of two healthy individuals may not be the same for many reasons. In young humans, the average visual acuity is 20/16 to 20/12.5. Some claim that about 1% of the population achieves 20/10 vision, while others believe it is much rarer. However, one unvalidated report stated that an Australian Aboriginal person had 20/5 vision. But how do humans cope in a virtual world championship of vision among all living creatures (**Figure 4**)? Pretty well, actually.[8] The winners are some birds of prey, likely having a visual acuity of around 20/4 (**Figure 5**). However, we might compete for the silver medal. Our close extinct relatives (and partly ancestors), the Neanderthals, had even larger orbitas and eyeballs than us, perhaps as an adaptation to see better in dim light while hunting.

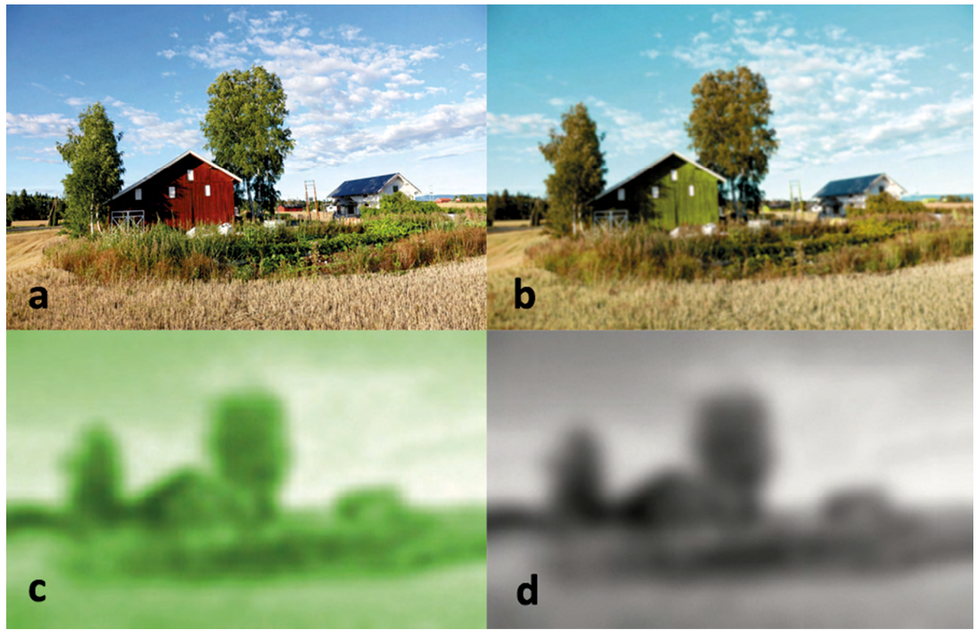

Figure 4. Vision in humans and some animals: The difference is 10,000 times between the worst and best visual acuity. What colors animals perceive varies. The simulated vision is of a human (a), cat (b), fly (c) and snail (d). Image: Atle Østern.

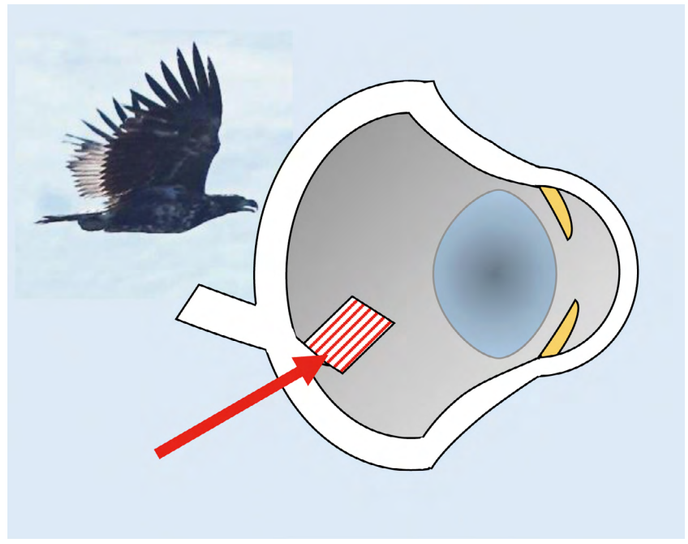

Figure 5. The unique shape of the eagle eye: The number of cones is much higher than in the human eye, and there is a second fovea. To accommodate better, the shape of the cornea is adjustable. The arrow points to the pecten, a pigmented comb-like part of the choroidea projecting into the vitreous, which provides nourishment for the retina. Photo and illustration: Atle Østern.

Even if we can never hope to see the world as keenly as an eagle, refractive surgery and corrective lenses can generate good visual outcomes. However, they come with a cost and risks. Then, perhaps brain training could be an alternative. Studies have shown promising results. Repeated practice can improve the contrast sensitivity and interpretation of visual information.[9] Exercise can delay the symptoms of presbyopia and enhance Vernier acuity.

Finally, to move from cerebral to celestial affairs, one piece of advice: don't go to Mars if you want to maintain your visual capabilities! You see, a study showed that astronauts, who are often former air force pilots, have poorer vision after returning from space, even years later.[10]

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Photo: Thor Balkhed / Linköpings universitet

There has long been a global shortage of donor corneal tissue for transplantation. In many parts of the world, advanced corneal stromal disease, including keratoconus, is the major indication for corneal transplantation. For over 110 years, however, there has been no viable alternative to the use of human donor corneal tissue that can provide visual outcomes similar to standard transplantation. In this study, a bioengineered tissue implant has been developed to mimic the human corneal stroma. The implant is made from an inexpensive and widely available byproduct from the food industry, porcine skin collagen. A series of experiments and preclinical studies show that the implant is capable of replacing the corneal stroma while fulfilling stringent requirements for human implantation. Importantly, the implant in a sterile and packaged form can be shipped globally and stored for up to two years in a refrigerator prior to use. In two landmark clinical studies, the implant was used with a new intrastromal surgical procedure to treat advanced keratoconus in 20 subjects, yielding results equivalent to the gold-standard corneal transplantation, but with a simpler, less invasive method that requires less recovery time, fewer postoperative medications, and fewer hospital visits than standard surgery. This technology could feasibly address a major cause of global visual impairment in many parts of the world.

We recently reported the first clinical results of a bioengineered corneal tissue implant, describing our efforts to address inequities in the treatment of advanced keratoconus, a major indication for corneal transplantation globally.[1,2] The World Health Organization has stated that although over 80% of global visual impairment is preventable, 90% of those who are blind or visually impaired live in low- and middle-income countries, where access to eye care is extremely poor.[3] Therefore, in July 2021, the United Nations General Assembly adopted the first-ever resolution on eye health as part of the Sustainable Development Goals (SDGs). This resolution is a commitment to reach 1.1 billion people with vision impairment, who presently lack access to eye care, by 2030.[4]

Achieving progress towards this goal will require a radical rethinking of how eye care is delivered globally. The solution will undoubtedly be multi-faceted, and biomedical innovations could contribute in a meaningful way. Our research in Linköping, Sweden, focuses on corneal visual impairment and blindness, which affects millions worldwide and with an especially dire situation in low- and middle-income countries.[5,6] Because the cornea is the clear outer 'window' of the eye, corneal transplantation can be required to prevent blindness or severe visual impairment in diseases where it loses its clarity or refractive function. However, challenges in treating corneal blindness include sourcing the donor corneal tissue in adequate quantities, delivering the tissue to where it is needed when it is needed, and performing the complex and potentially risky transplantation surgery needed to restore vision. A further difficulty is that the advanced tools and techniques developed in Western countries are often not available or feasible to implement on a large scale in low- and middle-income countries, and advanced methods are often developed and tailored for local populations in high-income countries.

A corneal disease, such as keratoconus, brings these disparities to light. Historically, keratoconus in its advanced form – where vision is no longer correctable with eyeglasses or contact lenses – was the leading indication for corneal transplantation in many parts of the world. In Western countries, including Scandinavia and the US, most cases of keratoconus can nowadays be detected early—before the disease progresses to a point where invasive surgery is needed. The ultraviolet-A/riboflavin crosslinking method (termed CXL) and its variants can effectively halt the disease progression early, and in many cases a combination of CXL and judicious use of contact or scleral lenses can provide excellent vision that remains stable for many years, potentially even decades.

Nevertheless, the situation in continental Europe differs, with these regions having more cases of keratoconus progressing to an advanced stage and requiring keratoplasty. In these countries, the availability of donor corneas for transplantation is still good but may, nonetheless, be the limiting factor in determining how many such transplantations can be performed (typically lamellar or full penetrating keratoplasties). When considering other geographical regions, such as Australia,[7] the Middle East,[8] and Asia,[5,6] keratoconus is still the most common indication for keratoplasty, and, despite advances in CXL, transplantations have not diminished. Unfortunately, relatively few scientific articles in the literature document the transplantation situation in low- and middle-income countries, but it is known that there is a significantly higher burden of keratoconus in Africa,[9] the Middle East,[8] and Asia,[5,10] and more cases in these regions reach an advanced stage requiring transplantation. There is a strong association of keratoconus with genetics

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"The authors have bioengineered a hydrogel that is robust, stable, transparent and easy to insert into the corneal stroma and that should be inexpensive to produce, package and store. The simple procedure described here may give sufficient vision for a long time to millions of people in low-resource countries"

—Claes H. Dohlman, MD, PhD, Professor Emeritus of Ophthalmology, Harvard University, USA, 2022 Antonio Champlimaud Laureate

and ethnicity, but it is also widely believed that environmental factors, such as sunlight exposure[10] play an important role.

It is worth noting that the burden of keratoconus is not fully addressed by early detection and CXL treatment. From a wider global perspective, many patients receiving CXL treatment for keratoconus are not satisfied with their refraction after the procedure, and many struggle with contact or scleral lenses for years after receiving CXL. Patients also receive CXL in various stages of the progressive disease, with thin and irregular corneas that no longer exhibit progression after crosslinking, but nonetheless have suboptimal refractive properties. These patients often struggle with lenses to achieve good vision.

With these challenges in mind, our team, as well as other teams around the world, have been focusing on bioengineering tissue to address the global shortage of donor corneas. At the same time, we must also be cognizant of the limitations of human allogeneic tissue. Difficulties and costs involved in human tissue procurement, the establishment of eye banks, and the creation of associated procedures and protocols for tissue storage and quality control, as well as the limited storage time and potential for disease transmission or rejection are some of the challenges of using donated human tissue. The remaining challenges noted above, namely lack of access to transplantable tissue where it is needed and the complexity of the surgery, are arguably equally as important as tissue supply, but unfortunately these practical aspects have received much less research attention.

Around 2012, we recognized that large-scale bioengineering of corneal tissue at low cost would require using sustainably sourced raw materials. Instead of developing novel synthetic molecules and complex materials on a small scale (and at high cost) in a laboratory, we sought a method that could be scalable to potentially meet the demand from millions of people with advanced keratoconus who require some form of transplant. We chose to use only natural type I collagen as a raw material, as this is the main component of the normal human corneal extracellular matrix. We were fortunate to find that type I collagen purified from porcine skin is produced commercially in relatively large quantities and at low cost. Porcine skin collagen is already used in regulatory-approved cosmetic procedures. Importantly, this collagen is sourced as a byproduct of meat production from the food industry, as the skin is overabundant and usually considered a waste product. We, therefore, used this collagen as the only raw material to create the final bioengineered corneal implant. The implant is cell-free and mimics the collagen extracellular matrix of the corneal stroma. Rather than containing cells, the implant is meant to augment or replace the corneal stroma as a 'scaffold' that can support eventual repopulation by the host's own cells. A cell-free implant also circumvents potential issues of tissue biocompatibility, immune stimulation, and rejection. The simplicity of the design and materials is key to feasibly manufacturing engineered tissues on a large scale.

Meeting the numerous and rigorous production and testing requirements for a class-III implantable medical device was essential for our work. This was an enormous undertaking, particularly for soft hydrogels, a relatively new class of implantable materials. Most implantable materials do not need to be optically transparent when implanted in the body; however, the demand for a high degree of transparency for vision places stringent constraints on the development and manufacturing processes of devices intended for corneal applications. The development and manufacturing of implantable devices could not feasibly be accomplished within the scope and resource constraints of academia. Therefore, a spinoff company, LinkoCare Life Sciences AB, with its own private investment, employees, and dedicated grant funding, was essential. Key advances made by the company were the stabilization of the collagen using multiple, chemical and photochemical, crosslinking methods and achieving stringent quality control, manufacturing, sterilization, and packaging to ensure the bioengineered tissue not only survived human implantation but could be shipped and stored for at least two years without a decline in performance. These aspects are vital for dissemination of the technology globally, to low- and middle-income countries and in remote areas lacking the infrastructure or resources for procuring, handling, testing, and storing human donor tissues. The packaged bioengineered corneal implant is a truly 'off-the-shelf' solution for replacing donor corneal tissue (**Figure 1**).

Figure 1. Bioengineered corneal implant made from collagen sourced from porcine skin. Courtesy of LinkoCare Life Sciences AB, Sweden. Photo: Thor Balkhed/Linköping University.

At the same time as the first prototypes were being produced by the company using purified porcine collagen, we explored options for a simplified surgery to implant the tissue. Traditional lamellar or penetrating corneal transplantation triggers a strong wound-healing response that often leads to scarring or haze in the tissue. Moreover, removing and replacing the corneal epithelium and/or endothelium (tissues that generally function well in keratoconus) places an added challenge on the postoperative wound healing and tissue integration response. Traditional procedures negatively impact the corneal nerves, which must be transected during transplantation. Corneal nerves are already pathologically reduced and altered in keratoconus,[11] so these would likely have a reduced capacity for regeneration following transplantation. Maintaining the neurotrophic status of the cornea would be desirable, if possible. Further challenges of the traditional lamellar and penetrating transplantation techniques include the often-long rehabilitation time, when patients must often take immunosuppressive medications for years. Multiple follow-up visits are necessary for monitoring, adjusting and removing sutures and managing postoperative suture-related complications, including induced astigmatism.

We appreciated these multiple drawbacks of standard corneal transplantation, and found that, in preclinical models, when a biomaterial was placed into the eye but remained exposed to the external environment (tear film, eyelids, and air), it quickly degraded or stimulated the native cornea to produce scar tissue. Protecting the material from the external environment was, thus, essential. We experimented with different implantation techniques,[12,13] and discovered that implanting a material within the corneal stroma (i.e., in an intra-stromal 'pocket') while leaving the native tissue above and below the material undisturbed, preserved the integrity, shape, and transparency of both the biomaterial and the surrounding cornea (**Figure 2**). The 'interface haze' often seen as a wound-healing fibroblastic response to lamellar transplantation was absent in the case of intra-stromal implantation. This is also an advantage for future envisioned applications of intrastromal lenticule implantation for refractive or therapeutic purposes. An added advantage was that the surgery did not require suturing and did not trigger a strong inflammatory or wound healing response, resulting in quick healing without prolonged use of immune-suppressing medications, like corticosteroids. This means that, in theory, a single procedure and hospital visit could suffice, with an eye towards future applications in remote areas, where return hospital visits may not be feasible. In our preclinical models, the intra-stromal surgery implanting the bioengineered material was observed to thicken and reshape the corneal stroma and we soon realized it could be used as a safer, less invasive, and simpler alternative to current surgical treatment for advanced keratoconus.

For advanced cases, where the cornea was still transparent, but the cornea was thin and very steep, the intra-stromal implantation of an implant to augment the existing cornea could serve to thicken the cornea while also regularizing the anterior and posterior curved corneal surfaces. The mid-stromal implant thus 'pushes outwards' the anterior and posterior stroma, achieving an effective flattening of the cornea. What surprised us was how well this approach worked to restore vision to subjects who were initially blind with advanced keratoconus (definition of blindness: logMAR BCVA ≥ 1.30 and contact lens intolerance). We did not specifically match the shape, thickness, or size of the engineered implants to each individual subject, but in our pilot clinical studies in Iran and India consisting of 20 patients receiving the implant, no person was blind after the procedure. What's more, three initially blind subjects attained 20/20 vision, stable to at least two years postoperatively (the final follow-up study visit). All 20 subjects in the study also regained tolerance to contact lens wear. The cornea was thickened by over 200 µm with the procedure, and keratometric flattening was > 10 diopters (**Figure 3**).

This was the first small pilot study, and, as such, the results are indicative rather than conclusive. Further studies are needed, ideally within countries with

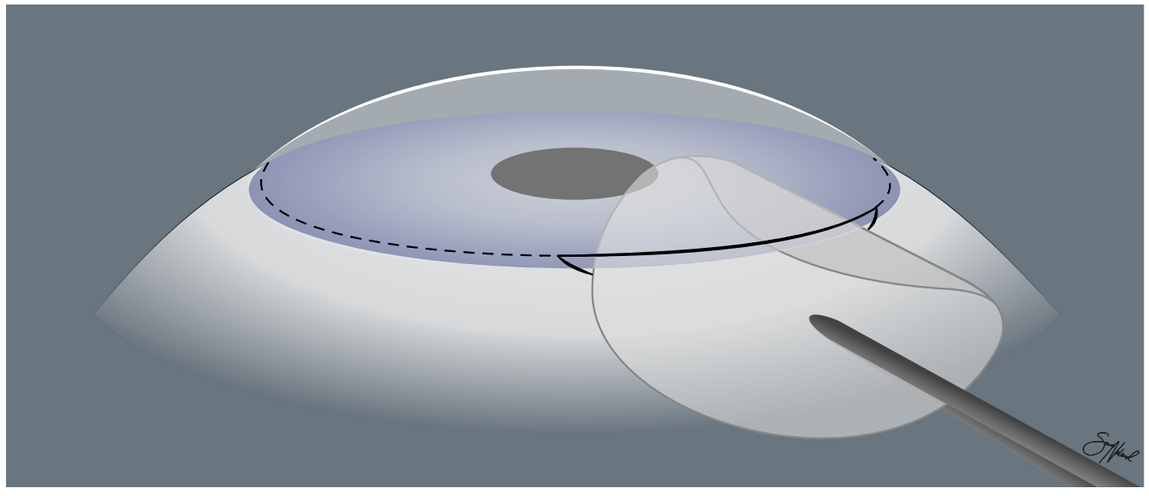

Figure 2. A minimally-invasive intra-stromal technique for treating advanced keratoconus when the cornea is still transparent. In the technique, an intra-stromal pocket is created, into which a thick (280 – 440 µm in the study) bioengineered implant is inserted via a small 2 to 4 mm peripheral incision. The technique does not remove native corneal tissue, does not require sutures, thickens the cornea, and reshapes it. The wound heals quickly, and postoperative medications are given for only eight weeks. Over 10 diopters of flattening can be achieved, resulting in major gains in visual acuity.

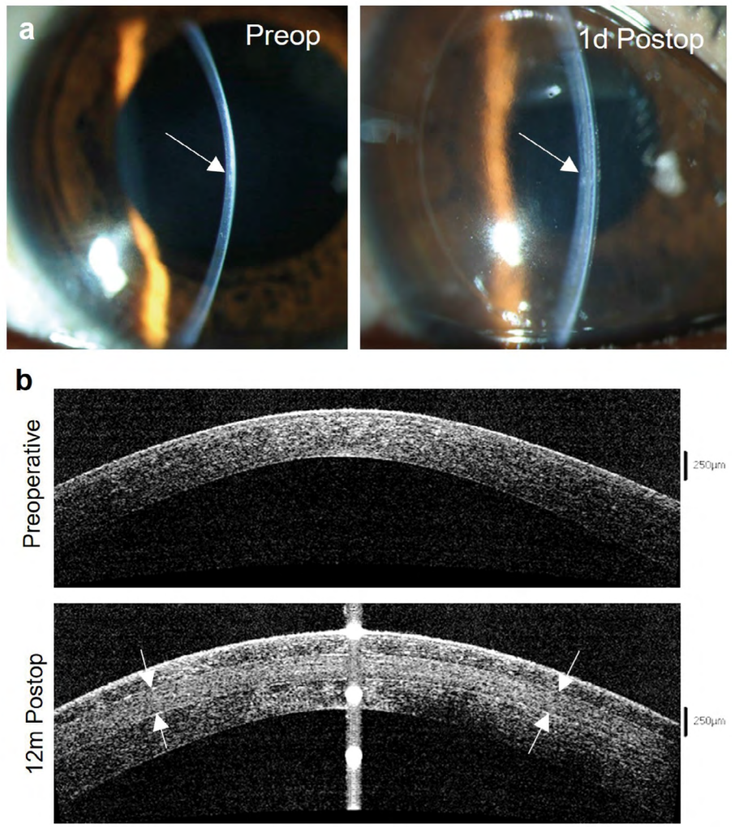

Figure 3. The bioengineered corneal implant after surgical intrastromal implantation in a subject with advanced keratoconus. (a) slit lamp photographs of the preoperative and postoperative cornea one day following implantation, indicating an immediate thickening and regularization of the corneal surfaces. (b) 1-year post-implantation, the cornea retains its increased thickness and transparency, with the implant remaining intact as observed by optical coherence tomography. Figure modified from Rafat et al. (2022), under Creative Commons Open Access license.

Key points:

- Keratoconus is a major cause of visual impairment with the heaviest burden in low- and middle-income countries.
- Standard corneal transplantation with donor tissue is not an accessible, available, or sustainable solution for millions globally with advanced keratoconus.
- A packaged bioengineered tissue can be made from abundant natural materials to meet requirements for human use, shipped to remote areas, and stored for up to two years.
- Intrastromal implantation of the bioengineered tissue in advanced keratoconus restored vision to patients equally well as standard transplantation.
- The new intrastromal technique is less invasive, simpler to perform, and requires less immunosuppression than standard transplantation techniques.

access to advanced knowledge and clinical research infrastructure, where the use of the biomaterial can be best refined. However, the ultimate goal remains the eventual translation and dissemination to populations where the burden of keratoconus is the greatest, namely in low- and middle-income countries.

Our work in a broader sense demonstrates that human tissue can be bioengineered and used to treat a widespread disease, with initial safety and efficacy at least on par with traditional treatment. As shown in several preclinical studies, our cell-free scaffold can be repopulated by host cells in vivo, which is suggestive that more complex tissues and even organs could be engineered by providing a suitable scaffold with or without cells; this goal is presently being pursued by many research teams. Ideally, the implantation surgery should not induce an excessive immune or wound-healing response, to maintain integrity of the implanted biomaterial. In our study, the implantation method was essential for restoring vision. Such methods should be further explored for treating other corneal stromal disease. Perhaps even when using donor tissue where available, for intra-stromal implantation, this method could have benefits relative to lamellar or penetrating keratoplasty for certain indications. The less invasive approach may also be less demanding for patients. Finally, shipping and delivering off-the-shelf tissues that can be stored for long periods at room temperature or in a refrigerator will enable new technologies to reach a much wider recipient population. We are hopeful that once our bioengineered implant is used clinically, surgeons will find new uses for it to treat conditions beyond what we originally envisioned.

We are enthusiastic for the future, as we work towards delivering this technology at low cost to those in most need. It is also our hope that innovations and new developments within the fields of tissue engineering and regenerative medicine in ophthalmology will be made available to all in an equitable manner.

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Work smarter, not harder:

Automated anterior chamber angle assessment

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Abstract

Primary angle-closure glaucoma (ACG) is a severe disease with a high risk of vision loss and follows a different treatment paradigm from primary open angle glaucoma. Anterior angle assessment is crucial for the diagnosis and management of glaucoma, but gonioscopy, the current reference standard, is not always performed and is subjective. Recent developments in anterior segment imaging and artificial intelligence (AI) offer the possibility of improved angle evaluation. We review recent developments in automated angle assessment and document both the strengths and weaknesses of current AI angle assessment systems. Recent AI performance is impressive, and, while challenges remain, automated angle assessment is largely ready for clinical use.

Introduction

Glaucoma is a group of optic neuropathies primarily classified according to the status of the angle between the iris and the cornea. The iridocorneal angle has long held central importance in glaucoma classification because patients with closed angles behave differently from those with open ones. Broadly, an angle is open when the trabecular meshwork is visible for more than 180 degrees and closed when it is not using gonioscopy (**Figure 1**). While many with angle closure never develop glaucoma, some do, mainly due to elevations in intraocular pressure (IOP). Proper IOP regulation relies on an open access of aqueous humor to the drainage pathway; blockage of this pathway is a common mechanism of IOP elevation and a hallmark of ACG.

ACG is a major health concern, with an estimated 23 million people affected.[1] Certain populations, primarily women, the elderly, and Asians, are at especially high-risk for ACG. Older Chinese women, in particular, have nearly a 25% chance of having angle closure.[2] Angle closure has potentially destructive consequences. In the long-term, angle closure can cause severe, bilateral vision loss through sustained elevation in IOP. Despite accounting for only about one quarter of glaucoma cases, ACG is the cause of half of all glaucoma-related blindness and represents an aggressive form of disease.[3] In China, ACG is responsible for over 90% of glaucoma-related blindness.[4] Angle closure is also the primary risk factor for the development of an acute attack, with potential for devastating vision loss over the course of hours. Furthermore, the recent EAGLE Trial documented the benefit of early lens extraction in ACG making it essential that clinicians assess the angle to select the best treatment approach for patients.[5]

Gonioscopy: a flawed standard

Gonioscopy is currently the standard approach to angle assessment. However, it has several shortcomings that make it a sub-optimal standard and likely contribute to insufficient or improper angle assessment by ophthalmologists.[6] Gonioscopy requires the instillation of numbing drops, a slit lamp, and a trained gonioscopist, usually a physician. Slit lamp gonioscopy also has a steep learning curve, and there is some evidence that ophthalmologist trainees feel inadequately prepared in this technique.[7] Perhaps the main problem with gonioscopy is that it is a subjective measure with only moderate inter-examiner agreement and documented variation with different light conditions.[8,9] Lastly, gonioscopy requires physical contact with the cornea that comes with a host of other concerns: corneal trauma, the need for anesthetic drops, anatomic distortion from lens compression, and patient discomfort.

Despite the significant drawbacks of gonioscopy, it continues to be the most widely used technique for angle assessment. Currently, only half of glaucoma patients have documented angle assessment.[10] Likewise, a recent study found that nearly 1 in 11 patients referred by ophthalmologists to a tertiary care center with the diagnosis of open angle glaucoma had angle closure.[11] Clearly there is need for a better approach to assessing the angle.

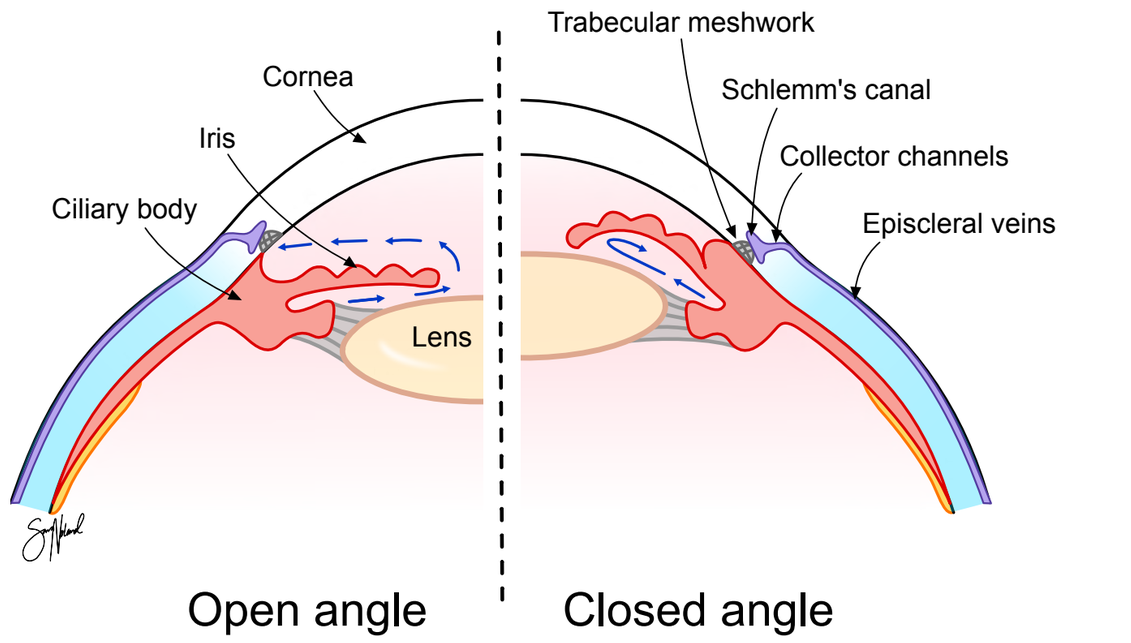

Figure 1. Conventional aqueous humor outflow pathway: *Aqueous humor is secreted by the ciliary body and circulates (blue arrows) from the posterior chamber to the anterior chamber through the pupil. With an open angle (left), aqueous humor exits the eye through the angle where it enters the trabecular meshwork, flows into Schlemm's canal, and merges into collector channels before finally emptying into the episcleral veins. With a closed angle (right), the outflow pathway is impaired.*

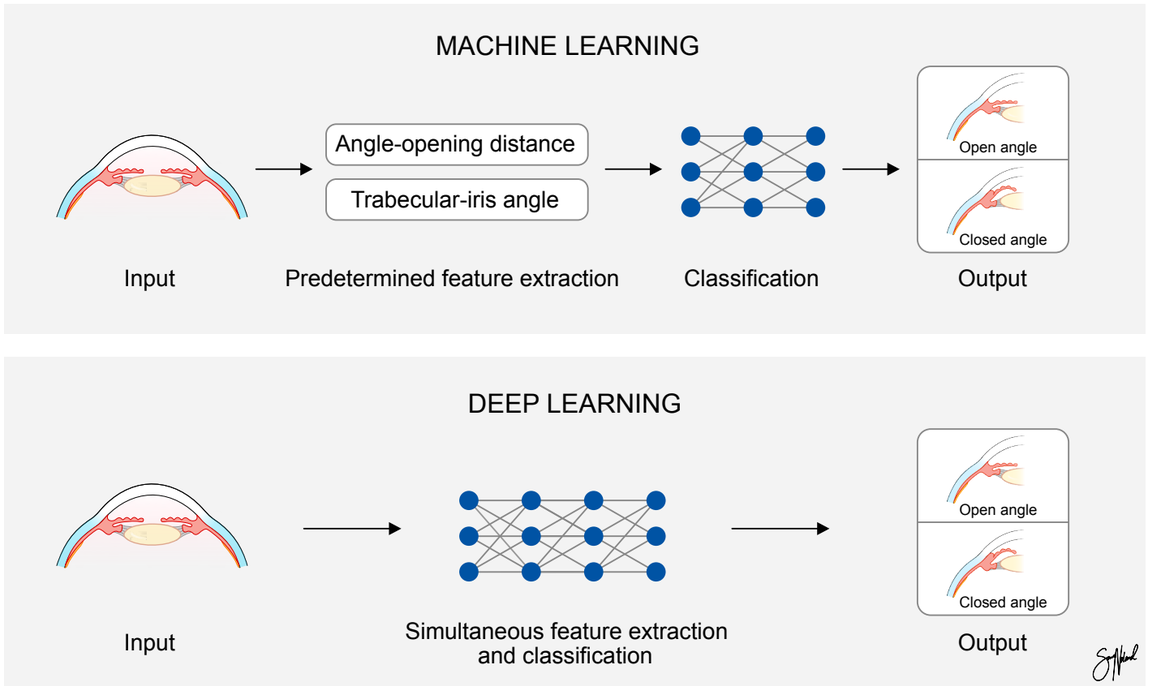

Figure 2. Key distinctions between machine learning and deep learning: Machine learning (top) involves classification based on pre-selected and defined features, whereas deep learning (bottom) enables classification simultaneously with feature selection and testing.

Artificial intelligence in angle-assessment

New, objective, and increasingly automated methods of angle imaging offer the possibility of improved angle evaluation. The two main angle imaging techniques are ultrasound biomicroscopy (UBM) and anterior segment optical coherence tomography (AS-OCT). These methods allow for objective angle assessment, the long-term storage of angle images, and automation.

Anterior segment images can be analyzed and classified by human graders, feature-programmed machine learning, or deep learning. Feature-programmed machine learning involves classifying images using up-front, manual-selected features. Deep learning does not use pre-selected features; instead, a trained algorithm (neural network), learns the most predictive features directly from the images (**Figure 2**). The process of training the neural network requires large datasets in which images have been expertly classified. For each image, the developing network compares its output to the training set value. The neural network then modifies its internal parameters to decrease classification error. With the right training data and after many repetitions, the neural network learns to classify an image accurately and efficiently—without human input.

The use of machine and deep learning in medicine has triggered considerable excitement and has demonstrated early success in the field of ophthalmology. Automated assessment of diabetic retinopathy screening recently gained FDA-approval, and there have been numerous studies using deep learning for age-related macular degeneration and glaucoma screening.[12–15] Using deep learning in the assessment of the anterior chamber angle has also gathered attention and undergone significant pre-clinical testing.

Ultrasound Biomicroscopy

UBM provides high-resolution images of the anterior segment, but its clinical use is limited by practical drawbacks: it is a cumbersome test that requires a skilled examiner, an immersion bath, and physical contact with the eye. UBM's main advantage is its ability to image posterior chamber structures, most importantly the ciliary body and lens zonules. This makes UBM a particularly helpful adjunct tool in diagnosing plateau iris, tumors, and ciliary body cysts.[16] Using UBM, a team of researchers recently described the use of a convolutional neural network (CNN) for angle classification as open, narrow, or closed.[17] They achieved high sensitivity and specificity (all above 96%) compared to physician UBM image grading for each classification using a test set of almost 200 images of each angle type. Likewise, a similar, more recent study demonstrated excellent accuracy and consistency in identifying relevant angle anatomy (**Figure 3**).[18] All intraclass correlational coefficients were above 0.93. Together, these studies demonstrate the promise for automated angle classification of UBM images.

Anterior Segment OCT

AS-OCT is a non-contact and objective imaging modality that can be performed rapidly and reproducibly.[19] While UBM and gonioscopy require a highly-skilled examiner, AS-OCT images can be captured by examiners with less training. AS-OCT clinical applications have expanded over the years as improvements in technology enabled faster image capture and enhanced resolution. Modern swept source systems can now capture circumferential anterior chamber imaging with a resolution of <10 nm x <30 nm at 30,000 A scans per second.[20]

Manual angle assessment requires the localization of landmark structures, particularly the scleral spur. Initially, the limited angle resolution of early AS-OCT devices was a major limitation; the trabecular meshwork could not be reliably identified, and the scleral spur was not visible by expert observers in 15-28% of images.[21,22] Reassuringly, spectral domain

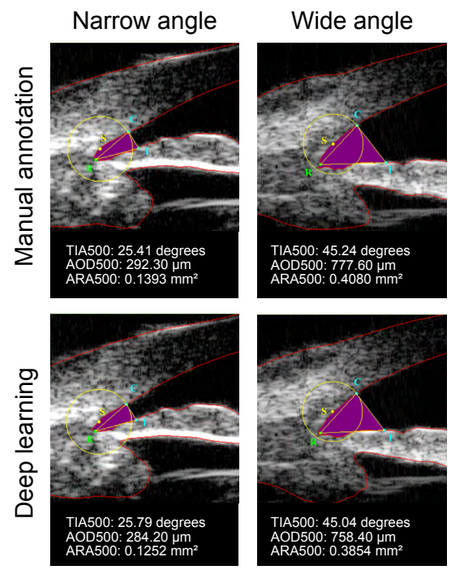

Figure 3. Ultrasound biomicroscopy angle parameter measurement results from manual (top) or deep learning (bottom) algorithms of narrow (left) or wide (right) angles: TIA500 is the angle between points C, R, and I; AOD500 is the distance between points C and I; ARA500 is the area of the purple section. Adapted with permission from Wang et al. Transl. Vis. Sci. 2021.[18]

AS-OCT devices allow for a substantially improved axial resolution and visualization of the scleral spur with high interobserver agreement.[23] Currently, localization of the scleral spur is of primary importance as angle closure in AS-OCT has been defined as any contact of the iris with the angle wall anterior to the scleral spur. Moreover, the scleral spur is used as the reference point to measure other useful angle parameters, including angle opening distance either at 500 or 750 µm anterior to the scleral spur (AOD500, AOD750), angle recess area (ARA), trabecular iris angle (TIA), and trabecular-iris space area (TISA) (**Figure 4**). Overall, AS-OCT has excellent sensitivity (>98%) but poor specificity (~45-65%) in detecting angle closure compared to gonioscopy.[24,25] Pressure- or light- induced angle widening during gonioscopy has been suggested as the cause for this high false positive rate. Therefore, one cannot be certain if gonioscopy is a suitable "gold standard" against which to determine the performance of AS-OCT.

Yanwu Xu et al. demonstrated an early role for AI in AS-OCT angle assessment. They used a computer-aided image processing system (histograms of oriented gradients) to localize the anterior chamber angle and extract several angle features.[26] By combining these extracted features together through the support of vector machine learning, they were able to classify angles as open or closed with higher accuracy (AUC = 0.83) than when using any individual angle feature alone. The next year, the same group presented an improved automated angle assessment system, trained on the same dataset of about 2000 images with an AUC of 0.92.[27]

Fu and colleagues then demonstrated the particular strength of deep learning in angle assessment.[28] They developed a deep learning system for angle classification and compared it to an

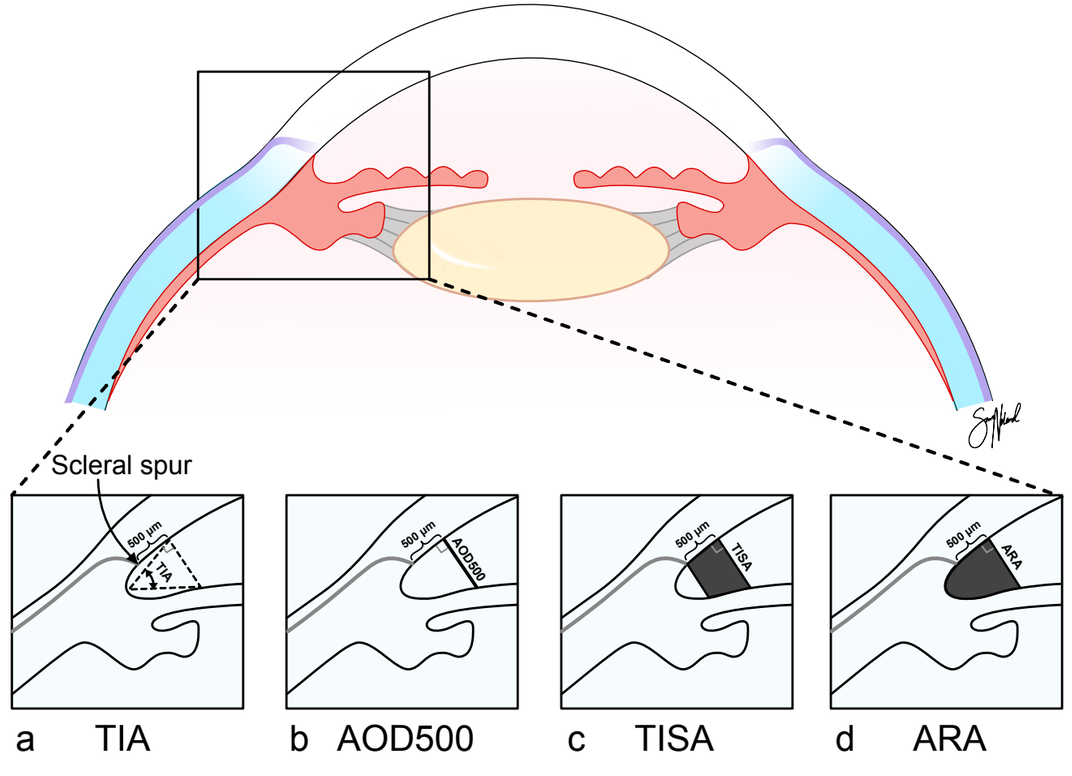

Figure 4. Measurement of various angle parameters: a) the trabecular iris angle (TIA) specifies the anterior chamber angle and is defined as the angle from the apex of the iris recess to the point on the trabecular meshwork 500 µm anterior to the scleral spur and the perpendicular point on the iris. b) the angle-opening distance (AOD500) is the distance from the point on the trabecular meshwork 500 µm anterior to the scleral spur and its perpendicular intersection on the iris. c) the trabecular-iris space area (TISA) is the area bound by the AOD500, iris, inner scleral wall, and line perpendicular to the scleral spur. d) the angle recess area (ARA) at 500 µm is the area of the angle enclosed by the AOD500.

automated, quantitative feature-based system, using physician AS-OCT angle grading as the reference standard (**Figure 5A**). Their quantitative-feature method resembled earlier angle assessment models with automatic segmentation and key feature measurement. Their deep learning model consisted of a VCG-16 network and appropriately identified and focused on the most relevant region to assess angle status (**Figure 5B**). When tested on a set of over 8,270 images (7,375 open angle and 895 closed angle), the deep learning system performed better than the automated quantitative feature-based system when compared to physician grading of the images (AUC 0.96 vs 0.90). This study indicated the ability of neural networks to extract and consider predictive features beyond what physicians currently recognize as relevant.

In 2020, researchers using data from the Chinese American Eye Study developed and tested the ability of a CNN to locate the scleral spur.[29] They trained a ResNet-18 CNN on a dataset of over 17,000 images with the coordinates of the scleral spur marked by one reference grader. In a test set of over 900 images, the CNN performed similarly to a human expert grader with over 80% of predicted coordinates falling within 80 µm of the reference coordinates in both X- and Y-axes, the suggested standard of clinical significance. Moreover, the CNN performed well in variable angle conditions, including eyes with narrow or closed angles, where the scleral spur is more difficult to assess. Work by Pham et al. similarly demonstrated the ability of a CNN to locate the scleral spur as accurately as an experienced ophthalmologist.[30]

Most recently, an international multi-center study using a total of over 1 million images was published. They used a 3-dimensional (3D) deep-learning system and "digital gonioscopy" to assess for angle closure and peripheral anterior synechiae (PAS).[31] This study was unique in several ways. First, it used 3D volume scans to improve image accuracy; second, gonioscopy was used as the reference standard; third, angles were evaluated in both light and dark conditions to simulate dynamic gonioscopy and evaluate for PAS. This deep learning system again demonstrated excellent accuracy, sensitivity, and specificity in detecting angle closure (0.94, 0.87, 0.88 respectively), which was comparable to expert ophthalmologists. More impressively, this "digital gonioscopy" was able to capture PAS using light and dark conditions with 90% sensitivity and specificity (AUC = 0.90) and provide insight into the mechanism of angle closure.

Challenges and Future Directions

Despite the many recent advances, challenges remain that will need to be addressed for AI to change the landscape of angle assessment in clinical practice. First, machine learning algorithms are only as good as the data on which they are trained. Currently, most automated angle-assessment AI systems are trained with datasets of homogenous populations. Thus, few automated systems have been trained or tested against diverse populations more reflective of the real-world.

Second, the absence of ground truth in angle classification poses problems for developing and accessing automated models. What should automatic AS-OCT classification be compared against? Manual AS-OCT classification is somewhat subjective and variable, and gonioscopy, too, is a flawed standard. Additionally, almost all training sets have been assigned "true value classifications" by one or two ophthalmologists. Consequently, automated systems learn any idiosyncratic grading style of their reference trainers, which may threaten external validity. Planning how interpersonal variation should be accounted for will help ensure consistency and widespread applicability.

Third, cost barriers and the variety of AS-OCT imaging modalities are challenges for widespread use of automated angle assessment. General adoption of swept source OCT anterior segment devices have been limited by their high costs, and less expensive alternatives are needed for widespread adoption to be feasible. Current AI algorithms are also limited to a single imaging modality with poor performance when tested on images from a new device. Thus, approval of no single AI system will enable wide-spread accessibility to automated angle assessment, which may slow the pace of development and regulatory approval.

Last, artificial intelligence in angle assessment is still a nascent field with hopefully many more advances and applications to come. One of the more exciting possibilities is the use of AI to predict more accurately who will benefit from prophylactic laser peripheral iridotomy. For AI to realize this potential, continued work is necessary with strategic focus on the transition to clinical models.

Key points:

- Current angle evaluation strategies are subjective and cumbersome.
- Imaging can reduce the burden of assessing the angle.
- Deep learning is an attractive strategy to bring angle assessment into the modern era.
- Deep learning in UBM and OCT have improved tremendously over the years and now demonstrate accuracy and reproducibility comparable to human experts.
- While challenges remain, angle closure screening using automated AI is essentially ready for clinical care.

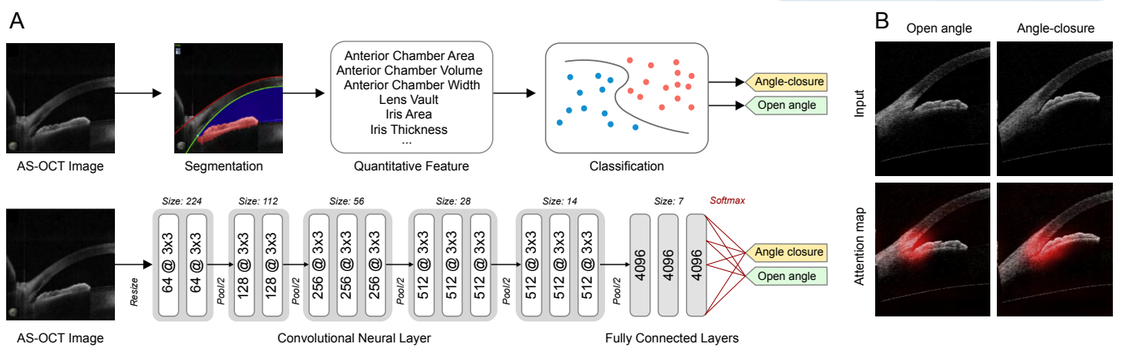

Figure 5A. Overview of automated angle closure detection systems: quantitative feature-based method (top) and deep learning method (bottom). 5B. Attention map of deep learning network highlighting locations of features used in angle classification in open angles (left) and angle-closure (right). Adapted with permission from Fu et al. AJO 2019.[28]

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