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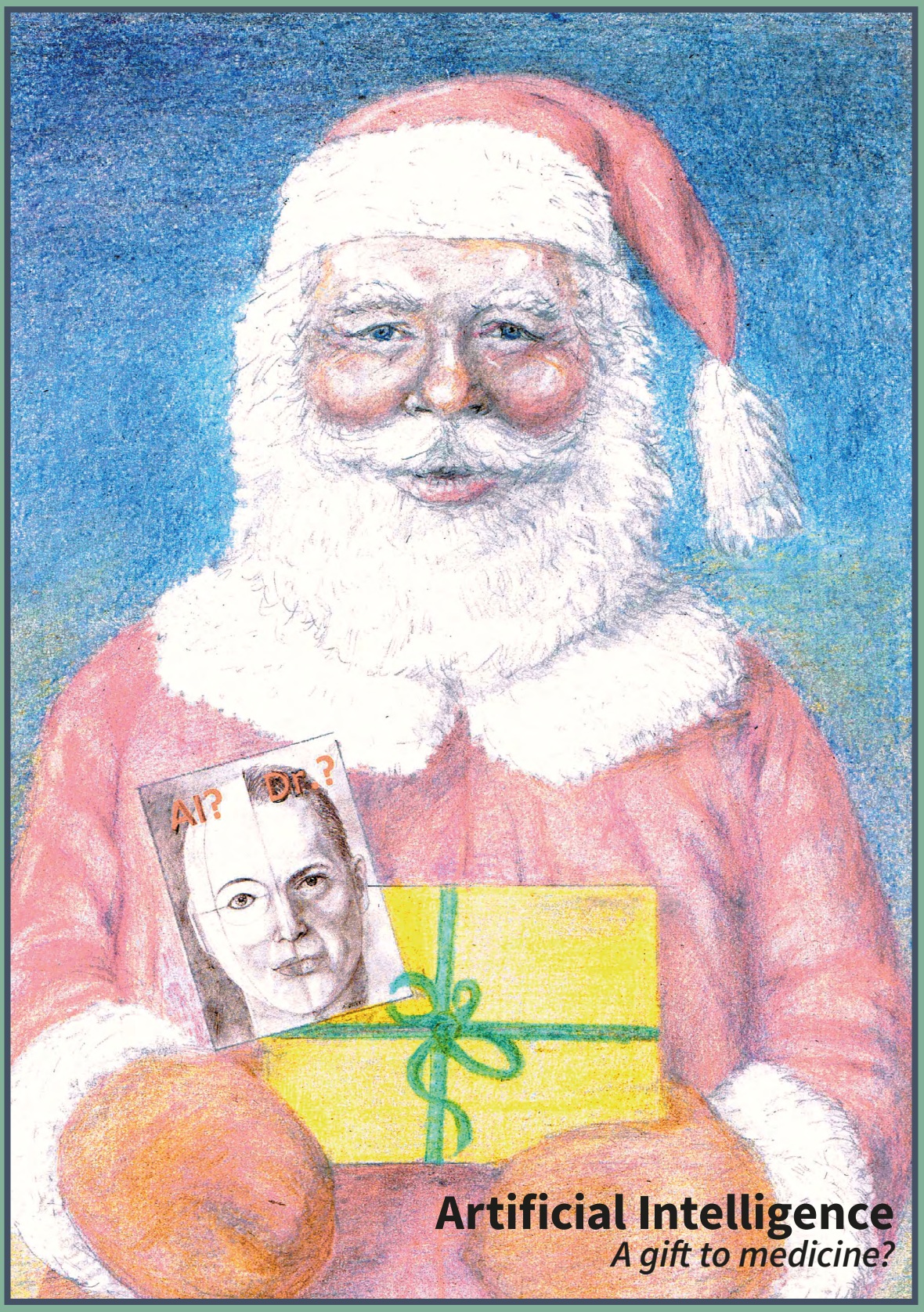
NO. 3 | DECEMBER 2022 | YEAR NO. 42

# OFTALMOLOG




## Artificial Intelligence

*A gift to medicine?*

EDITORIAL

Dear Colleagues,


*Tor P. Utheim*

We start off this issue with the *Oftalmolog* Outstanding Nordic PhD Awards. These awards highlight the important work performed by emerging scientists in ophthalmology. As last year, we determined the winners based on the total CiteScore of the papers published in their theses, described further on page 4.

We congratulate Ingemar Gustafsson from Sweden for winning first place, Marius Dalby from Norway who received second place, and Dýrleif Pétursdóttir from Iceland/Sweden who won the third place. We welcome anyone who defended their thesis in 2022 to reach out to us by October 1, 2023, to be included in the upcoming 2023 issues and be considered for the next PhD awards. The Editorial Board would also like to thank Atle Østern for making another great cover page.

In this issue, we present the highlights of five recent theses, covering topics that range from using new methods to see the unseen during surgery to helping children see clearly without glasses. We are pleased to present our latest series, *Oftalmolog's* Portrait of Excellence. Sten Kjellström, the new CEO of St. Erik Eye Hospital in Stockholm, is the first in the spotlight. Learn more about his vision for the hospital and how he became an accidental leader in the full interview on page 16. Nominations for future candidates are most welcome.

The article "Advances in Glaucoma Surgery" is a joint mini-review involving clinicians and scientists from each of the Nordic countries, discussing new technologies. Glaucoma is also among the topics in our special issue: "Extending What is Humanly Possible." In that issue, we have great contributions from the eye departments of Linköping University, Oslo University Hospital, and Harvard Medical School. Optical aberrations, adaptive optics, and neuroadaptation are explored in the article by Professor Jesper Hjortdal and Anders Gyldenkerne. They discuss how adaptive optics can be used to assess how the brain is accustomed to the eyes' imperfect optics after refractive surgery.

Finally, we present great memories from the very well-organized 2022 Nordic Congress of Ophthalmology in Reykjavik, Iceland, and highlight the upcoming European Society of Ophthalmology which will be in Prague from June 15-17, 2023.

We will consider all manuscripts submitted to *Oftalmolog* by April 1, 2023, for publication in our next issue. Please do not hesitate to reach out to us in case of any questions. All articles published throughout 2023 are eligible for *Oftalmolog*'s 2023 Best Paper Awards. The winners of the 2022 Best Paper Awards will be announced in the upcoming issue.

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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MANUSCRIPTS:

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Spring 2023

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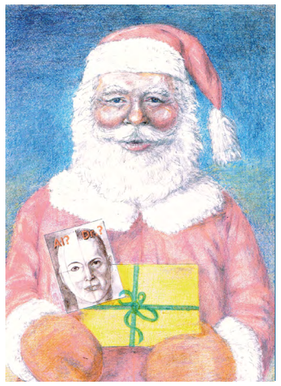
COVER:



This beautiful holiday cover was created by Atle Østern: doctor, writer, and artist. The inspiration was to highlight the dichotomy of the tools now available to us, such as AI. As there are more and more advances in technology, our capabilities continue to expand. With the promise of these developments, what more can we achieve and what unknown challenges await? This topic is discussed more in depth in the special issue, which explores the limits of human capabilities and how different types of technologies are allowing us to go further.

Both the cover art, as well as his article on supernormal vision in the Special Issue, were created while staying on the farm in Figure 4 on page 7 of the Special Issue.



Dissertations FROM THE NORDIC REGION

# Meet the 2021 nominees

## In previous issues

**Josephine Prener**
University of Oslo, Norway
*Rewriting the story of inherited retinal disease in Norway*

**Elma Jelin**
University of Oslo, Norway
*Patient Reported Outcome Measures in Treatment of Neovascular Age-related Macular Degeneration*

**Bjørn Gjerdrum**
University of South-Eastern Norway (USN)
*Improvement in refractive precision for intraocular lens power calculations in patients with a history of laser vision correction for myopia*

**Jesper Høiberg Erichsen**
Rigshospitalet-Glostrup, Denmark
*Optimizing Anti-inflammatory Prophylaxis in Cataract Surgery*

**Mads Forslund Jacobsen**
Rigshospitalet-Glostrup, Denmark
*Seeing into the future: Virtual-reality to ensure technical competence in cataract surgery*

**Ingemar Gustafsson**
Lund University, Sweden
*The Assessment of Disease Progression in Keratoconus and Corneal Crosslinking in Thin Corneae*

**Anders Gyldenkerne**
Aarhus University, Denmark
*The quality of vision following small-incision lenticule extraction for myopia*

**Marius Dalby**
University of Oslo, Norway
*Never too late? Reflections on outcomes of intraocular lens dislocation surgery*

**Andreas Viberg**
Umeå University, Sweden
*Fuchs' endothelial corneal dystrophy —Genetic etiology and as a risk factor in cataract surgery*

**Ayyad Zartasht Khan**
University of Oslo, Norway
*Culture and Storage of Retinal Pigment Epithelial Cells for Regenerative Medicine Purposes and the Use of Sericin to Improve Graft Quality*

**Moug Al-Bakri**
University of Copenhagen, Denmark
*Childhood cataract: effects on health and life*

**Dýrleif Pétursdóttir**
Uppsala University, Sweden
*Ophthalmological follow-up in young adults born premature and screened for retinopathy of prematurity*

# Outstanding Nordic PhD Awards 2021


## In this issue

**Trine Møldrup Jakobsen**
University of Southern Denmark
*Orthokeratology Lenses for Myopia Control in Scandinavian Children: A randomised 18-month clinical trial*

**Elin Bohman**
Karolinska Institute, Sweden
*Epiphora – Impact on vision, outcome of lacrimal surgery and investigations with ultra-high-frequency ultrasound*

We are very grateful to our generous sponsor, **Santen**, which provides the funding for the Outstanding Nordic PhD Awards. With their support, we are able to highlight some of the brightest minds and young leaders in their disciplines.



More information on the award can be found on our website, www.oftalmolog.com.

# The perspective of the Editorial Board

### Criteria

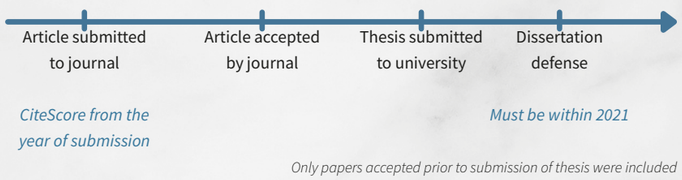
All dissertations defended in the Nordic region between January 1 and December 31, 2021, were eligible for nomination for the 2021 Outstanding PhD Awards. Nominations had to be submitted to *Oftalmolog* before August 1, 2021. Nominations were accepted from anyone.

We have decided to use the sum total of the CiteScores for each article included in the thesis. Review articles were excluded from the calculations. Although literature reviews are also valuable, not all universities accept these as thesis components. Additionally, journals solely focused on reviews generally have a higher CiteScore due to the nature of their content. Thus, by excluding reviews, we aimed to make comparisons fairer. Furthermore, correspondence letters were excluded.

All papers accepted for publication by a journal prior to the submission of the thesis to the university were included in the calculation. Manuscripts included in the thesis that were not accepted by a journal at the time of thesis submission were not included in the total CiteScore.

The CiteScore for each included article was determined based on the year the individual article was submitted to the given journal. For example, if a manuscript was submitted in 2018, the 2018 CiteScore was used, even if the paper was not published until 2019.

**Timeline for articles eligible for consideration for the Outstanding PhD Award**




### What is a CiteScore?

CiteScore is one of many metrics used to evaluate the impact of a journal. It was developed by Scopus, a subsidiary of Elsevier. Elsevier has created many metrics and databases, which can be useful for evaluating the quality of scientific publications.

The main benefits of using CiteScore include (1) it is stable and robust as it takes into account the citations over the past four years, which is important when comparing these with articles published in different years and (2) most publications are indexed in Scopus. More information and all CiteScores can be found at https://www.scopus.com/sources.

https://www.scopus.com/sources

## Deadline for nominations for 2022:

October 1, 2023

More information on the award can be found on our website, www.oftalmolog.com.

# Dissertations
FROM THE NORDIC REGION

2021 AWARD WINNER

## First place: **NOK 80,000**

Total CiteScore: 19.2

**Let's detect progressive keratoconus correctly**

*Ingemar Gustafsson*
*Department of Clinical Sciences, Lund University, Sweden*

2021 AWARD WINNER

## Second place: **NOK 30,000**

Total CiteScore: 16.4

**Never too late?** Reflections on outcomes of intraocular lens dislocation surgery

*Marius Dalby, MD, PhD,*
*Department of Ophthalmology, Oslo University Hospital, University of Oslo*

2021 AWARD WINNER

## Third place: **NOK 15,000**

Total CiteScore: 15.8

**Taking a sneak peek:** Preterm birth and long-term vision

*Dýrleif Pétursdóttir*
*Department of Surgical Sciences, Uppsala University, Sweden*
*Department of Ophthalmology, Landspítali University Hospital and Sjónlag, Eye Center, Iceland*

The Outstanding PhD Awards are sponsored by **Santen**

# Seeing clearly without glasses:

## Orthokeratology lenses (OKL) reduce myopic progression in Danish children

*Trine Møldrup Jakobsen*
*Department of Regional Health Research, Faculty of Health Sciences, University of Southern Denmark*

*On March 12, 2021, Trine Møldrup Jakobsen defended her thesis, "Orthokeratology Lenses for Myopia Control in Scandinavian Children: A randomised 18-month clinical trial" at the Department of Regional Health Research, Faculty of Health Sciences, University of Southern Denmark. The PhD project was conducted at the Dept. of Ophthalmology, Vejle Hospital. Associate Professor Flemming Møller, Department of Ophthalmology, Vejle Hospital was the main supervisor, with co-supervisors Anders Peter Søndergaard, MD, PhD, Dept. of Ophthalmology, Vejle Hospital, and Professor Birgitte Nørgaard, Dept. of Public Health, University of Southern Denmark.*

**Key points:**

- Orthokeratology lenses reduced eye growth in myopic Danish children.
- The efficacy was similar for Danish children as for other ethnic populations.
- There were no treatment-requiring or sight-threatening adverse events during the 18 months follow-up period.

### Introduction

The prevalence of myopia (near-sightedness) is increasing worldwide, and rates over 90% have been reported in Asia. In Denmark, the prevalence of myopia has increased from 13% in 2007 to 25% in 2020. This increase is worrying because of the sight-threatening conditions associated with high degrees of myopia such as retinal detachment, macular atrophy, and macular neovascularization.

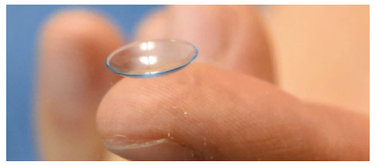


*Figure 1. Orthokeratology lenses are custom-fitted, rigid, gas-permeable contact lenses that are used every night during sleep. They induce a temporary flattening of the central cornea, thus reducing or eliminating the need for myopia correction after removal.*

### Methods

This 1:1 randomized controlled trial investigated the efficacy of myopia control and the safety of orthokeratology (ortho-k) lenses in Scandinavian children, with a control group using single-vision spectacles. The participants were 60 myopic, ethnically Danish children aged 6 to 12 years with myopia of 0.5 to 4.75 diopters spherical and up to 2.5 D regular astigmatism in both eyes. For secondary outcomes, we investigated the association between baseline relative peripheral refractive error and myopia progression in both groups, the change in relative peripheral refractive error in the ortho-k group and its association with treatment efficacy, and the correlation between cycloplegic spherical equivalent refractive error (SEQ) and axial growth to relate the results to clinical assessments for myopic patients.

### Results

Axial growth was significantly smaller in the ortho-k group compared to the single-vision spectacles group at all follow-up visits. No treatment-requiring or vision-threatening adverse events occurred during the study. The relative peripheral refractive error changed significantly from baseline to the 6-month follow-up in the ortho-k group. The baseline relative peripheral refractive error was not correlated to axial growth in either group. The initial change in relative peripheral refractive error was not correlated to the myopia control effect of the ortho-k lenses. In the single-vision spectacles group, the correlation between changes in SEQ and axial length at 12-month follow-up was 1 D = 0.55 mm for all participants, 0.60 mm for males, and 0.53mm for females. The correlation was higher in Danes compared to other ethnic groups.

### Conclusion

Ortho-k lenses effectively reduced the progression of myopia without adverse events. We found that ortho-k lenses induced relative peripheral myopic defocus, which may contribute to the altered axial elongation. However, neither the degree of relative peripheral refractive error change (ortho-k group) nor the baseline relative peripheral refractive error was associated with the myopic progression. Finally, we estimated the correlation between changes in SEQ and axial length, which can be used when monitoring myopic progression in Danish ortho-k patients in a clinical setting.

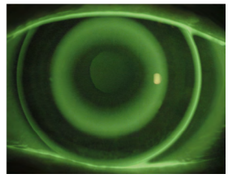


*Figure 2. The fit of an orthokeratology lens with fluorescein instilled*

**Remaining questions:**

- Can individual treatment efficacy be predicted by short term changes in choroidal thickness or higher order aberrations?
- Are spectacle lenses with peripheral defocus as efficient as orthokeratology lenses for myopia control?
- Can therapies be combined for an additive effect?

***References***

1. Jakobsen TM, et al. Control of myopia using orthokeratology lenses in Scandinavian children aged 6 to 12 years. Eighteen-month data from the Danish Randomized Study: Clinical study Of Near-sightedness; TReatment with Orthokeratology Lenses (CONTROL study). *Acta Ophthalmol*. 2022;100(2):175-182.
2. Jakobsen TM, et al. Peripheral refraction, relative peripheral refraction, and axial growth: 18-month data from the randomised study-Clinical study Of Near-sightedness; TReatment with Orthokeratology Lenses (CONTROL study). *Acta Ophthalmol*. 2022. doi: 10.1111/aos.15217.
3. Jakobsen TM, et al. Correlation between change in cycloplegic spherical equivalent refractive error and change in axial length in Danish children aged 6 to 12 year. *Acta Ophthalmol*. 202;99(7):e1249-e1250.

Photo: Johanna Hanno

*Elin Bohman*
*Karolinska Institutet, Department of Clinical Neuroscience, Division of Eye and Vision*

# Why is Grandma Crying?

## Epiphora — Impact on vision, outcomes of current treatments, and challenging paradigms

*On May 28, 2021, Elin Bohman defended her thesis, "Epiphora – Impact on vision, outcome of lacrimal surgery and investigations with ultra-high-frequency ultrasound" at Karolinska Institutet, Department of Clinical Neuroscience, Division of Eye and Vision. The main supervisor was Eva Dafgård Kopp, MD, PhD, with co-supervisor Maria Kugelberg, MD, PhD, both at Karolinska Institutet, Department of Clinical Neuroscience, Division of Eye and Vision.*

**Key points:**

- Epiphora *does* impact everyday life.
- Canaliculodacryocystoplasty is an inadequate treatment for obstructions below the lacrimal sac.
- Previous theories regarding the lacrimal sac pump may need to be revised.

Imagine trying to read the price tag in a store, but your eyes are so watery that it is almost impossible or writing while tears fall on the keyboard. You constantly feel that you are looking through a wet window. When you finally go to the doctor, they say, "Don't worry; your eyesight is perfect. You just have a watery eye." Epiphora is a common condition, mainly affecting women over 60, that often receives little attention. Excessive tears create an irregular and ever-changing tear film, affecting refraction and reducing vision. However, in a standard test situation, the visual acuity is seldom affected, leading to the misinterpretation that epiphora is a minor problem. Patients report social discomfort as a result of red eyes and constant eye wiping, and the misperception that they are sad or crying.

This thesis aimed to quantify the functional visual disability experienced by patients with epiphora, survey current management practices, and present the long-term outcome of two lacrimal drainage procedures. In addition, a novel imaging technique, ultra-high-frequency ultrasound, was used to visualize the upper lacrimal drainage anatomy and the lacrimal pump. Limitations on activities in daily life due to visual disability have long been recorded in the Swedish National Cataract Register and were used as an outcome measure. The Catquest-9SF questionnaire was validated for epiphora patients, and their visual disability was found to be on par with those of patients awaiting cataract surgery in their second eye.

We surveyed the current management practices in the Nordic countries regarding acquired lacrimal drainage obstruction. The results indicated that canaliculodacryocystoplasty (probing and silicone stent intubation) is used when treating obstructions below the lacrimal sac, a practice less common elsewhere. However, we found that approximately half of patients with multiple obstructions or nasolacrimal duct obstructions treated with canaliculodacryocystoplasty required additional surgery due to a recurrence of the obstruction. This proportion was significantly higher than when stenosis was confined to the canaliculi.

There is no consensus regarding the use of silicone stent intubation in conjunction with dacryocystorhinostomy. The duration of intubation has received little attention as a factor impacting outcomes. A 97% long-term success rate was found with a comparatively short intubation duration of one week. There may be an optimal duration of intubation with which the possible positive effects are achieved while the negative effects are minimized. Ultra-high-frequency ultrasound and motion tracking demonstrated that the motion of the lateral lacrimal sac wall was greatest in the anterior-posterior direction during blinking. This contrasts with an existing theory regarding the mechanics of the lacrimal pump.

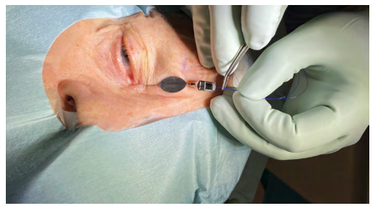


*Figure 1. In Canaliculodacryocystoplasty, the lacrimal drainage obstruction is bypassed with a probe and the system is intubated with a silicone stent.*

In conclusion, epiphora should be recognized as a debilitating condition affecting everyday life, and that the use of canaliculodacryocystoplasty to treat obstructions in the nasolacrimal duct should be reconsidered in the Nordic countries, as it may be an inadequate form of treatment. Furthermore, a very high success rate is possible with a short duration of intubation in dacryocystorhinostomy. Finally, the current theory regarding the lacrimal pump should be re-evaluated.

**Remaining questions:**

- Further studies should investigate the effects of intubation duration in conjunction with dacryocystorhinostomy.
- Increased knowledge of the mechanism of active tear drainage could lead to improved treatments.
- Solving the mystery of primary nasolacrimal duct obstruction pathogenesis may provide us with targets for future treatments that inhibit stenosis formation altogether.

*References*

1. Bohman E, et al. A comparison between patients with epiphora and cataract of the activity limitations they experience in daily life due to their visual disability. *Acta Ophthalmol.* 2018; 96: 77-80
2. Bohman E, et al. The first large pan-Nordic survey of the management of acquired lacrimal drainage obstruction in adults. *J Clin Exp Ophthalmol.* 2019; 10: 793
3. Bohman E, et al. Long-term outcome of lacrimal stent intubation for complete acquired lacrimal drainage obstructions. *Acta Ophthalmol.* 2020; 98: 396-99
4. Bohman E, et al. One-week intubation in external dacryocystorhinostomy - a report on long-term outcome. *Orbit.* 2021;40(4):287-291.
5. Bohman E, et al. Novel evidence concerning lacrimal sac movement using ultra-high-frequency ultrasound examination of lacrimal drainage systems. *Ophthalmic Plast Reconstr Surg.* 2021;37(4):334-340.



# Optical aberrations, adaptive optics, and neuroadaptation:

## How adaptive optics can be used to assess how the brain is accustomed to the eyes' imperfect optics after refractive surgery



*Jesper Hjortdal*
*Department of Ophthalmology, Aarhus University Hospital*



*Anders Gyldenkerne*
*Department of Ophthalmology, Aarhus University Hospital*

### Introduction

Vision is composed of two steps: (1) the formation of a high-quality image at the retina and (2) transmission and processing of the image in the visual pathways. It is the latter of which determines what we actually "see." The quality of the image projected onto the retina is determined by four distinct factors[1]: diffraction, scatter, chromatic aberrations, and wavefront aberrations (i.e., optical imperfections = refractive errors). For the vast majority of people, wavefront aberrations are what determine the optical quality of the retinal image.

Wavefront aberrations can be divided into lower-order aberrations (LOAs;; i.e., spherical defocus and astigmatism) and higher-order aberrations (HOAs), as seen in **Figures 1 and 2**. LOAs can be corrected with spectacles, contact lenses, or refractive surgery, whereas special methods such as corneal rigid gas-permeable contact lenses and wavefront-guided or optimized excimer laser surgery can be used to minimize the effect of HOAs.[2,3] However, adaptive optics are needed to fully correct HOAs and determine their influence.

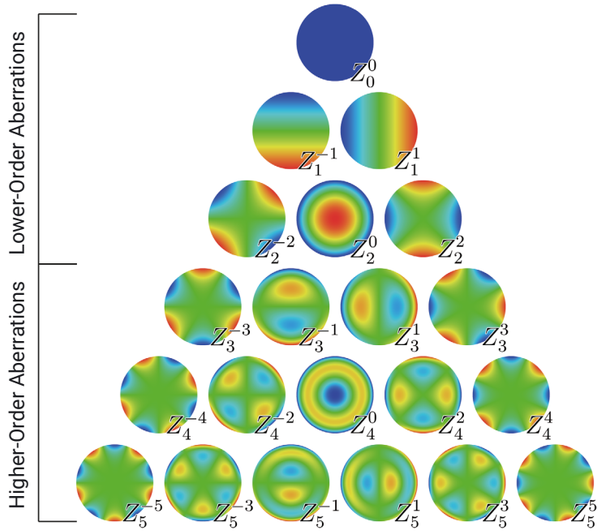



*Figure 1. The Zernike Polynomials. Orders 0-2 are known as lower-order aberrations, with the 2nd order containing spherical defocus and astigmatism (which can be corrected with spectacles/glasses etc.); 3rd order and above represent higher-order aberrations (HOAs) that cannot be corrected by traditional means (but can be corrected using adaptive optics). HOAs are induced by some corneal diseases and following corneal refractive surgery. (By Zom-B at en.wikipedia, CC BY 3.0 https://creativecommons.org/licenses/by/3.0, via Wikimedia Commons, modified by Emily Moschowits)*

### How aberrations affect our vision

The "perfect" optical system only exists in theory. In practice, all optical systems have aberrations to some extent. The most important contributors to the wavefront aberration are the LOAs (i.e., sphere and cylinder). However, HOAs can also affect vision but cannot be corrected by traditional

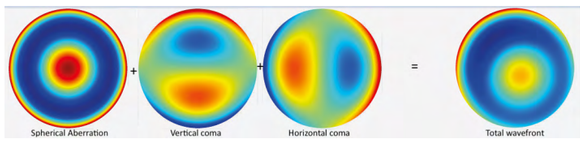



*Figure 2. The total wavefront can be decomposed into the distinct Zernike polynomials, and the addition of each component yields the total wavefront. Shown here is how spherical aberration (4th order HOA), and vertical/horizontal coma (3rd order) combine to yield a wavefront to the right that distorts vision. (Screenshot of VAO user interface. Used with permission from Voptica SL).*

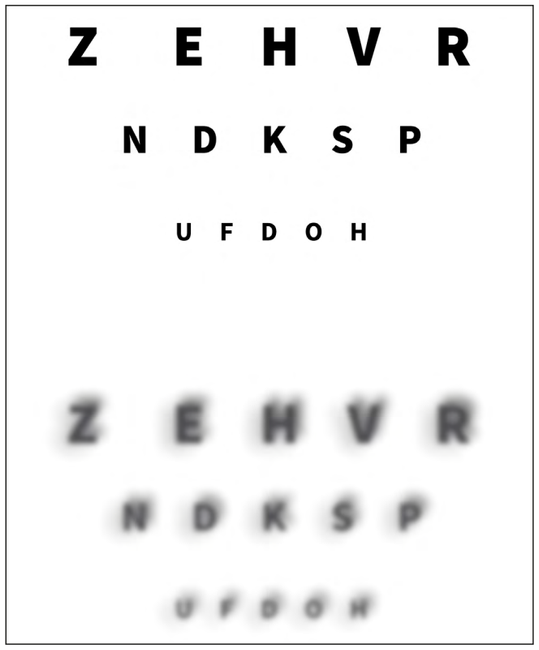



*Figure 3. Schematic showing how HOAs can distort vision; importantly, a patient can have 20/20 vision but still complain of "bad vision". However, the retinal image generated by the optics does not represent what the patient "sees" – the image is translated and converted by the visual pathways, and new distortions in the optics can be rectified by the brain through neuroadaptation (image produced by the author).*

means.

For most people, HOAs do not play a significant role in deteriorating vision, and standard methods of correcting the refractive error (such as glasses and contact lenses) are sufficient for obtaining good vision. However, some eyes have increased HOAs due to a variety of conditions, including keratoconus, cataract, and corneal refractive surgery. The most recent corneal refractive surgery technique, small-incision lenticule extraction (SMILE), has been shown to induce HOAs to a lesser extent than other types of corneal refractive surgery.[3–5] However, the problem of induced HOAs following refractive surgery remains. Research has shown that an increase in HOAs (particularly spherical aberration and coma) can cause visually bothersome symptoms, as shown in **Figure 3**.

It is possible to rather accurately predict how visual acuity diminishes due to uncorrected sphere and astigmatism,[6] but the situation is different with HOAs. Some HOAs deteriorate vision more than others, and HOAs further interact with one another. This means that an increase in a particular aberration can sometimes decrease or increase visual quality, depending on the level of other HOAs.[2] To complicate things further, research has shown that the human brain is to some degree accustomed to how our eyes see the world—and can adjust to new optical aberrations introduced by diseases, surgery, or optical corrections. This is called neuroadaptation.

## Neuroadaptation: how the brain interprets the optical image

As mentioned, "seeing" has two steps: (1) the creation of a high-quality image on the retina through the eye's optics and (2) transmission and ultimately processing of this image through the visual pathways. The second element is key in what is known as "neuroadaptation," the brain's plasticity as to how to process visual stimuli. This is a well-known phenomenon of the brain in general, used in, for example in the rehabilitation of patients who have had a stroke. Training can help patients recover lost skills through the adaption of non-affected, healthy parts of the brain. The same principle applies to the visual system. Well-known examples from the clinic are include "getting used to" bifocal glasses or a new astigmatism correction or after the implantation of multifocal intraocular lenses. Hence, "neuroadaptation" refers to how our brain can adapt to new visual stimuli in response to the altered composition of the image imposed on the retina.

Interestingly, our eyes are optically flawed by default. In fact, our eyes are actually poor in an optical sense. As Helmholtz famously remarked in the 1870s concerning the optics of the human eye:[7]

*"Now, it is not too much to say that if an optician wanted to sell me an instrument which had all these defects, I should think myself quite justified in blaming his carelessness in the strongest terms and giving him back his instrument."*

However, research has shown that our neural visual system is quite accustomed to our eyes' aberrations, meaning that some of the inherent blur in the image projected to the retina is "filtered out" by the visual system.[8] This is particularly important in the context of refractive surgery, where the optics of the eye are changed radically by intentionally decreasing LOAs but simultaneously inducing HOAs to some extent, thus projecting a different image to the retina than before surgery. The speed at which neuroadaptation occurs seems to vary somewhat depending on both the optical change and the individual, with examples ranging from very quick adaptations in the context of optical illusions[9] to adaptations following LASIK or multifocal intraocular lens (IOL) implantation that can continue for weeks, months, or, unfortunately for some patients, never occur.[10,11]

How to study the effect of neuroadaptation in the clinic? For this to be properly done, one needs a system able to record, and manipulate, the optics of the eye and then assess the psychophysical response of the observer. Luckily, this can be done—through the use of adaptive optics.


*Figure 4. The visual adaptive optics analyzer (VAO) developed by Voptica SL, Murcia, Spain, (https://voptica.com/vao/). The patient seated to the left is looking through an aperture in the device at images controlled by the operator to the right; the operator can record and manipulate all aberrations through adaptive optics. Used with permission from Voptica SL.*





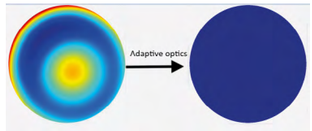



*Figure 5. The total wavefront to the left is corrected by the adaptive optics system of the VAO to the right – the wavefront generated is "flat", i.e. no distortions of the optics occur. Used with permission from Voptica SL.*

## Adaptive optics

An adaptive optics system is an optical system that can measure the wavefront aberration and alter it, usually through deformable mirrors.[12] Adaptive optics are used in space telescopes (for example, to better see distant galaxies), to obtain retinal images down to individual photoreceptors, and in vision science to correct all optical aberrations (including HOAs) that affect light going into the eye.[8,12–14] The use of adaptive optics has shown that by correcting all the eye's aberrations, obtaining superhuman visual acuity is possible, only limited by the cone mosaic and neural factors.[13,15]

Normally, adaptive optics systems are massive, highly sophisticated systems built on optical benches in vision science laboratories.[14] Recently, however, a commercially available adaptive optics device called the VAO (Voptica SL, Murcia, Spain, https://voptica.com/vao/) has been introduced for commercial use. Shown in **Figure 4**, this device can be employed in a clinical setting and was purchased a few years ago for research purposes at the Department of Ophthalmology, Aarhus University Hospital, Denmark. The device records aberrations through a Hartmann–Schack sensor and corrects aberrations (including HOAs) through a liquid crystal on a silicon spatial light modulator through a 4.5-mm pupil size.[16] The device can record the wavefront aberration of a patient's eye and subsequently perform visual testing with ETDRS letters, while the examiner can manipulate all of the patient's aberrations (both LOAs and HOAs) at will. Hence, both inducing and correcting all aberrations is possible if one so desires (**Figure 5**).

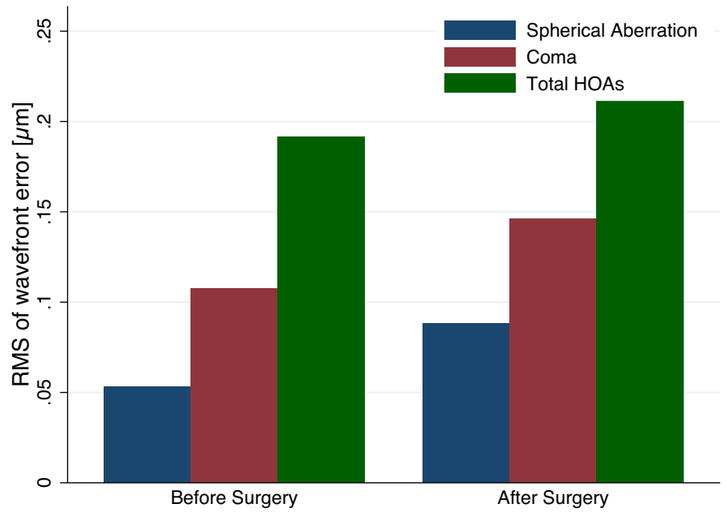



*Figure 6. Bar graph showing that individual and total HOAs increased following small-incision lenticule extraction for myopia as expected.*

## Correcting HOAs induced after SMILE: what's the gain?

We conducted a study on 51 patients successfully operated with SMILE for myopia in our department. The purpose was to examine how surgically induced HOAs affect visual acuity and how neuroadaptation may ameliorate their effect. Measurements were performed before and 3 months after surgery. We used the VAO to examine the visual acuity (1) with no HOA corrected, (2) with all HOAs corrected, and (3) at the 3-month postoperative visit, with the HOA set to the same level as the patients had before surgery, i.e., their "original" level of HOA.

The results are shown in **Figures 6 and 7**. As can be seen in **Figure 6**, all HOAs increased following surgery, as expected. However, as shown in **Figure 7**, the best visual acuity was in fact always achieved when HOAs were not corrected (both before and after surgery). Furthermore, the induction of preoperative HOAs after surgery (simulating the "original" level of HOA) also did not improve the visual acuity compared to that achieved with the "new" set of HOAs.

One might wonder whether these results were so because the machine did not correct HOAs properly; if so, one might expect that the higher the level of HOAs attempted to be corrected for a given patient, the larger the difference in visual acuity between the corrected and uncorrected state of HOAs. However, this was not the case (data not shown).

## The effect of HOAs and neuroadaptation on vision

Our results that short-term HOA correction did not, on average, improve the visual acuity conflicts with previous reports that HOA correction should always improve visual acuity.[13] However, we believe that neuroadaptation likely represents the reason for this: reports have shown that we are all accustomed to our "own" HOAs.[8,17] Furthermore, research on highly aberrated, keratoconic eyes has shown that the visual benefit of correcting HOAs is less than what would be expected but that training with the same HOA correction over time improves the visual function (due to neuroadaptation).[18] Thus, the reason for our results could likely be that the patients had adapted to their "new" set of HOAs induced by the SMILE procedure and that the manipulation of

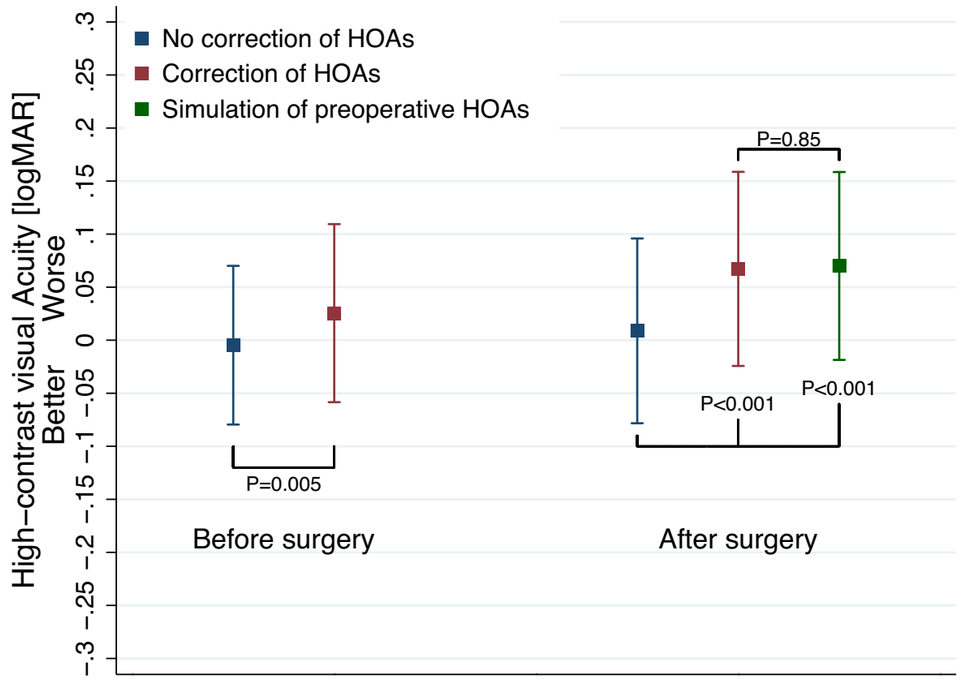



*Figure 7. Comparison of visual acuity recorded with the VAO; data shown as mean ± standard deviation. Before surgery, there was a significant deterioration of visual acuity when attempting to correct all HOAs. After surgery, the visual acuity was significantly worse with both all HOAs corrected and preoperative HOAs simulated as compared to no correction attempted. There was no difference between simulated preoperative HOAs and correction of all HOAs. (Postoperative data corrected for magnification gain in visual acuity).*

HOAs through the VAO did more harm than benefit. The induction of HOAs after SMILE is much less than what was seen after refractive surgery in the early 2000s;[3] perhaps the results would have been different if the eyes examined had been more aberrated (e.g., eyes with keratoconus). However, more studies on the matter would be preferable before any definite conclusions can be made.

## Future aspects of the clinical use of adaptive optics

Adaptive optics offers an exciting means of determining how aberrations affect our vision. It has already been used to predict how IOLs affect postsurgical vision before the surgery has been performed, as well as how presbyopia can best be managed by inducing spherical aberration.[19,20] However, as also seen with our results, adaptive optics used in a clinical setting can help establish to what extent even trying to correct all HOAs is of benefit. Research has shown that correcting all aberrations in fact makes our vision much more susceptible to small amounts of defocus (i.e., our normal set of HOAs "blends out" the effect of beginning presbyopia, for example).[12] Thus, it seems that trying to correct all HOAs does not improve functional visual quality. Rather, our optical interventions (e.g., refractive surgery, spectacles, contact lenses) should probably aim for the normalization of refractive errors. Future research will tell!

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# In the spotlight

## Sten Kjellström— the new CEO of St. Erik Eye Hospital

Photo: Danish Saroee

*For the new Portrait of Excellence series in* Oftalmolog, *we want to shine the spotlight on some of the greatest in the field. This series allows us to not only provide perspective on their outstanding work and contributions to shaping the future of ophthalmology, but also to provide insights into how they came to the position they are in today. We want to create a platform for them to share what they have learned throughout their careers and to provide advice for those who are just starting out.*

*In October, Tor Paaske Utheim sat down (virtually) with the new CEO of St. Erik Eye Hospital in Sweden. Since Kjellström was a resident in Kalmar, Sweden, he has done research at the NIH, ran departments that employed hundreds of people, and recently has begun his new role, heading one of the leading eye hospitals in Europe. During their candid conversation, Kjellström discusses his view on the future of the hospital, describes what it is like having such an important leadership role in the community, and opens up about how he recharges his batteries.*

### What are you most excited about for your new role as the CEO of St. Erik Eye Hospital?

It is a dream to have an entire hospital dedicated to ophthalmology and eye patients. To have everyone, from the IT department and HR to engineering, care so deeply about these eye patients and work together to make sure that we can treat our patients the best now and in the future is what excites me most about joining St. Erik Eye Hospital.

### What does a typical day look like as the CEO of this large eye hospital?

Every day is different. It's a big organization, but with a specialized focus. I work on both high theoretical level as well as on the ground practice. Sometimes I'm meeting with individual staff, some days I'm discussing St. Erik Eye Hospital's specialized responsibilities with politicians, and others I'm conversing with the industry on how we can advance therapies. Sometimes I'm talking to private clinics about how we can collaborate for our patients. But one thing is always the same, it's always for the patient's good. For every meeting that we have with politicians, with the staff, I think, "how can we advance so that our patients can get better treatment?" That is the one thing that stays the same. Everything else varies.

### What are your visions for St. Erik Eye Hospital regarding eye care, research, and innovation?

In general, I want to see St. Erik Eye Hospital as a positive force for ophthalmology in the Nordics. I see us as a hub for collaboration, bringing together world-leading expertise from across the Nordics for the benefit of patients. But it isn't the hospital or the location or the history; it is the staff here, how much they care about the patients, and how we work together with others that makes the hospital great. Connecting our staff to colleagues in Norway, Finland, Iceland, and Denmark to share knowledge means that together we can ensure the best care for the patient.

At the same time, it's crucial that we build a dynamic ecosystem within St. Erik Eye Hospital. We have a whole floor dedicated to research and innovation and a close collaboration with Karolinska Institutet. We have a corneal biobank, two labs for pre-clinical research, and a clinical pathology research lab as well. One of the success stories of this environment is Lexplore, a start-up that uses artificial intelligence to help diagnose dyslexia by tracking eye movements.

Our research environment also attracts leading industry partners to collaborate with us by sharing infrastructure and developing novel treatments. We are working to develop new frameworks to make this kind of collaboration easier for our clinicians and researchers. Having pre-clinical, clinical and industrial perspectives under one roof makes St. Erik Eye Hospital an exciting place to work at and drives innovation. My vision is to strengthen the connections between these partners. Professor Stefan Seregard, our Head of Research & Innovation, will be leading this important work. It's a huge priority, because we won't be able to take care of our patients in the future if we just continue to do what we do today.





*Family photo, Dangar Island, 1972, Sten is the one to the right (Photo: private)*

**Sten Kjellström**

***Service Positions***

- Swedish National knowledge-based healthcare organization–NPO Ögonsjukvård, *Board Member: 2018-2022*
- Swedish Ophthalmological Society, *President: 2018-2020, Vice President: 2016-2018*
- Swedish Retina Society, *Board Member: 2014-present*
- Swedish Ophthalmological Society, *Scientific Secretary: 2014-2016, Board Member: 2014-present*

***Education***

- Leadership Development Program, European Society of Ophthalmology, *2015-2017*
- PhD, Lund University & National Institute of Health, *2010*
- MD, Lund University, *1999*
- Electrical Engineering, Lars Kaggskolan, *1988*

### How do you refresh your batteries with such a demanding job?

You might not believe it, but I am very much an introvert. I charge my batteries when I'm "introverting," looking inside, reading a book, and so on. I love my job. I love talking to people. But generally, I prefer talking to people one-on-one or one-to-few, rather than big town hall meetings. When it comes to this kind of connection and conversation, I go from a little bit of an introvert to maybe about half an extrovert — I get energy from a good dialogue. I'd say good conversation brings so much to my life. Outside work, going to the gym is super important for me. Focusing on exercising gives me some peace. We also have a small house in the archipelago. I just sit there, on my little island, on my little blue bench, looking out. It's beautiful.


*Ämtö, Sten's summer place on an island on the east coast, where he recharges his batteries (Photo: private)*

*Climbing in Italy, Val Masino (Photo: private)*

### What are the most important lessons you have learned in your career so far? What advice would you give to a new doctor or researcher early in their career?

I would say, be humble, never assume that you know all the answers, and always stay curious. Don't underestimate the importance of good communication — it's probably the most important tool that we have. As a doctor or a researcher, we are always working with a team. Good communication lets us combine our colleagues' knowledge, experiences and perspectives to really make an impact.

I remember how overwhelming it was to get started in the research world. I think it's important for new researchers to stay curious and not get discouraged by the procedural elements. I would also tell new researchers not to underestimate the importance of communicating your research — not just to other experts in the field, but to anyone.

And then when it comes to new doctors, I would say, remember that every patient is an individual, even if it may be hard when we see 20 or 30 patients with macular degeneration per day. For each patient, before you go in the room, stand behind the door, take a deep breath and say, "now I'm going to meet So-and-So," and see every single one as a new patient. It's not just another AMD. It's a new patient. I believe most doctors think like this, but it's important not to forget. It is easy to get tired, but then you need to just take a step back and focus on the individual.

### How did you become a leader in the field and how have past leadership roles prepared you for your current position?

I am an accidental leader, even if my professional and personal life has in the end prepared me for this role. It started with a political decision on consolidating ophthalmology to only one location in Skåne. It probably wasn't the most thought through decision. Our bosses quit and there was a lot of uproar among my colleagues, but then I thought, "this is not the time to lay down. Who's going to stand up for the patient? We really need to stand up, not to fight for our rights, but for the patient's rights." I was asked by the division head to step up as temporary head of the clinic.

From there, I ended up with 650 employees, and I oversaw four different specialties. But, as I'm an ophthalmologist by training, I must admit that ophthalmology was the one closest to my heart. I was so happy with my job down in Skåne that I initially didn't apply for the job at St. Erik Eye Hospital. Again, I became an accidental leader here, but I know that I made the right decision. The work is very important and close to my heart.

Throughout my leadership journey, it has been so rewarding to see how my colleagues evolve. Seeing them grow and take on new responsibilities and challenges is always inspiring.

### What do you see as the biggest opportunities and challenges in the field of ophthalmology in the coming years?

The biggest challenge in the coming years is demographic change. We can expect demand for eye care to rise in the future as the population ages. At the same time, we expect that our workforce will decline as people retire and leave the labor market. That's a big challenge for us and for all of society. The big opportunity is technology. Think about the time before OCT. I mean, nobody really remembers that time—it was certainly a different era. And now we are seeing new opportunities opened up by artificial intelligence. But I think we actually have something that is just as important and that is PI: patient intelligence. New technologies will increasingly transform patients into active partners. Nowadays, things that were once only done by highly trained professionals in hospitals, such as monitoring of eye pressure, can be done by patients in their own home. Engaging our patients as partners in our work in this way has huge potential.

***St. Erik Eye Hospital***

- A leading eye hospital in Europe with a concentration of specialized eye care
- The most comprehensive ophthalmic and vision research institution in Sweden in close collaboration with Karolinska Institutet
- Owned by Region Stockholm
- Founded in 1990

**"I think we actually have something that is just as important [as AI] and that is PI: patient intelligence."**

***Get to know Sten Kjellström:***

I was born in Australia, Manly Hospital, 1969, and grew up on Dangar Island just outside Sydney until first grade. I then moved with my mother and three brothers to Kalmar, Sweden, where I later studied engineering. After enlisting in the Navy as an engineer for 15 months, I worked as a medical engineer at the hospital in Kalmar for a few years. I then studied medicine at Lund University, Sweden, before returning for an internship to the hospital in Kalmar. After medical school and internship, I got my first glimpse into the wonderful world of ophthalmology in Kalmar and later continued with my residency in Lund. Through my research, I got the chance to work at National Institutes of Health (NIH), 5 years on-site in Bethesda, Maryland, as a visiting fellow, and 4 years commuting back and forth as a Consultant Research Fellow. My dissertation research was conducted both at the NIH and Lund University on the topic of ocular gene therapy.


Photo: St. Erik Eye Hospital

### What do you consider most important when you are building a team?

Being open-minded and able to see the bigger picture are important characteristics. I try to understand how applicants see the world. I look for people who put patients first and ask, "how can I make the whole system better for the patient?" and not "what's in it for me?" It's important that they believe that we can work together toward a better future. Collectively, contributing to a positive work culture is the responsibility of every employee. I look for people who support their colleagues and patients to build community. Communication, collaboration, and self-reflection are keys to creating a good team.





***Key figures for St. Erik Eye Hospital (2021)***

- 8,500 operations (6,300 ambulatory operations)
- 150,000 outpatient visits
- 1,300 inpatient visits
- 24,000 emergency visits
- 16 inpatient care beds
- 15 day surgery beds
- 12 operating theaters


Photo: Jens Sølvberg

***Human resources at St. Erik Eye Hospital (2021)***

**440 employees**

- 73 specialists
- 33 residents, fellows
- 115 nurses
- 9 orthoptists
- 29 master opticians
- 71 assistant nurses
- 59 secretary and technical support
- 53 administration and others

***Research at St. Erik Eye Hospital***

- 35 employees are active in clinical research, of which two are professors at Karolinska Institutet
- 35-40 scientific publications yearly
- 6 research groups
- High degree of external funding
- Part of northern Europe's largest Life science cluster
- Strong collaboration between healthcare, academy and industry

Photo: Jens Sølvberg

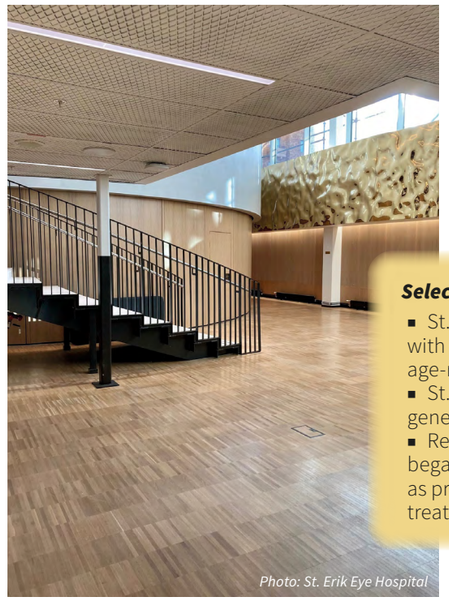

Photo: St. Erik Eye Hospital

***Selection of clinical trials at St. Erik Eye Hospital***

- St. Erik Eye Hospital is a sponsor of a phase 1 study being conducted together with NovoNordisk and Karolinska Institutet regarding a potential treatment of age-related changes in the macula. The study is funded by NovoNordisk.
- St. Erik Eye Hospital is conducting a phase 1 study on behalf of Novartis for a gene therapy for a variant of retinitis pigmentosa.
- Researchers at Umeå University, Karolinska Institutet and St. Erik Eye Hospital began a larger clinical study in the spring of 2022 on vitamin B3 (nicotinamide) as protection for the optic nerve. In the long run, the trials may result in a new treatment method for glaucoma

# Focus on Medical Retina- Treatment Recommendations From the Medical Retina Club and the 2021 Annual Report from the Swedish Macula Registry

**The Swedish Macular Registry[1] (SMR) has recently published the annual report for 2021. When registry keeper Inger Westborg looks back on Covid-impacted years, she can ascertain that the coverage rate regarding wet macular degeneration (AMD) remains very high and that registrations in the two new modules for diabetic retinopathy and retinal vein occlusions (thrombosis) have also gained momentum during this period. Everything indicates that Swedish eye care handled the challenging pandemic years well, largely owed to the rapid implementation of clear guidelines; patients with active treatment were prioritized, while the number of visits was to be minimized.**

**Frequent treatment visits are burdensome both for patients and the healthcare system even in normal conditions. This is something that the Swedish Medical Retina Club, MRK, has taken note of in its recommendations regarding therapy choices for wet AMD[2].**
*– We can proudly say that we are the first registry in the world for wet AMD. Sweden is good at this, and we must keep up the good work, says Inger Westborg, who has been the registry keeper for the SMR since 2010.*

*Photo: © Kurt Rebry*

*Inger Westborg is the register holder for the Swedish Macular Register (SMR), the national quality register for follow-up of the treatment of wet AMD, macular edema due to diabetes or retinal occlusions. She looks forward to being able to offer all registry users a new visualization tool.*

A couple of years ago, the AMD register was supplemented with two additional modules, one for diabetic retinopathy and another for retinal vein occlusions (thrombosis).

- We have worked with these new modules for many years prior to implementation. It is important to weigh the relevance of each added variable carefully, as the most crucial thing is to ensure willingness to register among users. It all boiled down to us registering the eye parameters. There are always opportunities to coordinate with, for example, the national diabetes registry to obtain more data.

We also have ongoing research projects where we are studying which variables that may be interesting to include in the future, relevant to both thrombosis and diabetes.

## Good Coverage From Eye Care Departments in Sweden, During the Pandemic

Despite the turbulent pandemic years 2020 and 2021, the coverage rate on intravitreal injections for macular degeneration in the SMR was around 85%:

- We have very high requirements for the degree of coverage because we compare each individual injection with those found in the patient register. The fact that the users have taken the time to register so diligently under these conditions, is quite amazing.

- In my opinion, Swedish eye care did very well during the pandemic in issuing clear guidelines quickly regarding which patients should be prioritized and how care for these could be conducted in the safest way possible. The treatments were prioritized while trying to minimize physical contact and the time patients spent in hospital, says Inger Westborg.

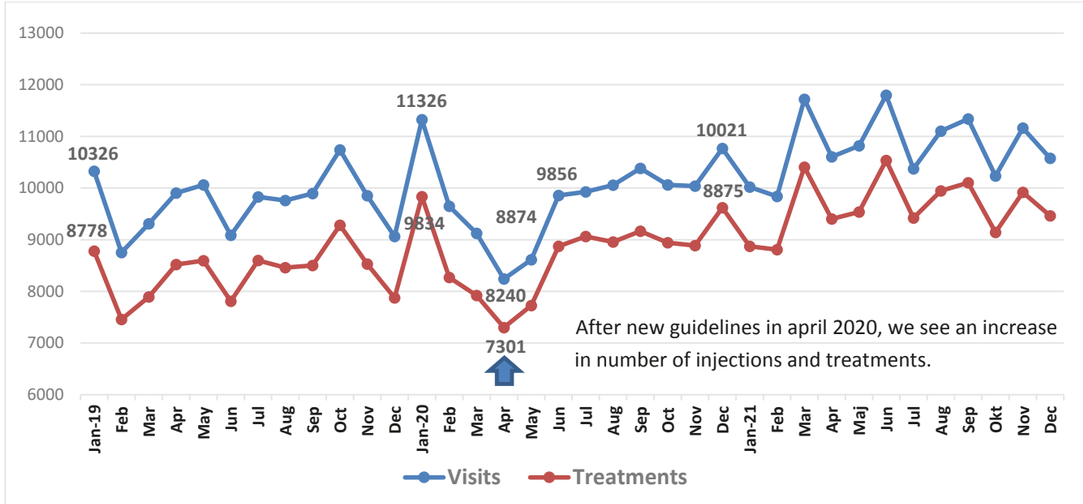


*Figure 1: A significant decrease in the number of visits and AMD treatments due to the COVID pandemic was reported in the spring, but a recovery was seen starting in June. During 2021, the number of visits and treatments returned to previous levels. Similar gains in vision were observed during the first year of treatment.*
*Graph adapted from the Swedish Macular Registry's Annual Report 2021.*

*The median age at the start of treatment for wet AMD is 80 years, which has not changed significantly since SMR was initiated in 2003. For many older patients, it is both difficult and anxiety-ridden to go to the healthcare system to receive their injections in the eye, which MRK takes note of in their recommendations.*

## Quality Registries Offer Unique Opportunities

Covid effects can be observed in the corresponding annual reports. For example, a significant reduction in the number of visits and treatments related to AMD is demonstrated between February and May 2020. However, the majority of clinics reported that patients who cancelled their planned visits during spring, would later take contact themselves due to deterioration of vision. During 2021, the number of visits and treatments returned to previous levels.

When comparing a group of patients with newly diagnosed wet AMD shortly before the pandemic and a group with treatment initiation at the beginning of the pandemic, similar gains in vision were observed during the first year of treatment. The maintained good treatment results are most likely due to clinicians being able to prioritize the injection visits and thereby reducing delays. In consequence, fewer vision tests were carried out in the pandemic group affecting the follow up data available in SMR.

- Our statistician is currently looking at the data from the Covid-impacted years in more detail, so we do not yet have all the answers. But it will be specifically followed up, and it will be exciting to read the results.

The data from the Swedish Macular Registry thus provides a unique opportunity to draw conclusions about the ultimate impact due to the pandemic in patients with retinal diseases. It is a clear example of the significant value that quality registers may have, if used correctly.
- Well-functioning quality registers are important for obtaining both real-world data for research, and data for operational optimization at clinic level, says Inger Westborg.

The collaboration with the National Working Group (NAG)

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within Medical Retina is also important. NAG is currently developing national guidelines for AMD: - Here the Swedish Macular Registry can contribute with important background data, and we have, for example, submitted proposals for target values to the NAG groups.

## Long Treatment Intervals Are in Demand

While awaiting the publication of the national guidelines, it can be mentioned that the Medical Retina Club, MRK, updated their recommendations regarding the choice of therapy for AMD during 2021. Here, care logistics and patients access to their treatment were in focus. In summary, MRK stated that the choice of therapy for wet AMD should be based on three cornerstones: duration of effect of anti-VEGF drugs, patient perspective and logistical challenges.

Many of the elderly, who often have comorbidities, find it both practically challenging and anxiety-inducing to visit the healthcare system to receive an intravitreal injection. Additionally, a large proportion of patients are also dependent on a relative or other accompanying person and have expensive transport costs for each visit.

There are studies showing that decrease in compliance is associated with increased treatment frequency, which can lead to both impaired vision and quality of life[3,4].

Frequent visits and treatments are burdensome also for the caregiver. Patient volumes will continue to increase as the population ages. The cost-effectiveness principle is important, but according to MRK it cannot not be the only aspect taken into account. The principle of human values and the principle of solidarity must also be considered, and MRK mentions the fact that “it may seem strange to use a medicine with the shortest duration of effect putting many clinics to the brink of a logistical collapse”.

## Coordination Provides Additional Knowledge

As wet AMD varies greatly between different patients, an individualized anti-VEGF treatment is pursued, enabling individual patient to achieve the best possible visual acuity gain with as few intravitreal injections and as few side-effects as possible. This is important both from an ethical patient perspective and from a logistical clinic perspective, says MRK in its recommendations.

Treatment side-effects are a typical area where SMR can provide a lot of insights. Additional insights can be obtained by linking to other large Swedish quality registers.

- We are currently working on an article where we look at strokes after anti-VEGF treatment, by coordinating with the Swedish stroke registry Riksstroke. Who are the patients? Are they different from other stroke patients? Regardless of what you find out - whether anti-VEGF treatment increases the risk of stroke or not, it is of course very important information, says Inger Westborg.

## Visualization as a Tool Towards Equal Care

During 2021, a long-awaited visualization tool in the SMR was completed and later implemented in March 2022. The aim is to facilitate for users in making relevant analyses and to create even more opportunities than are possible today’s standard reports.

- I believe visualization is the future. To be able to continuously monitor various parameters, to get clear answers to questions regarding capacity challenges and to be able to easily compare oneself with other clinics, regions, and the whole country. In the long run, this creates the best possible equal care, notes Inger Westborg.

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### *Facts*

***MRK’s recommendation regarding the choice of therapy for wet AMD is:***

- ***to use approved and safe medicines with good duration of effect to reduce the burden of care for treating clinics***
- ***to use medicines that reduce the need for visits and treatments in an aging patient group***

***There are currently four anti-VEGF preparations on the Swedish market that have been approved for the treatment of wet AMD[5].***




***References***

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3. *Varano, M., Eter, N., Winyard, S., Wittrup-Jensen, K. U., Navarro, R., & Heraghty, J. (2015). Current barriers to treatment for wet age-related macular degeneration (wAMD): findings from the wAMD patient and caregiver survey. Clinical Ophthalmology (Auckland, NZ), 9, 2243.*
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# *Highlights from* the Nordic Congress of Ophthalmology 2022

## Great moments in Reykjavík

- **3** beautiful days in Iceland
- **2** congresses (NOK2022 & RIWC2022)
- **999** participants from **25** countries
- **5** Keynote speeches at NOK2022
- **3** Presidents on stage at once
- **46** symposia
- **Many** great performances by Icelandic association of the visually impaired

Photo: Emily Moschowits

# *The 44th Nordic Congress of Ophthalmology 2022 in Reykjavik*

Dear friends and colleagues,


Photo: María Kjartansdóttir

The combined NOK2022 and RIWC2022 meeting was a fantastic experience, thanks to all 999 participants from 25 countries.

A special thanks to all those who participated in planning the congress. The NOK2020 was ready for take-off when the pandemic struck. No one knew what was coming, so the NOK committee discussed postponing the congress to the autumn of 2020 or the summer of 2021. Thankfully, it was finally decided to postpone the NOK2020 meeting to 2022. And what a feeling of gratitude we experienced when we welcomed you all in Harpa on 9 June 2022.

Photo: María Kjartansdóttir


Photo: María Kjartansdóttir

We were honored to have the President of Iceland welcome us at the opening ceremony, where we enjoyed fantastic music by members of the Icelandic Association of the Visually Impaired.

Photo: Thorkell Thorkelsson


Photo: Thorkell Thorkelsson


Photo: María Kjartansdóttir


Photo: María Kjartansdóttir





Photo: Thorkell Thorkelsson

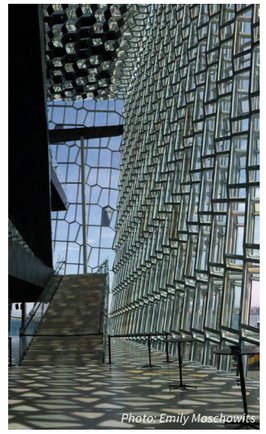


Photo: Emily Moschowits


Photo: María Kjartansdóttir


Photo: María Kjartansdóttir

The keynote speakers gave us insights and inspiration in advanced glaucoma, innovation in ophthalmology, decision-making when the stakes are high, inherited retinal diseases, as well as the genetics of common eye disease and stem cell therapy for macular degeneration.

## Keynote Speakers

### *"From biological treatment to gene and cell therapy in retinal disease"* — Anders Kvanta

Anders Kvanta is a professor in ophthalmology at Karolinska Institutet and a senior consultant in vitreoretinal surgery at St. Erik Eye Hospital. He published more than 70 studies on translational retinal research, ranging from angiogenesis to gene therapy. Professor Kvanta is a principal investigator and lead researcher in clinical gene therapy and stem cell-based trials for retinitis pigmentosa and age-related macular degeneration.

Photo: María Kjartansdóttir

### *"Far advanced glaucoma—are we making a difference?"* — Leon Herndon

Photo: Thorkell Thorkelsson

In this lecture, Dr. Herndon examined novel treatment approaches in the management of far advanced glaucoma. We also heard from a patient who lost vision due to glaucoma as he gave us a glimpse into his life. Leon W. Herndon, Jr., MD, is a professor of ophthalmology at Duke University Medical Center in Durham, North Carolina. Dr. Herndon's research interests include novel treatment approaches in the diagnosis and management of glaucoma. He has ongoing research projects evaluating the high prevalence of primary open-angle glaucoma in Ghana.

# Keynote

## *"Pilots and physicians, passengers and patients: Making decisions when stakes are high"* — Tamara R. Fountain

Dr. Tamara R. Fountain, MD, told the story of her father, a pilot who taught her many important lessons, which she cared into her professional medical career. Dr. Fountain served 15 years with the Ophthalmic Mutual Insurance Company, chairing the Audit, Strategic Planning, Risk Management, and Insurance and Marketing committees before being elected chair of the Board of Directors. Understanding the importance of routines and how people make decisions under high-pressure situations is vital in both medicine and aviation.


Photo: Thorkell Thorkelsson

# Speakers

## *"Phenotyping and Genotyping in Inherited Retinal Diseases"* — Bart Leroy

Photo: Thorkell Thorkelsson

Bart Leroy from the Department of Ophthalmology and Center for Medical Genetics at Ghent University in Belgium discussed care for patients with inherited retinal diseases (IRD) and discussed his work. In his lecture on IRD, Professor Bart Leroy examined the importance of phenotyping and genotyping for proper patient care.

## *"Physician innovators: A field guide"* — Eugene de Juan

Retinal surgeon, inventor, and entrepreneur Dr. Eugene de Juan, Jr. provided great insight into how to be an innovator in the field. de Juan holds over 120 patents and has authored over 250 peer-reviewed academic publications. In his presentation, he explained why innovations in medicine are so rare, while explaining the importance of balancing dreaming and doing in order to progress the field. His inspiring talk gave great perspective to those wishing to make a difference in the field.

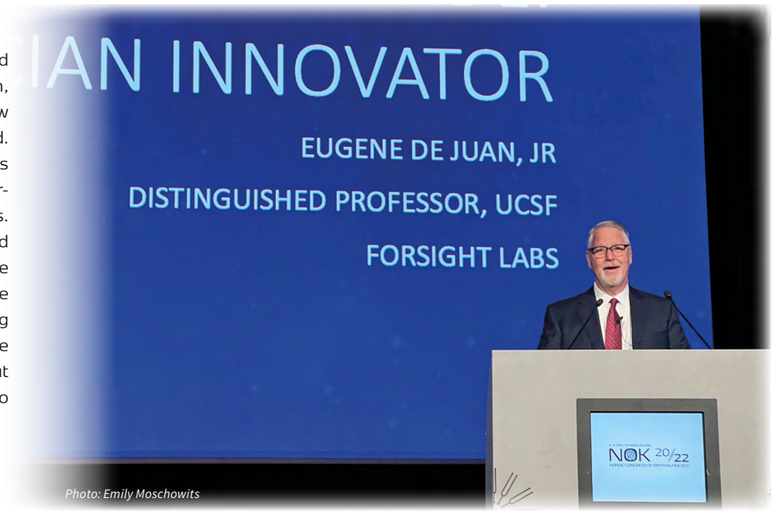


Photo: Emily Moschowits





Professor Tero Kivelä gave the Acta honorary lecture "Fighting firework-related eye injuries." The 46 symposia covered all the different subspecialties in ophthalmology, with inspiring talks and discussions. The NOK plenary session focused on the similarities, differences, and future challenges in training in ophthalmology.


Photo: Thorkell Thorkelsson

Photo: Thorkell Thorkelsson

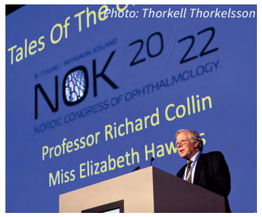


Photo: Thorkell Thorkelsson


Photo: María Kjartansdóttir

Photo: María Kjartansdóttir

The collaboration with the Retina International World Congress was a unique experience in optimism and inspiration, where ophthalmologists, vision scientists, and global leaders in patient advocacy and peer support joined forces. All of this would not have been possible without the support of the industry that presented the newest technology and therapies.


Photo: María Kjartansdóttir

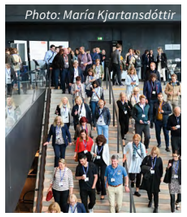


Photo: María Kjartansdóttir


Photo: María Kjartansdóttir

Even the weather was great during the congress, especially during the weekend, with 25°C and sunshine—that is, 11°C on Friday and 14°C on Saturday. Unfortunately, or thankfully, there were no volcanic eruptions or earthquakes during the congress, although there was a small eruption just before and another right after the congress. It is probably impossible to plan such events in the congress program!

Thank you all, and we look forward to seeing you all in Kuopio, Finland, on 4–8 August 2024 (www.nok2024.fi).


Photo: Thorkell Thorkelsson

Photo: María Kjartansdóttir


Photo: Thorkell Thorkelsson

Gunnar Már Zoega
President NOK2022

Photo: María Kjartansdóttir

Jóhann Ragnar Guðmundsson
President of the Icelandic Ophthalmological Society

# Advances in glaucoma surgery:

## How far have we come?


### Abstract

*Glaucoma surgery is a field in constant development. Over the past 10 years, numerous new procedures have been introduced including a group called minimally invasive glaucoma surgery (MIGS). MIGS procedures seem to have a modest IOP-lowering effect but can often reduce the use of medications. In addition, new subconjunctival drainage devices have been introduced to compete with traditional glaucoma surgery procedures. Although many of these techniques have been widely adopted already, more rigorous scientific evaluation is needed. Most notably, little is known about the long-term effect and how disease progression is affected by the procedures. Cost-effectiveness analyses are also needed. New procedures relevant to the Nordic countries are outlined and discussed in the article.*


### Background

Glaucoma surgery has always had a reputation for success rates with room for improvement and a complication rate needing reduction. Although cataract surgeons have been spoiled with happy patients with 20/20 vision, glaucoma surgeons have often left the clinic in agony over too high or low intraocular pressure (IOP). The methods for cataract surgery have become increasingly sophisticated over time: from couching to intracapsular or extracapsular cataract extraction, and now phacoemulsification. Quality and safety have followed accordingly. Numerous glaucoma surgeries and devices have been developed over the years but disappeared again. The graveyard of glaucoma surgery has many tombstones, and experienced surgeons can talk about treatment fads of the past. When it comes to the bottom line, trabeculectomy and tubes (Ahmed or Baerveldt) from the 1990s remain the bread and butter of glaucoma surgeons. The strong tradition for deep sclerectomy in Finland is worth mentioning, with many surgeons preferring it over trabeculectomy and considering it the best compromise between IOP reduction and safety. In the past 10 years, much attention has been focused on less invasive procedures, a group called minimally invasive (or micro-invasive) glaucoma surgery (MIGS). Devices designed as possible alternatives to deep sclerectomy or trabeculectomy and traditional tubes have also been introduced. Some of these procedures have been coined micro-invasive bleb surgery (MIBS) since they rely on the formation of a subconjunctival filtering bleb. In the United States, a significant amount of glaucoma surgery today is MIGS procedures combined with cataract surgery, often performed by a cataract surgeon. The purpose of this article is to provide an overview of new surgical treatment options for glaucoma that are relevant for the Nordic reader.

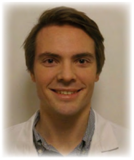
### Minimally invasive glaucoma surgery

MIGS procedures are characterized by minimal anatomical disruption, a high safety profile, ease of use, the possibility to combine with cataract surgery, less need for postoperative care, and a clinically relevant IOP reduction.[1] MIGS procedures are not designed to replace filtering surgery but provide an alternative to patients who may not require maximal IOP reduction. The mechanisms by which the procedures work can be grouped into three different categories: re-establishing conventional trabecular outflow, bypassing the trabecular meshwork, and increasing the uveoscleral outflow by diverting fluid to the suprachoroidal space. All techniques use an *ab interno* approach: the surgery is performed intracamerally using corneal incisions (**Figure 1**). Techniques targeting the conventional trabecular outflow are limited by the episcleral venous pressure, and hypotony is thus not possible. On the other hand, the suprachoroidal space has no natural brake, and hypotony will develop unless flow is controlled. Most randomized clinical trials of MIGS have evaluated them in the setting of a combined procedure together with cataract surgery. Essential here is including a control group that consists of cataract surgery alone since cataract surgery can result in considerable IOP reductions in itself.

#### *Suprachoroidal space*

The IOP-lowering potential in the suprachoroidal space is well-known to ophthalmologists for traumatic cyclodialysis, which can induce profound hypotony. Few ophthalmologists today have experience with creating cyclodialysis to lower IOP, but that has been a treatment in the past. The fibrotic response in the suprachoroidal space is much lower compared to the conjunctiva. Therefore, the suprachoroidal space has long been an interesting target for glaucoma surgery. One issue has been diverting the fluid to the suprachoroidal space in a controlled manner, i.e., without risking hypotony. The first suprachoroidal MIGS device was the CyPass (Alcon), which received FDA approval in 2016. CyPass was a 6.3-mm-long fenestrated polyimide stent (internal lumen 0.3 mm) that was placed in the angle and diverted fluid to the suprachoroidal space. The device was tested in a large randomized clinical trial (cataract surgery and CyPass versus cataract surgery alone) that demonstrated a significant IOP reduction after two years.[2] The mean IOP reduction was 7.4 mmHg for the CyPass and cataract surgery group versus 5.4 mmHg in cataract surgery alone. The proportions of medication-free patients were 85% versus 59%, respectively. In 2018, the device was withdrawn from the market due to five-year data showing significant reductions in corneal endothelial cell count. Surprisingly, early postoperative IOP spikes were often





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seen.[3] The American Society of Cataract and Refractive Surgery CyPass Withdrawal Task Force suggests monitoring all patients with CyPass for the development of clinically significant corneal edema and in these cases, trimming the proximal (intracameral) end of the device.

The only suprachoroidal MIGS procedure now is the MINInject (iStar). The MINInject is 5 mm long with cross-sectional dimensions of 1.1 x 0.6 mm. It is made of porous silicone, which allows fluid to seep through the sponge-like material. It is placed in the angle in the same manner as the CyPass. In a prospective non-randomized multicenter study, the IOP was lowered from 23.2±2.9 mmHg to 13.8±3.5 mmHg after two years, and 48% of the patients were medication-free.[4] The study had no control group. The MINInject is currently being tested in further studies. It appears safe, but limited data is available so far.

### *Schlemm's canal plumbing*

Canaloplasty, where a suture or catheter is run through Schlemm's canal, has the purpose of opening the normal outflow system. The procedure is performed *ab interno*, via corneal incisions, and a small incision in the angle is created that allows introducing the probe into Schlemm's canal. Catheters exist that have been developed for the purpose, some of which can inject viscoelastica (visco-canaloplasty). The purpose of the latter is to dilate Schlemm's canal and open the system further downstream, at the collector channels. The techniques require some technical skills to master. In general, the techniques have not been studied in as rigorous a manner as other MIGS procedures, and more studies are needed to assess their efficacy. This may explain why the techniques have not been widely adopted in the Nordic countries. However, the concept of simply flushing and re-establishing the normal outflow pathway of the eye is appealing, but efficacy is crucial; therefore, high-quality studies are needed.

### *Trabecular meshwork: to puncture or to remove?*

#### iStent

iStent (Glaukos) is probably the frontrunner in the MIGS era. It is a 360-µm-long titanium stent that punctures the trabecular meshwork, and the tip is placed in Schlemm's canal, thus bypassing the resistance in the trabecular meshwork. Two iStents are placed, separated by a few hours. The first generation iStent was introduced 10 years ago, whereas the second generation iStent (iStent inject) received FDA approval in 2018 and was evaluated in a randomized clinical trial.[5] At two years, the IOP reduction was significantly lower in the cataract surgery plus iStent group compared to cataract surgery alone, with a mean of 7.0 mmHg versus 5.4 mmHg, respectively. There was also lower mean use of ocular hypotensive medications: 0.4±0.8 versus 1.6±0.8. The rate of medication-free patients was also higher in the iStent group, at 84% versus 67%. Complications are most commonly hyphema and device obstruction.

#### Hydrus

The Hydrus (Alcon) is an 8-mm-long stent made of a nickel-titanium alloy. The stent is placed in Schlemm's canal and dilates it and a small portion of it bypasses the trabecular meshwork. By permanently expanding Schlemm's canal, it has an additional mechanism of action compared to the iStent. The Hydrus was evaluated in the HORIZON randomized clinical trial (cataract surgery plus Hydrus versus cataract surgery alone).[6] After two years, a significantly lower IOP was found in the combined procedure group compared to cataract surgery alone: 16.9±3.3 mmHg versus 19.2±4.7 mmHg, respectively. More patients were medication-free with the Hydrus, at 73% versus 38%. After five years, a similar IOP was found in both groups but with the help of significantly fewer medications in the combined procedure group: 0.5±0.9 versus 0.9±0.9.[7] The rate of filtration surgery was included as a secondary endpoint in the trial. At three years, the number was 0.6% in the cataract surgery plus Hydrus group compared with 3.9% in the cataract surgery alone group, and at five years, it was 2.4% and 6.2% respectively, both statistically different. Visual fields have been analyzed retrospectively at one study site and the results presented at conferences this year, demonstrating reduced visual field progression in the combined procedure group. Complications include hyphema and device obstruction.

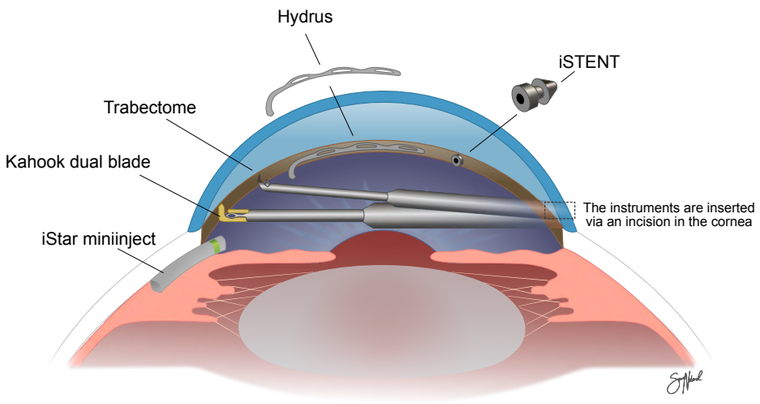


*Figure 1. Illustration of MIGS procedures: Hydrus, iStent, and iStar MINInject are devices that are placed in the angle using preloaded injectors via a corneal incision. Trabectome and Kahook Dual Blade on the other hand are instruments that are inserted via a corneal incision and used to remove part of the trabecular meshwork. Aqueous outflow is increased via the uveoscleral outflow (iStar MINInject) or the conventional trabecular outflow (Hydrus, iStent, Trabectome and Kahook Dual Blade)*





#### Kahook Dual Blade

The Kahook Dual Blade (KDB, New World Medical) is a goniotomy blade designed to completely remove the trabecular meshwork over a few hours. This is in contrast to other goniotomy or trabeculotomy techniques where the trabecular meshwork is incised but not removed. It has only been evaluated in a small randomized clinical trial (n=42), where no difference existed in IOP reduction or medication reduction between the combined procedure and cataract surgery alone. Retrospective studies suggest that the KDB may be more effective than the iStent, but this has not been replicated in a randomized controlled trial,[8,9] so it is premature to conclude. Complications are most commonly hyphema and IOP spikes.

#### Trabectome

Whereas the KDB uses sharp blades to excise the trabecular meshwork, the Trabectome (NeoMedix) ablates the trabecular meshwork by generating high-frequency electrocautery. It has been used for more than 10 years. Despite being used extensively for a long time, the scientific evidence supporting its efficacy is poor.[10] Many surgeons who initially adopted the technique have moved on to other MIGS procedures. The complication profile is similar to the KDB.

### What can we expect from MIGS and what should we use?

MIGS are relatively safe and reduce IOP to some extent, which translates to reduced use of IOP-lowering medications. The iStent is the MIGS procedure that has been most extensively studied in terms of the number of publications. However, quantity does not necessarily equal quality. Similar to most other MIGS devices, the surrogate markers IOP and medication use have been chosen as endpoints in almost all studies, and most studies have not been randomized. With very few head-to-head comparisons of MIGS, it is difficult to say which procedure is the most effective. Data so far seem to suggest that the Hydrus is slightly more effective than the iStent, but the clinical relevance of any difference is unclear. The effect of MIGS is probably exaggerated in non-randomized studies due to bias and the absence of a control group (cataract surgery can affect IOP significantly), which is worth keeping in mind when non-randomized studies are read.

### *Subconjunctival drainage devices*

Much variation exists in how a trabeculectomy is performed, depending on the surgeon. Therefore, although the basic concept of guarded outflow under a scleral flap is the same for all trabeculectomies, how this is constructed varies. Every part of creating the outflow pathway is in the hands of the surgeon, and if not performed to perfection, the result will not be optimal and may range from poor to lost vision. Unpredictability and manipulations or interventions in the postoperative weeks are part of the standard trabeculectomy follow-up. The reason to use some kind of tube to divert flow out of the eye and reduce IOP is therefore simple (**Figure 2 and 3**). It reduces human variability (surgeons and patients), flow is fixed, and it increases the ease of flow creation. There is less to go wrong, but also less to manipulate if needed (e.g., reducing the IOP further). The new subconjunctival drainage devices can be divided into two categories: micro-invasive bleb surgery (MIBS) and glaucoma tube shunts. Both groups rely on the formation of a subconjunctival filtering bleb but use different principles. MIBS are thin tubes that terminate freely approximately 4–6 mm behind the limbus and form a fluid bleb. Glaucoma tube shunts are thicker tubes connected to a tube plate that is sutured to the sclera. The anterior edge of the plate is more than 8 mm behind the limbus. The bleb forms over the plate and is thus much more posteriorly placed compared with the MIBS blebs.

#### Micro-invasive bleb surgery

*XEN-45*

The XEN-45 (Allergan-Abbvie) is a 6-mm-long porcine gelatin tube with an internal diameter of 45 µm (220 µm outer diameter), which is designed for placement in the subconjunctival space via an *ab interno* approach. The dimensions of the tube are designed to provide enough resistance to prevent hypotony. The procedure is combined with subconjunctival injection of mitomycin C. The procedure is unique since it provides subconjunctival drainage without a peritomy. No randomized clinical trials have been published. The IOP reduction at two years was in a meta-analysis determined to be 7.44 mmHg (95% CI: 4.91–9.97).[11] The same study found that at least 38% required a minimum of one

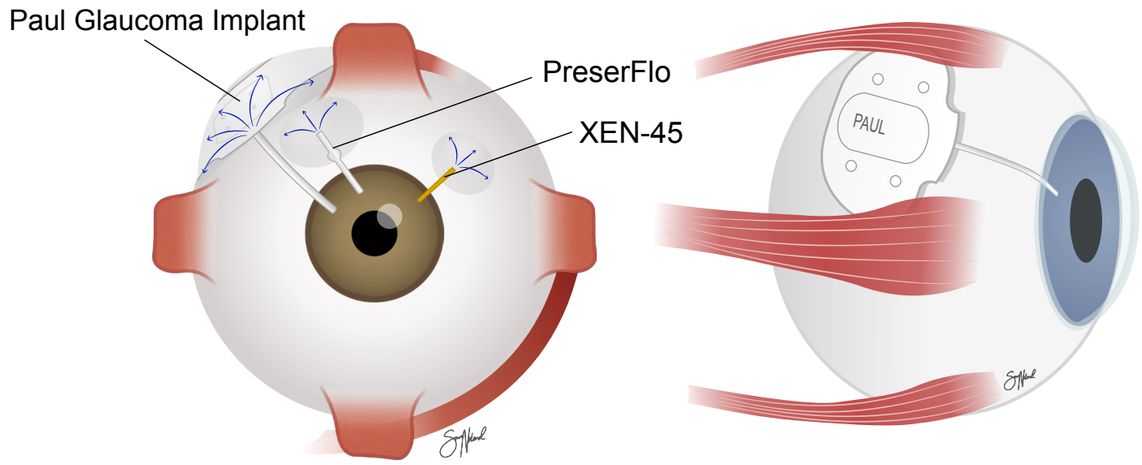


*Figure 2. Illustration of new subconjunctival drainage devices: The three devices are typically placed in the positions as shown in the figure (left). XEN-45 is most often implanted from the inside of the eye via a corneal paracentesis. Paul Glaucoma Implant and PreserFlo-Microshunt are implanted from the outside, which requires a conjunctival peritomy and dissection of a large conjunctival pocket. The plate of the Paul Glaucoma Implant is tucked under the rectus muscles and sutured to sclera (right). XEN-45 can also be implanted from the outside using the same approach as PreserFlo-Microshunt.*

*Table 1. Overview of new surgical treatments in glaucoma.*

| Device | Purpose | Theoretical outcomes and advantages | Documented effect in RCTs | Disadvantages |
|---|---|---|---|---|
| MIGS (iStent, Hydrus, iStar MINInject, Kahook Dual Blade and trabectome) | Early surgical intervention for light to moderate glaucoma | 1) Reduced IOP and medication use<br>2) Reduced need for future filtration surgery<br>3) Increased quality of life because of reduced drop burden | Reduced drop burden | 1) Price<br>2) Modest efficacy |
| XEN-45 & PreserFlo Microshunt (MIBS) | Safer and more predictable alternative to trabeculectomy | 1) Lower hypotony rates<br>2) More predictable outcomes<br>3) Less intense post-operative course | Good IOP reduction (RCT evidence only for PreserFlo) | 1) Price<br>2) Inferior to trabeculectomy in terms of IOP reduction<br>3) Higher needling rate versus trabeculectomy |
| Paul Glaucoma Implant (Glaucoma tube shunt) | Safer and more predictable alternative to Ahmed and Baerveldt tubes | 1) Lower hypotony rates<br>2) Reduced loss of corneal endothelial cells | No RCT evidence | None - yet |

*RCT = Randomized Clinical Trials* *MIGS = Minimally Invasive Glaucoma Surgery* *IOP = Intraocular pressure* *MIBS = micro-invasive bleb surgery*

needling. The procedure can be combined with cataract surgery. Difficulties with achieving a trabeculectomy-low IOP and a high needling rate have led to fading of the initial excitement over the procedure. Some advocate an *ab externo* approach, with a conjunctival peritomy, to avoid the device becoming entangled and blocked in tenon tissue. A new XEN-63, which has a 63-µm internal diameter, has recently been introduced. The goal is to achieve greater IOP reduction because of a bigger internal diameter. The most common complications are transient post-operative hypotony and scarring with frequent need for needling.

*PreserFlo-Microshunt*

The PreserFlo-Microshunt (Santen) is an 8.5-mm-long poly (styrene-block-isobutylene-block-styrene; SIBS) tube with an internal diameter of 70 µm (outer diameter 350 µm), designed for placement *ab externo* after a conjunctival peritomy (**Figure 4**). Mitomycin C is placed far posteriorly under the tenon using shields. The device was thoroughly evaluated in a randomized clinical trial of 527 patients who were randomized to either trabeculectomy or PreserFlo-Microshunt. The study was designed as a non-inferiority trial. One-year results have so far been published in this ongoing study, and the non-inferiority criteria were not achieved at this time point. The reason was primarily superior IOP reduction in the trabeculectomy group: average IOP 11.1±4.3 mmHg compared with 14.3±4.3 mmHg in the PreserFlo-Microshunt group. Fewer medications were also used in the trabeculectomy arm: 0.3±0.9 medications versus 0.6±1.1 medications. A higher rate existed of transient, not treatment-requiring, hypotony (numerical hypotony) in the trabeculectomy group. Otherwise, complication rates were similar. An expert consensus on the use of the PreserFlo-Microshunt was published this year.[12] The panel of 11 experienced glaucoma surgeons (including >100 PreserFlo-Microshunt operations) concluded that PreserFlo-Microshunt was effective in reducing IOP in open-angle glaucoma patients with an IOP of >21 mmHg. Performing the surgery with cataract surgery is feasible, but data are lacking on the efficacy of combined surgery. The most common complications are transient post-operative hypotony and scarring.

## Glaucoma tube shunts

Whereas the XEN-45 and PreserFlo-Microshunt target primary open angle glaucoma (POAG) patients, the main target group for glaucoma tube shunts is patients at high risk of fibrosis (e.g., uveitis, neovascular glaucoma, previous failed glaucoma surgery). The Ahmed (New World Medical) and Baerveldt (Johnson&Johnson) tube shunts were developed in the 1990s, both with their advantages and disadvantages. In contrast to the XEN-45 and PreserFlo-Microshunt these tubes are connected to a tube-plate that is sutured to the sclera at least 8 mm behind the limbus and a filtering bleb forms over the large plate. The new Ahmed ClearPath (New World Medical) shares the same features as the Baerveldt tube (plate size, tube diameter, and no valve) but has a different plate design and is produced by a different company. It can probably be regarded as a modified Baerveldt tube. The major innovation in this category is the Paul glaucoma implant.

*Paul glaucoma implant*

The Paul tube strives to be a mixture of the best of the Ahmed and Baerveldt tubes. It provides instant IOP reduction (like the Ahmed), but at the same time, it has a large surface area and low plate height (two Baerveldt features). A large surface area has been suggested to result in greater IOP reductions in the long term. The plate is made of flexible silicone and is designed to be placed under the two adjacent rectus muscles and sutured to the sclera at least 10 mm behind the limbus. The surface area is 342 mm$^2$ (Baerveldt 350 mm$^2$, Ahmed 184 mm$^2$), but the plate is longer and narrower compared to the Baerveldt 350. Less of the plate is thus hidden under the rectus muscles, and more is available for bleb formation. Both the external (467 µm) and internal diameter (125 µm) are smaller than Ahmed and Baerveldt (600 µm external and 300 µm internal for both). The diameter of the tube is still too big to provide enough resistance to prevent hypotony. Therefore, most surgeons place a 6-0 Prolene suture in the tube lumen (**Figure 4**), which can be removed later if additional IOP reduction is needed. The Paul tube has not been tested in any randomized clinical trial. Prospective and retrospective studies suggest that the tube is non-inferior to the Baerveldt tube, and an IOP around 13 mmHg on around one medication seems to be realistic.[13–15] Hypotony is rare. The smaller tube size should make it easier to place it posteriorly to Schwalbe's line and thus reduce endothelial cell loss,[16] but this remains to be proven. Similar to the two large studies comparing the Ahmed and Baerveldt tubes,[17] a Paul versus Baerveldt trial is needed.

## Subconjunctival drainage devices from a historical perspective

Interestingly, the first tubes were short tubes without a plate, thus similar to the XEN-45 and PreserFlo-Microshunt. However, they quickly turned non-functional because of scarring and fibrosis around the tubes. The tubes first became a success when Molteno introduced the tube plate and most importantly moved the plate posteriorly, far away from the limbus. One is therefore left wondering what the reason was for XEN-45 and PreserFlo-Microshunt going back to concepts that have been tested without positive results. There are probably two reasons. The first is new ways to produce tubes. New, more biocompatible materials, in theory reducing fibrosis, are available. The tubes can also be produced with exact dimensions, and the resistance can be determined precisely. The second reason, and probably the most important, is the introduction of mitomycin C in glaucoma surgery. Mitomycin C reduces the fibrotic response, which was the predominant reason for the poor success of the first short tubes without a tube plate. The PreserFlo-Microshunt was originally developed to be used without mitomycin C, but successful results were first achieved when mitomycin C was added to the procedure, confirming the crucial role of antifibrotic drugs for tubes without a plate.

## *Summary of MIGS and new subconjunctival drainage devices*

The European Glaucoma Society (EGS) suggests that MIGS fit into the treatment algorithm for glaucoma as a combined procedure with cataract surgery to reduce the use of IOP-lowering medication but not to lower IOP (**Table 1**). Good evidence supports this standpoint. However, the effect is not dramatic. A review from last year over Cochrane analysis and network meta-analysis determined the absolute reduction in the number of IOP-lowering drops to be approximately half a drop per day on average for the iStent, Hydrus, and CyPass.[18] Depending on the number of medications used, this may result in the patient becoming medication-free. The procedures are relatively safe. The Hydrus is the only procedure that has been shown to reduce the need for future filtration surgery, with a number needed to treat of 26–30 (i.e., 26–30 Hydrus implementations to prevent one eye from receiving a filtration surgery).[7] The PreserFlo-Microshunt and XEN-45 are alternatives to trabeculectomy for patients with an IOP of >21 mmHg. The Paul glaucoma implant seems to be non-inferior to the Ahmed and Baerveldt tubes and may be used instead of both.[15] In theory, it has some advantages, but these are not yet backed by scientific evidence.

## *Reflections and perspective*

Numerous new glaucoma procedures have been introduced in the past 10 years, and the most relevant ones have been mentioned and outlined in this article. Despite this, trabeculectomy does not seem to be ready for retirement. Current evidence and expert opinion still point to trabeculectomy being the gold standard procedure for maximal IOP reduction and the only procedure to reach single-digit IOPs.[12,19] Although new subconjunctival drainage devices, such as MIBS, can have a role in the management of glaucoma, it is worrisome if this leads to the art of trabeculectomy dying because a group of patients needs it. Trabeculectomy requires skills and volume to master. When you have those patients who need single-digit IOP, you must have confidence that your trabeculectomy will deliver this. From that perspective, preserving the teaching of trabeculectomy for glaucoma fellows is also important since it is still the gold standard procedure, and how long the new subconjunctival procedures will exist is unclear.

The majority of new devices can be categorized as MIGS, and the target population is patients with mild to moderate primary open-angle glaucoma. In terms of outcome, the expected result is a reduction in IOP-lowering medications. Although this population is large, whether it is the one in most need of new surgical treatments is doubtful. The patients most in need of improved care are probably those with advanced and progressive glaucoma, and these are the patients at high risk of developing blindness. Everyday life for the patient with advanced glaucoma becomes increasingly difficult as the disease progresses, and the cost for society grows as the patient needs support. These patients often need maximal IOP reduction, which increases the complexity of developing new procedures. A smaller patient population and a more difficult task make engaging in developing new treatments for these patients less appealing from a commercial perspective. Can early intervention with MIGS reduce the number of patients progressing to advanced glaucoma or blindness? High-quality data are needed to answer this question properly. One can argue that the challenge is not to early diagnose and intervene but to avoid late detection. Little is known of the clinical effectiveness of MIGS measured in other ways than IOP and medication use. To what extent MIGS can reduce the need for filtration surgery has only been studied in one randomized clinical trial for one device (the Hydrus in the HORIZON trial), where ≈25 Hydrus surgeries were needed to prevent one filtration surgery over five years in this large cohort of patients with light to moderate glaucoma.[7] The effect is statistically significant, but the clinical impact should be considered. We still do not know the optimal time to intervene surgically in glaucoma in terms of the EGS mission statement: "the goal of care for people with, or at risk of, glaucoma is to promote their well-being and quality of life within a sustainable health care system."

The capacity of the healthcare system matters when we choose treatments. In a survey of 43 glaucoma specialists in the UK (poster at EGS 2022), a reduced number of postoperative follow-up visits and shorter surgical duration were the two major reasons for choosing the PreserFlo-Microshunt over trabeculectomy, which may reflect a healthcare system under pressure. How the healthcare system is organized also matters when we choose treatments. Reimbursement and insurance systems provide a strong economic incentive for the treating physician in the United States to add a MIGS procedure to a cataract operation. With cataract surgeons incorporating MIGS procedures in their practice, the accessibility of MIGS has increased radically. Therefore, economic incentives and high accessibility can explain why MIGS is much more common in the United States compared with Europe. We also know that tertiary academic centers

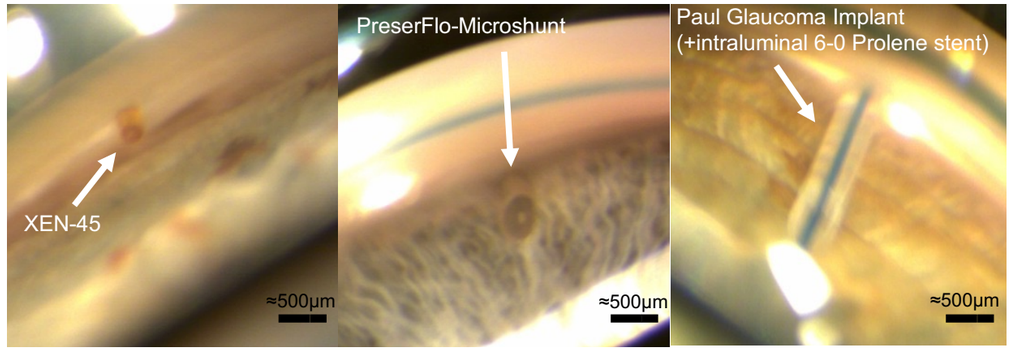


*Figure 3. Gonioscopic view of the subconjunctival drainage devices: The outer/inner diameter of the three devices varies: XEN-45 (220µm/45µm), PreserFlo-Microshunt (350µm/70µm) and Paul Glaucoma Implant (467µm/125µm). The blue intraluminal prolene suture is to prevent early hypotony and can be removed in the post-operative weeks-months.*

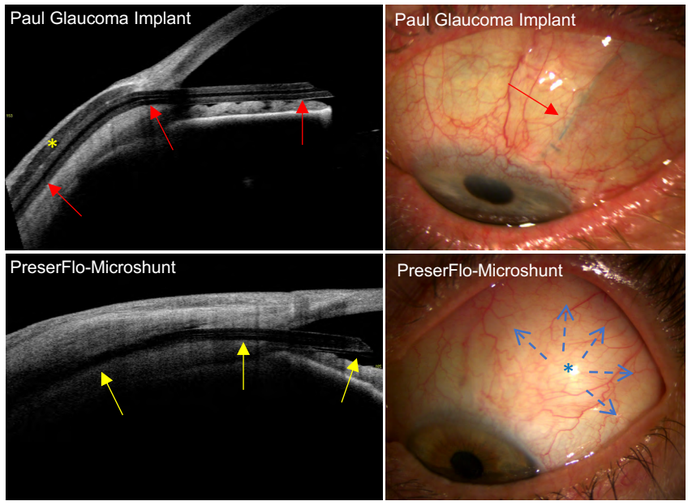


*Figure 4. PreserFlo-Microshunt and Paul Glaucoma Implant: Anterior segment optical coherence tomography (OCT) images showing a Paul Glaucoma Implant (red arrows) covered by a cornea patch graft (asterisk). To the right a photo of a different patient is shown with a Paul tube (red arrow), covered by a cornea patch graft and with a blue intraluminal prolene suture to prevent early hypotony. The end of the tube and tube plate is just covered by the eyelid. The bottom two images shows the slightly thinner and shorter PreserFlo-Microshunt (yellow arrow), resulting in less posterior outflow. Blue asterisk marks the approximate end of the tube and the resulting bleb (blue arrows).*

are more likely to care for patients with advanced disease and that the standard surgical treatment for this group is trabeculectomy and tubes.[21] In the Nordic countries, patients with early to moderate glaucoma, the target population for MIGS procedures, are much more likely to be in the hands of cataract surgeons or ophthalmologists who practice outside academic institutions. If the healthcare system does not support MIGS procedures outside academic and public hospitals, then it is likely that a large proportion of glaucoma patients will not be offered MIGS procedures for financial reasons.

It is unclear whether offering MIGS to patients with mild glaucoma leads to higher patient satisfaction and what impact this has on everyday life. Patient-related outcome measures are notoriously lacking in randomized clinical trials. In the LIGHT study, newly diagnosed glaucoma patients were randomized to primary treatment with selective laser trabeculoplasty (SLT) or medication.[20] Before starting the study, group interviews revealed that becoming medication-free was a top priority among patients. With this in mind, it is a bit surprising that very little difference existed after three years in quality of life, as analyzed with four different quality of life questionnaires, between the medication group and SLT group (70% were free of medications). Indeed, some patients are very happy to be drop-free or would appreciate once-daily instead of twice-daily drops (a realistic expectation for many MIGS), but for many, it may not make a big difference. Cost-effectiveness analysis also differs between countries, depending on how the healthcare system is organized, which general recommendations difficult from a healthcare economic perspective. If all the MIGS were priced at 1€, the recommendation would possibly be that all glaucoma patients undergoing cataract surgery should have a MIGS added to the procedure. However, that is not the reality. Given the new EGS guidelines where MIGS is recommended into the treatment algorithm for glaucoma as a combined procedure with cataract surgery, and keeping in mind—from a socioeconomic perspective—that optimizing the use of the taxpayer's money is required, then the cost for the MIGS devices can be a decisive factor. Schlemm's canal procedures have a similar effect but vary considerably in cost (≈350€–1400€).

In summary, despite their being widely adopted, we lack to a large degree randomized clinical trials with head-to-head comparisons for many of these new procedures. Randomized clinical trials are also needed that integrate patient-related outcome measures and objective measures of disease progression, ideally visual field testing, as well as cost-effectiveness analysis. Such trials would make it possible to go from the current educated guess to an evidence-based approach on how to optimally integrate these new procedures in the treatment of glaucoma from both the patient's and society's perspectives.

So how far have we come in glaucoma surgery? Definitely far, but there is still a long way to go before the perfect glaucoma operation has been developed, if it exists.

***Key points:***

- Minimally invasive glaucoma surgery (MIGS) procedures can be used to reduce the use of ocular hypotensive medications. MIGS can be performed as stand-alone procedures but are primarily indicated in combination with cataract surgery.
- New subconjunctival drainage devices are an alternative to trabeculectomy for selected patients.
- More randomized clinical trials are needed to allow the precise integration of new procedures into the treatment algorithm for glaucoma.

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*Photo: Ine Eriksen, OUS*

# New insights into ocular findings in Marfan syndrome

***Gunhild Falleth Sandvik***
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***Key points:***

- Ectopia lentis may develop or progress in adulthood.
- Patients with Marfan syndrome reported increased symptoms of photophobia and glare.
- Understanding pupil size and changes in pupillary function associated with Marfan syndrome is important if surgery is needed.

*On September 5, 2022, Gunhild Falleth Sandvik defended her thesis "An ophthalmological study of adults with Marfan syndrome: Ten-year of follow-up and an evaluation of photophobia, glare and pupillary response" at the Faculty of Medicine at University of Oslo (UiO). The PhD project was conducted at the Department of Ophthalmology at Oslo University Hospital (OUH) and the Institute of Clinical Medicine at UiO. The main supervisor was Olav Kristianslund MD PhD, Department of Ophthalmology, OUH, Institute of Clinical Medicine, Faculty of Medicine, UiO, with co-supervisors Professor Liv Drolsum, Department of Ophthalmology OUH, Institute of Clinical Medicine, Faculty of Medicine at UiO and Svend Rand-Hendriksen MD PhD, Sunnaas Rehabilitation Hospital.*

Patients with Marfan syndrome often have ocular involvement. The most prevalent ocular manifestation is ectopia lentis — a dislocation of the biological lens—which has been assumed to be present from birth or early childhood in these patients. Other findings commonly seen include myopia, increased axial length, flatter corneal curvature, and hypoplastic iris. These features have been investigated in several studies, but a long-term follow-up has been missing. The diagnosis of Marfan syndrome is based on a list of criteria, and ectopia lentis is one of the cardinal features. If ectopia lentis develops in adulthood in persons previously not fulfilling the criteria, this could possibly lead to a definitive diagnosis. The visual prognosis for patients with Marfan syndrome is often good. However, it is known that Marfan syndrome is associated with a higher prevalence of retinal detachment and cataract. In addition, it has been speculated that patients with Marfan syndrome have increased symptoms of photophobia; however, no findings have previously been published.

This PhD study is the ophthalmological part of the Norwegian Marfan study, where all relevant organs of 44 patients with verified Marfan syndrome were examined at baseline in 2003-2004 and follow-up in 2014-2015. Further, a matched control group for the follow-up examination was included. The thesis aimed to assess changes in ocular features during a ten-year period and to compare photophobia, glare, and pupillary response between patients with Marfan syndrome and a matched control group.

Results from the study revealed that ectopia lentis may develop or progress in adulthood. Other ocular manifestations were stable over the ten-year period; however, an increased risk of cataract and retinal detachment was seen. Independent of these findings, the visual prognosis was good. Evaluation of photophobia and glare showed that patients with Marfan syndrome reported increased symptoms, and measurements of ocular straylight revealed a higher value compared to the matched control group, even after adjustments for cataracts and several other features prevalent in Marfan syndrome. When measuring the pupillary response, we found a smaller pupil size, slower contraction velocity, and longer re-dilation time. The small pupil size was associated with increased straylight in the eye; however, it could not fully explain the difference in straylight between the two groups.

Overall, these results indicate that lacking fulfillment of the diagnostic criteria for Marfan syndrome may change during adulthood, e.g., if ectopia lentis develops. Further, the findings in this PhD project may help when informing newly diagnosed Marfan syndrome patients about what symptoms and changes they may experience in the years to come.

***Remaining questions:***

- What is the reason for the increased photophobia and glare in patients with Marfan syndrome?
- Could findings of ocular manifestations at an early age predict other disease characteristics in patients with Marfan syndrome?

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# Seeing the Unseen:

## Novel perfusion monitoring in oculoplastic surgery

***Johanna V. Berggren***
***Faculty of Medicine, Lund University, Sweden***

*On April 29, 2022, Johanna V. Berggren defended her thesis "Perfusion Monitoring in Oculoplastic Reconstructive Surgery" at the Faculty of Medicine, Lund University, Sweden. The PhD project was conducted at the department of Clinical Sciences Lund, Ophthalmology, Skåne University Hospital, Sweden. The supervisors were Malin Malmsjö, M.D., Ph.D., Karl Engelsberg, M.D., Ph.D. and Sandra Lindstedt, M.D., Ph.D. at the Department of Clinical Sciences, Skåne University Hospital, Lund University.*

***Key points:***

- Perfusion is higher in myocutaneous than in cutaneous flaps.
- In axial flaps, perfusion is maintained for longer flap lengths, suggesting that these flaps can be made longer than random flaps.
- Post-surgery, random flaps are more rapidly re-perfused than free skin grafts.
- Laser speckle contrast imaging enables perfusion monitoring during reconstructive surgery.

### Introduction:

After tumor excision in the periocular area, tissue might be limited, and flaps or free, full-thickness skin grafts are often needed. The successful design of flaps and grafts is vital for the outcome and survival of the tissue. Therefore, the understanding of the vascular supply and reperfusion is critical. However, many surgical reconstructive techniques were developed before there was any objective way to monitor blood perfusion. Today, non-invasive, laser-based techniques, such as laser speckle contrast imaging (LSCI), can be used to monitor the perfusion in skin flaps and grafts. LSCI illuminates the tissue with a near-infrared laser and the interference pattern created by the backscattered light is used to determine perfusion, as the movement of red blood cells causes the pattern to change, allowing the blood perfusion to be quantified. In this thesis, LSCI was used to monitor the blood perfusion in human flaps and full-thickness skin grafts frequently used in periocular surgery. An axial flap is perfused by a specific blood vessel, while a random skin flap is not based on a specific vessel for its perfusion. Instead, its blood perfusion originates from the dermal plexus of the base of the flap. Oculoplastic surgery was used to assess the clinical implications of this novel bioimaging technique.

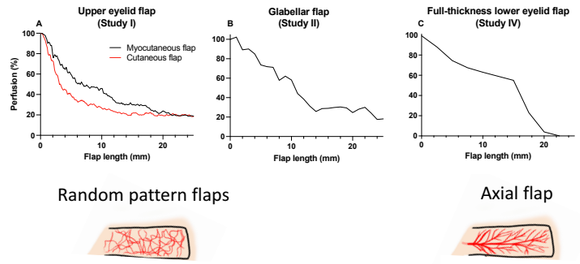


*Figure 1. Perfusion shown as a percentage of a reference point near the flap base in upper eyelid flaps, glabellar flaps, and full-thickness lower eyelid flaps. The upper eyelid flaps (A) and the glabellar flaps (B) are random patterned flaps, while the full-thickness lower eyelid flaps (C) contain vessels of the marginal arcade and, therefore, can be seen as a model for axial flaps. Note that the decrease in perfusion was less pronounced in the axial flaps.*

***Future directions:***

- Larger studies allowing subgroup analyses of factors known to affect blood perfusion, such as smoking and diabetes
- Monitoring the perfusion and reperfusion of flaps and skin grafts in other areas of the body
- Simultaneous monitoring of perfusion and oxygenation using laser speckle contrast imaging and hyperspectral imaging

### Flap length:

The perfusion over the flap length during surgery was investigated on random flaps, without a specific blood vessel. In Study I, upper eyelid flaps were raised in patients undergoing blepharoplasty. The perfusion gradually decreased from the base to the tip of the flaps. Perfusion was better in myocutaneous flaps (including skin and orbicularis muscle), than in cutaneous flaps, where the muscle had been removed. Similar results were found in the glabellar flaps in Study II. The perfusion of the flaps in both studies was limited beyond 15 mm. Beyond this point, the flap resembled a free skin graft, that could, if necessary, be replaced with a free graft.

### Axial vs. random patterned flaps:

Study IV was performed on axial flaps, containing an anatomically named blood vessel. Full-thickness lower eyelid flaps were raised as part of a modified Quickert procedure. The decrease in perfusion over the length of the flap was less pronounced than for the random flaps in Studies I and II (**Figure 1**). This indicates that axial flaps can be longer, while maintaining adequate perfusion.

### Reperfusion:

The proximal parts of glabellar flaps (Study II) were rapidly re-perfused, within 1 week. Similar results were found in the reperfusion of random advancement flaps that were raised in a bipedicle advancement flaps procedure (Study III). In Study V, reperfusion of free full-thickness skin grafts took longer (7 weeks), probably as they, in contrast to the flaps, lacked a vascular connection and depended on de novo angiogenesis.

### Conclusion:

LSCI enables detailed perfusion monitoring during and after periocular surgery. The periocular area is well-perfused, and it would be of value to monitor perfusion in less vascularized body areas. Further studies could lead to a deeper understanding of the healing process and provide opportunities to optimize surgical procedures.

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# Evaluation Criteria for the 2023 **Best Paper Awards**

1) How interesting the subject is to our readers
2) Quality of language, pictures, illustrations, and figures

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There will be three article prizes in 2023. The first prize (gold) is NOK 80,000, whereas silver and bronze will be awarded NOK 30,000 and NOK 15,000, respectively. All articles published in Oftalmolog in 2023 will be evaluated for the prize, regardless of subject. There are no guidelines attached to the prize money; thus, how it is spent is limited only by the imagination.

The editors hope that the article prizes will attract high-quality articles in *Oftalmolog* from authors of all ages in the field of ophthalmology. We call for collaboration, where younger clinicians and researchers can draw on the experience of more established eye doctors.

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We are very grateful to our generous sponsor, Théa, for their donation and support in making these awards possible.



The **2022 Best Paper Award** winners will be announced in the next issue!

*Niina Harju*
*Faculty of Health Sciences, School of Pharmacy, University of Eastern Finland, Kuopio, Finland*

# A Hot Topic:

## RPE cells as critical players in the retina

*On September 23, 2022, Niina Harju (ex-Bhattarai) defended her thesis "Regulation of oxidative stress and inflammatory responses in human retinal pigment epithelial cells" at Faculty of Health Sciences, School of Pharmacy, University of Eastern Finland, Kuopio. The main supervisor was Anu Kauppinen, Professor, University of Eastern Finland, with co-supervisors Kai Kaarniranta, Professor, University of Eastern Finland and Kuopio University Hospital and Yashavanthi Mysore, PhD, University of Eastern Finland.*

### Introduction

Age-related macular degeneration (AMD) is the main cause of blindness in western countries. The prevalence of AMD is increasing, and it has been estimated to reach 288 million by 2040. There are two forms of AMD: dry (85-90% of cases) and wet (10-15% of cases). Retinal pigment epithelial (RPE) cell degeneration, eventually leading to RPE and photoreceptor cell death, occurs especially in the dry form of AMD. Typical features of the wet form are pathological neovascularization and subsequent RPE degeneration, as well as a more rapid progression of blindness. RPE cells are post-mitotic cells that appear as a single cell layer in the back of the eye, and they are important for the maintenance of the retinal homeostasis and photoreceptors functionality. During the development of AMD, protein aggregation, inflammation, NLRP3 inflammasome activation, oxidative stress, and impaired autophagy in RPE cells are all critical contributors to the disease onset (**Figure 1**). Therefore, understanding the mechanisms underlying this process is key to developing novel therapies.

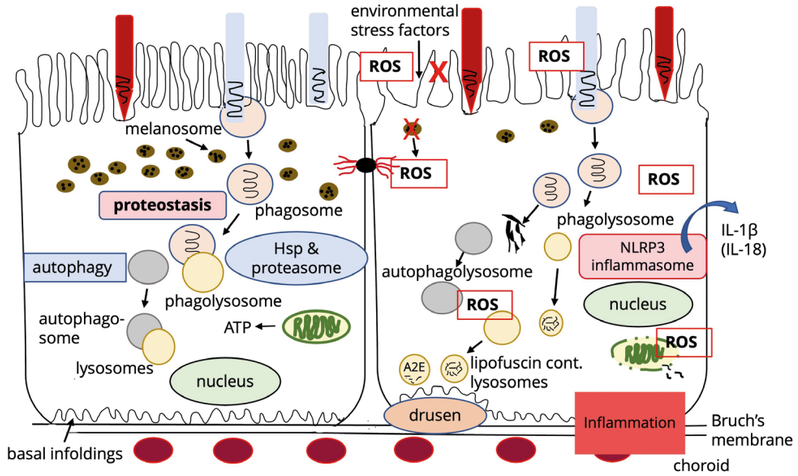


*Figure 1. Comparison of a normal polarized RPE cell (left) to a dysfunctional RPE cell (right) in AMD. (Harju, N. (2022) Acta Ophthalmologica, 00, 1–58. from: https://doi.org/10.1111/aos.15275)*
*ROS= reactive oxygen species*

### Hydroquinone predisposes to the degeneration, whereas Resvega relief RPE cell responses

In my dissertation, we found hydroquinone, a component of cigarette smoke, induced NADPH oxidase-mediated ROS production and predisposed RPE cells to degeneration by reducing vascular endothelial growth factor (VEGF) level. Hydroquinone increased NLRP3-independent IL-18 release even as NLRP3 accumulated inside the IL-1α-primed RPE cells. Resvega, an antioxidant mixture including omega-3 fatty acids, vitamins C and E, copper, zinc, lutein, zeaxanthin, and resveratrol, reduced hydroquinone-induced ROS production and NLRP3 inflammasome activation induced by impaired protein clearance in RPE cells.

***Key points:***

- Cigarette smoke is the most important environmental risk factor for age-related macular degeneration (AMD).
- Oxidative stress, NLRP3 inflammasome activation, and inflammation contribute to AMD.
- Hydroquinone, a component of cigarette smoke, induces NADPH oxidase-mediated ROS production but reduces NF-κB activity in human retinal pigment epithelial (RPE) cells.
- Hydroquinone predisposes RPE cells to degeneration through reduced VEGF, which increases the risk of wet AMD, and is important for RPE cell viability and integrity of the retina.
- The antioxidant mixture, Resvega, reduced hydroquinone-induced oxidative stress and NLRP3 inflammasome activation induced by impaired protein clearance in RPE cells.

### Looking forward

The mechanism for hydroquinone-induced cell death should be studied further as caspase-1 was not activated in degenerated RPE cells. As well, the mechanism of the IL-18 cleavage and NLRP3 inflammasome accumulation after hydroquinone exposure should be examined in more detailed. Since oxidative stress and NLRP3 inflammasome activation both contribute to the AMD, more studies are needed to figure out the potential of Resvega as a treatment option for AMD, including an optimized administration route for targeting straight to the RPE cells in the eye.

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Our SOE Keynote Speakers will cover the following topics:

**Professor Gerd Auffarth**
is the chairman of the Department of Ophthalmology at the Heidelberg University Eye Hospital. He has received more than 200 awards for his scientific work. He has published over 300 peer-reviewed articles and 370 book chapters, and he has delivered over 800 invited talks. His main research interests include biomaterial and implant research in cataract and laser surgery of the eye. Professor Auffarth will deliver the José Barraquer Lecture at SOE 2023 in Prague.

**Professor Marc de Smet**
is the founder and head of MIOS SA, dealing with the diagnosis and treatment of retinal disease. He has led numerous experimental programs and clinical trials in ocular inflammation, imaging and microsurgery of the retina. While at the University of Amsterdam, he discovered new treatments such as the use of methotrexate for the treatment of ocular lymphoma and Ocriplasmin in vitreomacular traction. Professor de Smet will give the Robert Machemer Lecture during SOE 2023.

**Dr. Michèle Beaconsfield**
is an honorary consultant in oculoplastic surgery at the Moorfields Eye Hospital in London. After first doing general surgery and later, neurosurgery, she chose the field of ophthalmology. She has been a consultant oculoplastic surgeon since 1991 with a particular interest in surgical rehabilitation and she initiated the specialized lid oncology service at Moorfields. She has always been passionate about training and is an examiner for the Royal College of Ophthalmologists and the European Board of Ophthalmology. Dr. Beaconsfield will deliver the Richard Collin Lecture.

Abstract submission is now open at https://soe2023.soevision.org/scientific-programme/abstract-submission

Registration is open as of November 2022. For more details go to https://soe2023.soevision.org
The venue for SOE 2023 will be the Prague Congress Centre. June 2023 will be a perfect time to be in Prague with its rich architecture as a backdrop to the Congress.

Welcome to SOE 2023!

**Wagih Aclimandos,** *SOE President*

# SOE 2023
## European Society of Ophthalmology

The organization's history dates back to the years following the Second World War when discussions considering the creation of a European society for ophthalmology began. In 1956, the organization was created and the Latin name, Societas Ophthalmologica Europæa (SOE), was chosen so that no language was preferred at the expense of another. Today, the society has representatives from 44 national ophthalmology societies across Europe

One of the main tasks of the organization is to arrange the SOE congress every second year. It also supports young Eastern European ophthalmologists so that they can travel to one of the SOE-recognized European training centers. In addition, SOE provides teaching grants for those who are involved in active residency training in select Eastern European countries. Through this, SOE wishes to strengthen links among teachers and their institutions.

In 2014, the first European Meeting of Young Ophthalmologists (EMYO) was held in Porto in Portugal. Since then, the meetings have gathered increasing attention, and the 4th EMYO meeting in Brussels, Belgium, July 2022 gathered more than 400 participants.

The SOE Lecture Initiative was established in 2005. The lectures are held at the national ophthalmology meetings by the most promising young (under 45 years) clinicians or researchers selected by the national societies. The honorary lecturers receive a voucher and participate at the next SOE congress for free. Travel and hotel costs are covered by the national ophthalmology societies.

I wish to congratulate the 2022 SOE lecture awardees already announced from the Nordic region:

- Ulrika Kjellström (Sweden) for the talk "Phenotypes and Genotypes in Retinal Dystrophies"
- Josephine Prener Holtan (Norway) for the talk "The Story of Inherited Retinal Disease in Norway"
- Trine Møldrup Jakobsen (Denmark) for the talk "Myopia: A Problem? Ortho-what?"

I am looking forward to seeing you in Prague in June 2023!

**https://soe2023.soevision.org/**

**Bente Haughom**
MD ophthalmologist, Oslo, Norway

Moments from SOE 2019 in Nice, France

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