OFTALMOLOG

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Dear colleagues,

I hope you all are doing well in these challenging times. Oftalmolog has received several exciting manuscripts for this issue. Atle Østern starts off by discussing various aspects of light and vision. Opportunities for research and collaboration in a European Network on rare disease are then presented by Neil Lagali.

Miriam Kolko's group describes challenges and opportunities using internet based perimetry. Effective screening of diabetic retinopathy using telemedicine is presented by Jakob Grauslund and potential for further improvements using artificial intelligence is discussed. Do's and Don'ts in times of Covid-19 is the topic of our last paper.

Anthony Mukwaya and Neil Lagali received the so far largest Nordic Best Paper Award (NOK 100,000; Gold) for their paper "Regulation of ocular inflammation and angiogenesis using corneal models – new insights based on recent research". Silver (NOK 25,000) was awarded to Zaynab Ahmad Mouhammad, Daniel Tiedemann, Miriam Kolko and Che J Connon. Congratulations!

Many thanks to the evaluation committee for their efforts to carefully evaluate all papers published in 2019. Congratulations to Marit Lippestad and Erlend Sommer Landsend on their dissertations, which are summarized in Oftalmolog.

The Editorial Board encourages our readers to contribute with manuscripts that are perceived to be of high interest to our colleagues. The next deadline for submission is on November 1, 2020.

On behalf of the editors, I wish you all a nice autumn.

Kind regards,

Tor Paaske Utheim
Editor-in-Chief

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Manuscripts

. . . can be sent to oftalmolog@grafia.dk. For guidelines about manuscripts, deadlines and distribution: www.oftalmolog.com

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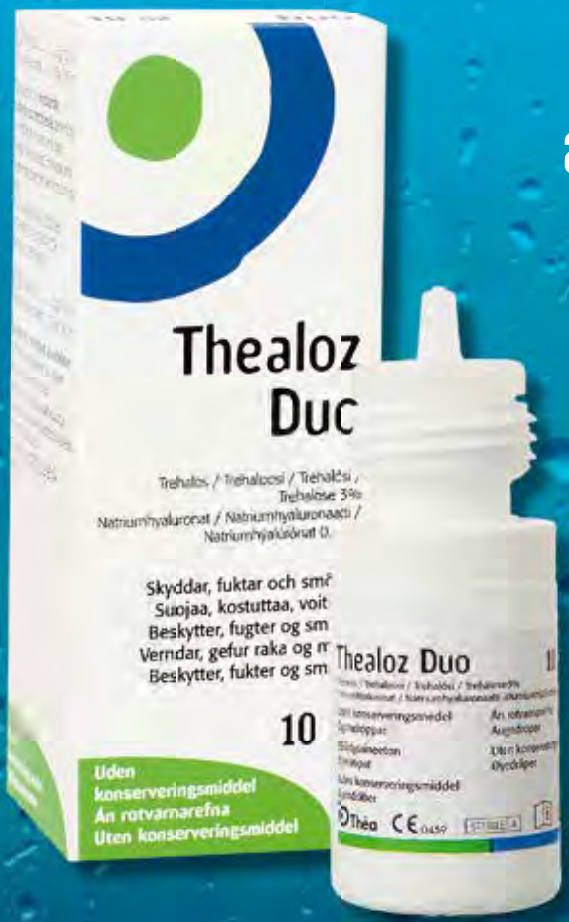
TØRRE ØYNE?

Du trenger mer enn bare fukt!

Med trehalose fra naturen

Unik kombinasjon av cellbeskyttelse og smøring



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Théa let's open our eyes

THSE2019120-756

Atle Einar Østern

The light we (don't) see

We depend on light to see. Visible light constitutes a narrow part of the much wider electromagnetic spectrum. Why does the visual system only detect this small fraction? Why not infrared or ultraviolet light? Or radio waves like in Wi-Fi? Do we really experience light in the same way? These basic questions are the focus of this paper.

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In Genesis, it is written: "Let there be light". For billions of years, our planet was mostly illuminated by celestial objects and the sun. Electromagnetic radiation propagates through outer space, carrying energy, by wave-particle duality. Frequency and wavelength of the particles, or photons, define different types of electromagnetic radiation. Photons are either reflected, absorbed or transmitted by atoms as they enter our atmosphere, depending on the wavelengths and corresponding energy levels. Hence, this substantially constricts the frequency bands which are available for any earthbound visual systems to potentially perceive

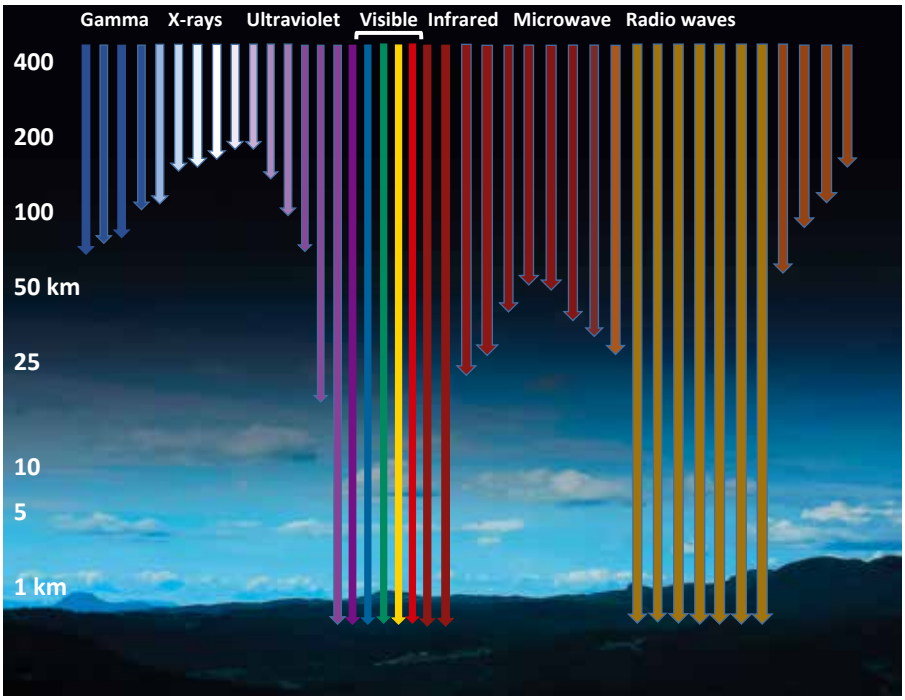

Figure 1: The optic window is composed of the electromagnetic waves which are visible for humans. Photo/illustration: Atle Østern

from above. All other wavelengths will be naturally inaccessible to living organisms. Only ultraviolet (UV) rays, visible light, infrared (IR) radiation and radio waves reach the Earth's surface (Figure 1). So, why don't we see them all?

Radio waves are widely exploited by humans in modern technology, but they will forever be beyond the realm of possibility for us to naturally detect with our eyes. The reason has to do with physics. Their energy is simply too low to trigger any biochemical reactions in cells, including in photoreceptors.

That leaves light around and within the visible spectrum. The visible portion of sunlight has the most intense radiation. This is optimal for electron transitions in pigments to occur. The outcome was that life adapted to utilize this available extraterrestrial energy source. First photosynthesis evolved 3 billion years ago in plants and then, much later, a complex visual sense in animals about 550 million years ago to navigate.

As is well known, the frequency variation in light is distinguished as different colours. Colour vision in animals varies. Birds and reptiles usually have four colour-sensitive cones. Mammalian ancestors converted from a similar cone-dominated to a largely rod-based vision as an adaption to the prolonged period of nocturnal living during the reign of dinosaurs. This era ended less than 66 million years ago when a huge asteroid blasted into the Gulf of Mexico, triggering cataclysmic mass extinctions. Consequently, most contemporary mammals still retain only two cone types; they are dichromatic. Their world is less colourful than ours (Figure 2). On the other hand, some invertebrates have multiple opsins. The mantis shrimp has the record, with 12-16 photoreceptors. It can detect UV, IR and polarized light, as well as move its eyes independently.

The human small (S), medium (M) and long (L) cones are named based on the wavelengths with the corresponding highest spectral sensitivities (Figure 3). Following a duplication of a gene for the longwave opsin in our primate ancestors, the M- and L-receptors arose about 35 million years ago. As a result, the now trichromatic eyes of diurnal monkeys became sensitive to red and green objects. This became important when foraging for ripe fruits and young leaves which were the main food sources. Another potential benefit was the ability to discriminate skin tones of bare-faced members of the same group since social interaction is of great importance to primates and humans. For instance, emotions and conditions are often revealed through reddish colouration, such as when the eye is irritated, skin tissues are inflamed or we blush.

Figure 2: To the left is what humans see, to the right what cats see. Photo: Atle Østern

The combined colour perception, with our ability to differentiate 2-10 million chromaticities, is a result of a complex brain processing. However, there is, in fact, natural variability in human cone density and visual cortex size. Can we then be certain that what appears as red for you is not really what I would describe as blue? In 2015 a video became a viral phenomenon worldwide where people disagreed about the colour of a dress (black and royal blue or gold and white). Other controlled experiments have confirmed stark

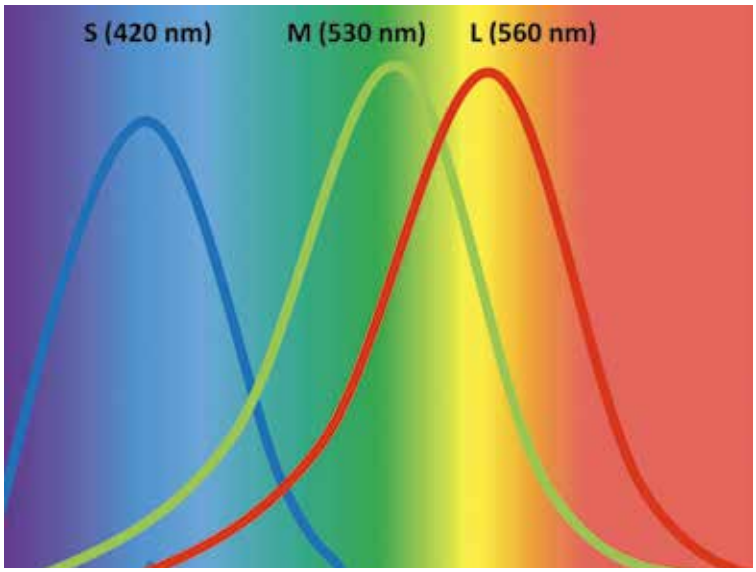

Figure 3: The wavelength sensitivity of the three colour receptors. Figure: Atle Østern

Figure 4: Both the common starling and bees have UV vision according to research. Photos: Atle Østern

differences. The fascinating answer to the question is that colour perception is not always similar, even in the absence of an acquired or congenital colour vision deficiency. Scientists believe that different opinions are due to chromatic adaption and how the brain recognizes colours. The need for colour consistency, the context of illumination and light contrast, influence how we interpret colours as well. Thus, the same objectives can appear darker or lighter depending on the surrounding conditions. We can even be tricked to see colours where there are none. Is this an innate or adaptive feature? Research indicates that whether you are an early or late riser might be part of the explanation in the now-famous dress example above. However, it is also possible that the first time the brain encounters a colour as an infant it is determined how it will be perceived in the future. In addition, studies suggest that language and culture are of importance. For instance, members of the Berinmo tribe in Papua New Guinea categorize and discriminate hues differently from English speaking natives. Blood supply to the eye and the season of the year may also matter. Colour appearance changes as a persistent calibration to greyness in the environment. Colours can even be subtly distinctive in healthy left and right eyes. They are also affected by moods and earlier memories. Light and contrast sensitivity is reduced in depression. Some, usually females, are also tetrachromatic, having a fourth photoreceptor. Consequently, in some cases, they can theoretically discriminate between perhaps 100 million colours. So, to conclude, your world may look different from mine!

The visible frequency range diverges across species. It is influenced by survival strategies and needs. Humans recognize wavelengths from about 400 to 720 nanometers (nm). UV radiation designates wavelengths from about 100 to 400 nm. Many vertebrates possess retinal photoreceptors devoted to the (near) UV, with a multitude of roles in vision (expansion of colour vision, navigation, camouflage, foraging and communication). The capacity to respond to UV is found in many fishes, amphibians, reptiles and birds (with UV reflecting feathers), but previously not in mammals. Recently, UV vision has surprisingly been revealed in reindeer in the Arctic which can identify UV absorbing hair and urine from wolves. Why have humans not preserved this ancestral trait? It has been demonstrated that even humans still have UV sensitive pigments. Research suggests that our primate ancestors switched from originally UV vision to blue light sensitivity through multiple mutations over several million years. The reason is that UV exposure would otherwise cause blurry images due to chromatic aberration and harmful photodamage by the formation of free radicals. While the ozone layer blocks toxic UVC radiation (consisting of wavelengths shorter than 280 nm), cornea absorbs almost all UVB rays (280-315 nm) and the biological lens most of the remaining UVA rays (315-400 nm) in extant humans. The downside is that we have lost the ability to perceive almost otherworldly beautiful flower patterns created by UV-absorbing pigments, which birds and bees can (Figure 4). In other words, this is a trade-off between costs and benefits. However, children, in addition to aphakic patients, can still under some conditions notice near-UV radiation down to 380 nm.

IR light has longer wavelengths (>700 nm) and less energy than that of visible light. It can be reflected off or emitted as heat from objects. IR imaging allows thermal body temperatures to be observed (Figure 5). In nature, this could be potentially beneficial for nocturnal predators. Indeed, many snakes have holes on their faces, called pit organs, which detect IR energy up to a distance of one meter. Nonetheless, these organs are wired up to the somatosensory system and react to heat instead of light. The reason why near-IR vision has been regarded as impossible in vertebrate eyes, albeit exceptions have now been discovered, is that it triggers noise (frequent false alarms)

Figure 5: Infrared thermal image. Photo: Atle Østern

Figure 6: Night vision goggles, where the visual field and objects appear green, is used by Norwegian military pilots on the new NH90 Helicopter. Photo: Atle Østern

in visual pigments. This interferes with light detection. Therefore, according to most textbooks, humans are not able to see IR light. New research suggests that this is not necessarily the case. One study demonstrated that when powerful lasers emitted short IR pulses with a wavelength of 1000 nm, a double absorption of photons in a photoreceptor generated the same amount of energy as a single photon of 500 nm. Individuals perceived this as green light flashes. Interestingly, this implies that under certain conditions the human eye can see beyond the visible spectrum. A possible future application is an ophthalmological instrument to examine and stimulate specific parts of the retina to evaluate functionality.

In dim light our vision changes. It has recently been discovered that some primates (like lemurs) maintain colour vision at night, but in humans, only the rods are of course stimulated in darkness. The rods are sensitive to wavelengths between blue and green light. Dark adaptation increases the light sensibility of the eye up to 100.000 times. Already in 1941, it was established that as few as 5 single photons were enough to trigger an awareness of light. However, in ordinary low light conditions, the visual acuity (VA) is reduced to approximately 20/200, with potentially increased night myopia, weakened depth vision and glare problems. To improve the situation in (near) total darkness a device called "night vision goggles" (NVG) amplifies IR or low light to produce a monochromatic vision. NVG is for instance used by military forces. Yet, they have some limits. NVG produces a VA of 6/12 or less, which creates an illusion of longer distances to terrain obstacles and prevents pilots from seeing power lines. The first Norwegian military helicopter casualty linked to use of NVG occurred in 1995 (Figure 6). In addition to an NVG camera, the new Lockheed Martin F-35 Lightning combat aircraft, which has been bought by Norway and Denmark, also has 6 IR receptors to monitor the surroundings. This enables the pilot to see "through" the floor of the cockpit.

In the permanent absence of daylight, many animals have, besides losing VA or even functional eyes, evolved the ability to create artificial light. This is called bioluminescence. Probably less known is that even humans glimmer with a light intensity 1000 times less than the sensitivity of our eyes. This is due to direct and rhythmic emissions from our bodies of photons within the visible spectrum, related to changes in energy metabolism.

Beyond the use of visual aids, is it possible to extend our predetermined sensitivity to electromagnetic radiation? A new study suggests that this can be achieved by a medical procedure. Mouse eyes were experimentally injected with nanoparticles which adhered to the photoreceptors. The mice gained IR vision in the aftermath, sufficient to sort out shapes. This may lead to new technological breakthroughs in civilian encryption, security and military operations.

Superman has x-ray vision. Perhaps his mother planet Krypton lacked the protecting atmosphere which shaped our visual system? We will never equal his level, but in the coming decades, we may perhaps be liberated from our biological restrictions and expand our light-sensitive capabilities in unknown ways. Only time will tell if there will be a "bright" future. ■

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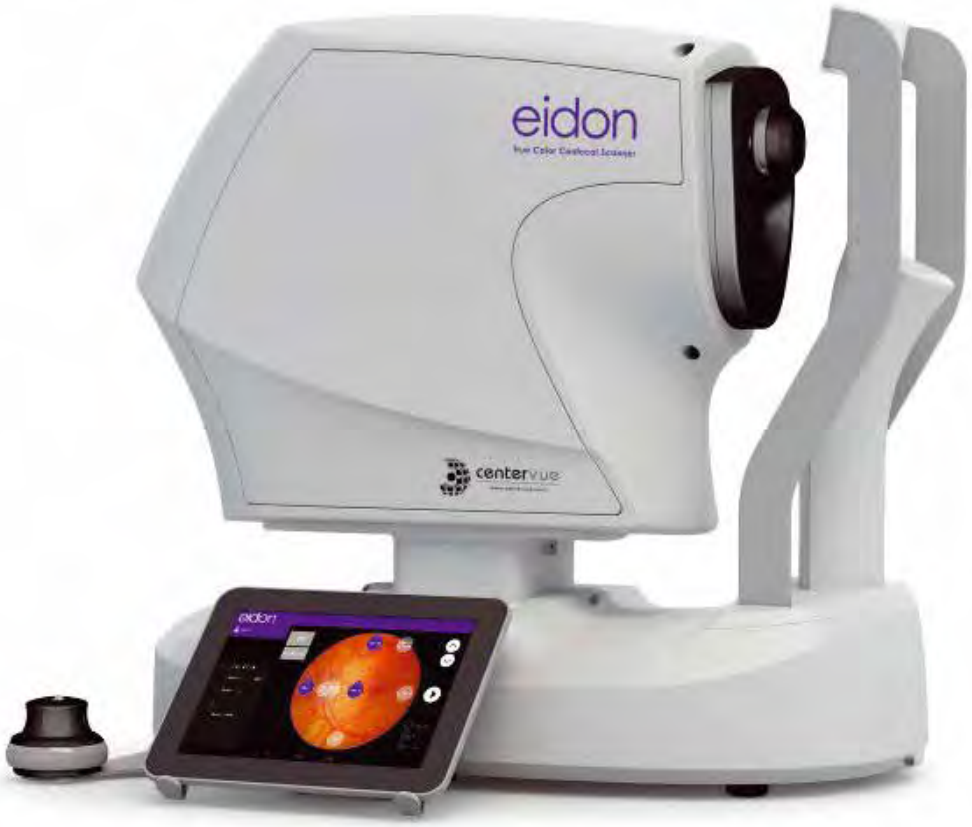

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Neil Lagali

New rare disease **European Network** led by **Sweden**

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Aniridia is a rare congenital eye disease, affecting about one in 80.000 people, and requiring intensive eye care, social and community support from birth and throughout an individual's lifetime. Most ophthalmologists will have come across one or more cases of aniridia during their careers. Although classified as a rare disease, congenital aniridia is a pan-ocular disease characterized by an underdevelopment or improper development of eye structures, often leading to iris and foveal hypoplasia, nystagmus, cataract, glaucoma, limbal stem cell insufficiency, keratopathy and dry eye. For this reason, despite its rarity, aniridia requires significant eye care throughout life, and many subspecialties will have contact with persons with aniridia. Congenital aniridia is caused primarily by a mutation in the PAX6 gene responsible for ocular development *in utero,* however, over 500 unique mutations in this gene have been reported, resulting in a range of ocular phenotypes and prognoses. This complexity, combined with the rarity of the disease, means that very few effective treatments are available. What is needed is adequate-sized patient populations to conduct coordinated clinical and research activities, and improved information exchange in assessing and treating aniridia, with expertise being shared across geographically dispersed centers.

ANIRIDIA-NET (www.aniridia-net.eu) is a pan-European bottom-up network of researchers, ophthalmologists, trainees, aniridia patient organizations, industry and special interest groups funded by the European Union's Cooperation in Science and Technology (COST) program *(www.cost.eu)* for the period May 2019 – April 2023. The network is chaired by Prof. Neil Lagali in Linköping, Sweden with Vice-Chair Prof. Claus Cursiefen from Cologne, Germany. ANIRIDIA-NET currently consists of 28 European member countries and 2 near neighbor countries (Figure 1), with all the Nordic Countries represented. The overall goal of ANIRIDIA-NET is to improve clinical management of aniridia and promote innovative research and development of new alternatives for its diagnosis and treatment. This network encourages communication among healthcare professionals, researchers, and patient representatives to share their ideas and foster collaboration to improve aniridia management through evidence-based research, harmonized clinical protocols, pooling/sharing of samples and models and consensus activities.

Figure 1. Geographical distribution of ANIRIDIA-NET members, including 30 participating countries, 28 COST full or cooperating members (darker blue) and 2 near neighbour countries (lighter blue). Date updated: 14/04/2020. Created with mapchart.net.

ANIRIDIA-NET will achieve its goals through directed tasks and activities aligned along six different themes, each being the responsibility of a specific working group:

(1) **Clinical guidelines.** Harmonization/consensus on clinical examinations, treatment guidelines, patient information and clinical endpoints.
(2) **Clinical and cohort studies.** Development of clinical and cohort multicenter studies with patient data, and/or biological samples for biomarker, genetic and high-throughput molecular analysis.
(3) **Stem cells and regenerative medicine.** Approaches of stem cell research, tissue engineering, genetic techniques for developing translational regenerative therapeutic strategies.
(4) **Transplantation, inflammation and immunity.** Evaluation of emerging surgical techniques for aniridia associated pathologies.
(5) **Aniridia models for collaborative research.** Development of aniridia animal models and novel research techniques for the identification of new therapeutic stragegies.
(6) **Patient-driven research.** Support of patient participation in aniridia-focused research to raise awareness toward unmet patient needs and challenges.

The ANIRIDIA-NET consortium had a first kickoff meeting in Brussels in April 2019 (Figure 2), followed by a further meeting in Paris in September 2019, and a third meeting in Lisbon in late February 2020 (Figure 3). In June 2019, ANIRIDIA-NET co-organized a Nordic Countries Aniridia Conference held at the Hurdal vision rehabilitation center on a picturesque lake north of Oslo. A panel of expert researchers, clinicians and a geneticist presented information to patients and answered their questions in lively discussions. Additionally, ANIRIDIA-NET supports conference symposia such as a Special Interest Session on aniridia held at the European Vision and Eye Research annual congress in Nice in October 2019, where investigators across Europe presented their latest findings in aniridia-related research.

Figure 2. ANIRIDIA-NET members at the Action's kick-off meeting held in Brussels on April 2019. Networking meetings serve as essential support for collaboration, knowledge sharing and research promotion.

Figure 3. ANIRIDIA-NET members at the 3rd scientific meeting held in Lisbon in February 2019, coinciding with Rare Disease Day. Culture and assessment of limbal stem cells, clinical multicentre studies, harmonized clinical protocols, aniridia pathophysiology, post-transplant immunosuppression and MSCs for eye diseases were some of the topics covered during this networking event.

Training is an important component of ANRIDIA-NET, and in 2020-2021, two Training Schools will be organized, and these are open to doctoral, postdoctoral and resident trainees across Europe. Training schools combine lectures given by experts with hands-on practical wetlabs, workshops and social activities to foster networking among the trainees. Another important feature of this COST Action is the possibility for researchers or clinicians to obtain funding for cross-border research within the Short-Term Scientific Mission (STSM) scheme. Collaborative projects of scientific or clinical relevance, along with training and capacity-building, can be established through the exchanges of trainees or investigators in STSMs (Figure 4).

Any individual interested in aniridia research in the Nordic Countries is welcome to join and participate in ANIRIDIA-NET activities. This network is an open and inclusive group following EU-mandated principles. For more information and contact points for each working group, please visit the website www.aniridia-net.eu.

Figure 4. Elena Danielle, a MSc postgraduate at the Veneto Eye Bank Foundation (Italy), during a Short Term Scientific Mission (STSM) at the research group led by Heli Skottman at Tampere University (Finland). The goal of this STSM was to share knowledge on primary limbal stem cell culture and characterization techniques. STSMs give researchers the opportunity to foster linkages and build capacity in research.

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The role of **the omega-3 fatty acid biosynthetic products resolvin D1 and resolvin E1** in maintenance of **ocular surface health**

On February 28, 2020 Marit Lippestad defended her thesis "The role of the omega-3 fatty acid biosynthetic products resolvin D1 and resolvin E1 in maintenance of ocular surface health" for the degree of PhD at Institute of Clinical Medicine, Faculty of Medicine, University of Oslo (UiO).

Ocular surface inflammatory diseases such as dry eye disease and allergic conjunctivitis are common diseases and the prevalence of these diseases are increasing. Treatment options are limited, and new management methods are warranted.

Omega-3 fatty acid biosynthetic products named resolvins may actively stop inflammation. Resolvins have shown promising results as treatment of inflammatory diseases in the eye, including dry eye disease and allergic conjunctivitis. Before resolvins are used in treatment of ocular inflammatory disorders, the mechanism of action of the resolvins in healthy, non-diseased patients should be understood.

The aim of this project was to determine how the resolvins Resolvin D1 and Resolvin E1 work in healthy conjunctival goblet cells. Conjunctival goblet cells were studied since disruption in secretion of the goblet cell mucin MUC5AC is associated with both dry eye disease and allergic conjunctivitis. MUC5AC also plays an important role in ocular surface health as it lubricates the ocular surface and removes pathogens and allergens from the tear film, thus preventing inflammation.

Goblet cell function was studied in cultured rat and human conjunctival goblet cells. We identified the receptors for resolvin E1 in goblet cells using RT-PCR, western blot and immunohistochemistry. The calcium concentration in the cytosol of goblet cells and the amount of mucin secretion were measured after treatment with specific signaling pathway inhibitors added before stimulation with either resolvin D1 or resolvin E1. Our studies showed that the resolvins activate multiple signaling pathways to stimulate goblet cell mucin secretion. We believe that resolvins are important both in maintenance of ocular surface health and prevention of disease. Thus, resolvins may be potential new treatments of ocular inflammatory diseases.

All the work for the PhD was performed at Schepens Eye Research Institute/Massachusetts Eye and Ear, Department of Ophthalmology, Harvard Medical School under the supervision by Professor Darlene A. Dartt.

This summary was first published at UiO.


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Alvilda T. Steensberg


Ane Sophie Olsen


Miriam Kolko

Internetbaseret **perimetri**

– en mulig screeningsmetode for uopdagede synsfeltsdefekter?

Standardautomatiseret perimetri er i dag guldstandard ved test af patienters synsfelter. Dette er omkostningskrævende både i anskaffelse af udstyr samt uddannelse af personale, som skal guide patienten igennem testen. Internetbaseret perimetri bliver i dag udviklet og afprøvet som en mulig screeningsmetode, men ingen er endnu valideret til professionel brug.

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På verdensplan estimeres det, at 39 millioner mennesker er blinde. Den hyppigste irreversible årsag er glaukom[1]. Glaukom er en øjensygdom, som trods et fremskredent stadie med store synsfeltsdefekter kan forblive asymptomatisk. Undersøgelse af synsfeltet kan opdage asymptomatiske synsfeltsdefekter og lede til en tidligere diagnosticering af glaukom samt behandling med antiglaukommedicin, hvilket kan forebygge blindhed.

I takt med at befolkningen bliver ældre, vil antallet af patienter med glaukom stige, da der findes en klar sammenhæng mellem alder og prævalens[2]. Et nyere dansk studie har vist, at 4% af befolkningen >50 år benytter antiglaukomatøse dråber[3].

I dag testes synsfeltet oftest med standardautomatiseret perimetri (SAP)[4]. Humphrey Visual Field Analyzer (HFA) samt Octopus perimetre er oftest brugt til SAP. Disse metoder kræver instruktion af uddannet personale samt omkostningskrævende udstyr. Gennem de senere år er der blevet udviklet internetbaserede synsfeltstests, men det har ikke været muligt at finde en valideret screeningsmetode til professionel brug.

Screening er en metode til at konstatere ikke-diagnosticeret sygdom. Screening udføres på tilsyneladende raske individer. I 1968 opstillede Verdenssundhedsorganisationen (WHO) ti kriterier for vurdering af befolkningsrettede screeningsprogrammer også kaldet Wilsons kriterier. De ti oprindelige kriterier er sidenhen blevet modificeret bl.a. set i lyset af den genteknologiske udvikling, og i 2014 gav Sundhedsstyrelsen sit bud på anbefalinger vedrørende nationale screeningsprogrammer[5]. Glaukom vurderes at opfylde hovedparten af Sundhedsstyrelsens anbefalinger, da et screeningsprogram bl.a. vil kunne reducere den sygdomsspecifikke sygelighed, tilstanden udgør et væsentligt sundhedsproblem, samt der findes effektive metoder til udredning og behandling. Udfordringen er punkt fire på kriterielisten; "De anvendte testmetoder skal være simple, sikre, præcise, validerede og acceptable"[5]. Netop dette arbejdes der for tiden på rundt omkring i verden.

For at gøre en mulig screeningsmetode omkostningsmæssig fordelagtig foreslås internetbaseret perimetri. Det er vigtigt at understrege, at synsfeltsscreening via internettet ikke skal bruges diagnostisk, men som et nyttigt redskab til at opdage en synsfeltsdefekt og herefter lede til grundigere undersøgelser.

I det følgende præsenteres internetbaseret perimetri som en mulig screeningsmetode til at opdage asymptomatiske synsfeltsdefekter. Følgende metoder vil blive gennemgået: Peristat, Testvision, Visual Fields Easy og Melbourne Rapid Fields.

Peristat kræver adgang til en computer, er tilgængelig via "www.keepyoursight.org" og er gratis[6]. Testpersonen instrueres til korrekt hovedposition ved hjælp af det blinde punkt. Det øje, der testes, skal fiksere på et centralt punkt gennem hele testen, mens stimuli dukker op forskellige steder på skærmen. Testpersonen trykker på musen eller tastaturet, hver gang et stimulus registreres. Et studie fra 2005 validerede Peristat og fandt en sensitivitet på over 80% og en specificitet på over 94%[6].

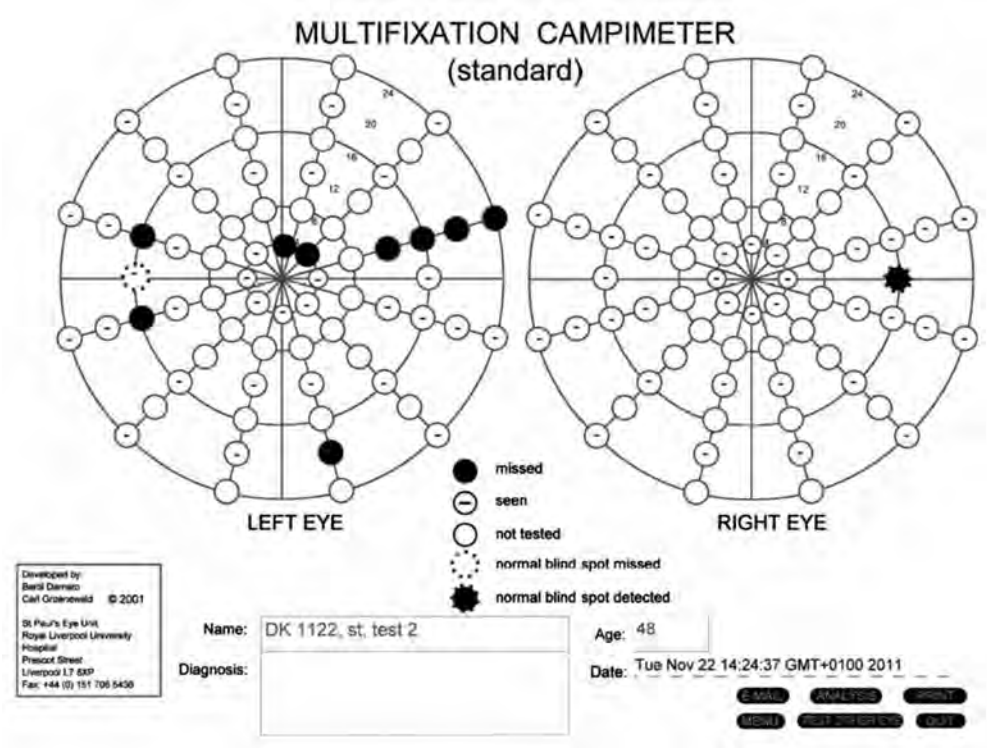
Testvision, også kaldet Damato Multifixation Campimetry Online (DMCO), er tilgængelig via "www.testvision.org"[7]. Testen kræver adgang til en computer og er gratis. Testpersonen instrueres til korrekt hovedposition ved hjælp af det blinde punkt. Denne testmetode er okulokinetisk, hvilket betyder, at testpersonen bevæger øjet rundt på skærmen til punkter, som dukker op løbende. Der findes tre versioner af testen: Standard, basis og avanceret. Den seneste validering af metoden er fra 2016, hvor der for standardversionen blev fundet en sensitivitet på 11,8%, 71,4%, 100% og 100% for henholdsvis mild, moderat, alvorlig og svær glaukom samt en specificitet på 98,1%[7].

Visual Fields Easy er en iPad-baseret screeningsmetode. Testen er fra 2012 og benytter suprathreshold-perimetri. Et studie fra Nepal har vist lovende resultater for opdagelse af synsfeltsdefekter ved moderat og svær glaukom[9].

Melbourne Rapid Fields er en nyere iPad-baseret synsfeltsundersøgelse fra 2016. Testen er udviklet af samme forskningsgruppe som Visual Fields Easy og er således en forbedret version af testen. Til undersøgelse af synsfeltet benyttes threshold-metoden[10]. Testpersonen

Figur 1. Skærmbillede af computerskærmen, når en testperson udfører synsfeltsundersøgelsen Peristat. Den grønne ring blinker i testpersonens blinde punkt og kontrollerer, at hovedpositionen holdes.

instrueres i at benytte en snor til at måle en afstand på 33 cm fra skærm til næseryg. Testen er todelt; under første del skal personen fiksere på midten af skærmen. Her testes det mest centrale synsfelt. Under den anden del rykkes fikseringspunktet på skift ud i hjørnerne af skærmen for at teste de mere perifere områder af det centrale synsfelt. Når et stimulus registreres, taster testpersonen på skærmen eller på et tastatur forbundet via Bluetooth. En stemme guider personen gennem hele testen på engelsk. Forskergruppen har sammenlignet Melbourne Rapid Fields med HFA og fundet dem stort set lige gode[11,12]. I et uafhængigt studie fra 2017 fandt man, at HFA og Melbourne Rapid Fields resultater var så godt som sammenlignelige. Således var der



Figur 2. Resultatudskrift fra Damato Multifixation Campimetry Online (DMCO). Testpersonen er en mand på 48 år, som for nylig har fået diagnosticeret glaukom i det venstre øje.

Figur 3. Testperson udfører Melbourne Rapid Fields på en iPad efter at have målt afstand på 33 cm fra skærm til næseryg.

ingen signifikant forskel på sensitivitet eller specificitet i de to tests[13].

Generelt er udfordringerne ved internetbaseret perimetri at få testpersonen til at sidde i en uændret position gennem hele testen og at sikre fiksering af pupil. Herudover kan udfordringer som varierende belysning i testlokalet påvirke resultatet.

På trods af fejlkilder og umiddelbare udfordringer ved internetbaseret perimetri er der væsentlige fordele som de lave omkostninger og lettere tilgængelighed. Der er derfor god grund til at arbejde videre med internetbaseret perimetri, som på sigt kan blive et vigtigt værktøj til opsporing af uerkendte synsfeltsdefekter. Det er dog vigtigt at understrege, at der på nuværende tidspunkt fortsat ikke findes en internetbaseret synsfeltstest, som er blevet valideret til brug som en pålidelig screeningsmetode.

References:
www.oftalmolog.com


Jakob Grauslund

Screening for **diabetisk retinopati**

– etablering af en regional screeningsklinik

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”Hej Jakob. Vil du hjælpe mig med at oprette en regional øjenscreeningsklinik, som kan være med til at hjælpe de 70.000 patienter med diabetes i Region Syddanmark?” Året var 2018, og stemmen i den anden ende af telefonen tilhørte Jan Erik Henriksen, som just var tiltrådt som direktør på det nyetablerede Steno Diabetes Center Odense (SDCO).

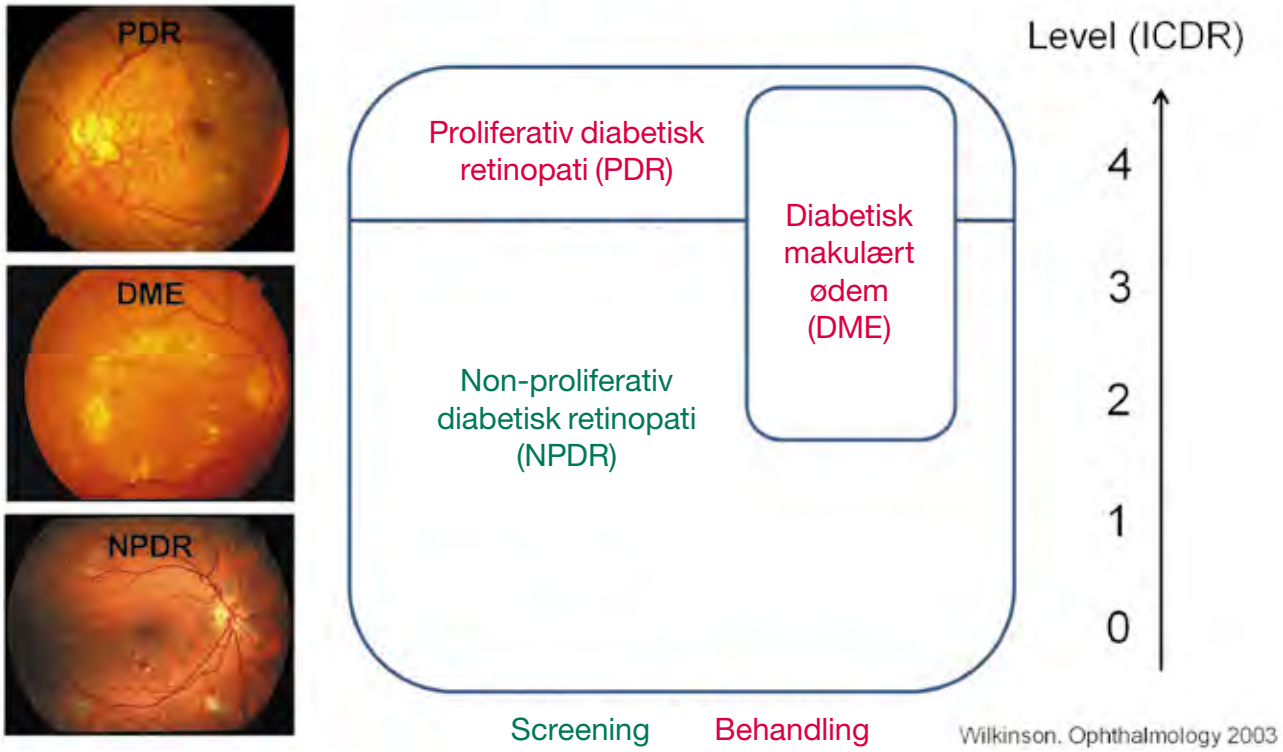
Diabetisk øjenscreening

Baggrunden for at foretage diabetisk øjenscreening er, at asymptomatiske patienter risikerer at udvikle synstruende diabetisk retinopati (DR) med irreversibelt synstab (Figur 1). Det er derfor vigtigt at følge patienterne med regelmæssig øjenscreening, så de kan henvises til behandling, hvis de udvikler proliferativ diabetisk retinopati (PDR) eller (diabetisk makulært ødem) DME. Man har i en række år tilbudt regelmæssig øjenscreening til alle danske patienter med diabetes, og omkring 100.000 patienter tager årligt imod tilbuddet[1]. Hovedparten af patienterne har ukompliceret type 2 diabetes, og disse screenes oftest hos de praktiserende øjenlæger. Blandt den resterende gruppe ses overvejende patienter med type 1 diabetes eller kompliceret type 2 diabetes. Disse patienter er ofte tilknyttet et diabetesambulatorium på et sygehus, og flere steder i landet er dette koblet til en øjenscreeningsklinik. På øjenafdelingen på Odense Universitetshospital (OUH) havde vi således i ti år haft et godt samarbejde med diabetesafdelingerne i Odense og Svendborg, og planen var netop at lave en regional overbygning på dette samarbejde.

Samme dag under samme tag

Den direkte anledning til samtalen var, at SDCO var etableret på baggrund af

Klassifikation af diabetisk retinopati



Figur 1: Diabetisk retinopati (DR) i henhold til International Clinical Diabetic Retinopathy (ICDR) skalaen med graderne 0 (ingen DR), 1-3 (mild til svær NPDR) og 4 (PDR)6. Ved udvikling af synstruende DR (PDR eller DME) henvises patienterne til behandling på nærmeste øjenafdeling.

en bevilling fra Novo Nordisk Fonden til Region Syddanmark. SDCO er en offentlig sygehusklinik beliggende på OUH, som varetager den ambulante behandling af patienter med diabetes nær Odense. SDCO arbejder tæt sammen med de andre diabetesambulatorier i Region Syddanmark og er opbygget omkring en række kerneaktiviteter. En af disse aktiviteter er forebyggelse af diabetiske senkomplikationer ved hjælp af sammedagsscreening ud fra one-stop-shop princippet "alt under samme tag på samme dag". Ideen er, at patienter med diabetes kan få foretaget alle relevante diabeteskontroller på samme dag og afslutningsvis tale med en diabeteslæge, som giver alle prøvesvar og aftaler en behandlingsplan med patienten.

Tidligere gik mange patienter til øjenkontrol ét sted, fik undersøgt fødder et andet sted og fik målt blodtryk og blodsukker et helt tredje sted. De mange undersøgelser kostede meget tid for patienterne, og information forsvandt i kommunikationen mellem de forskellige instanser. Der kunne fx gå lang tid fra udførelsen af en undersøgelse, til patienten havde tid på sygehuset, og ofte nåede svaret aldrig frem til diabetesambulatoriet.

Nye vinde

Det forestående arbejde gav anledning til at revidere vores tilgang til øjenscreeningen. Sideløbende med etableringen af det nye screeningscenter havde jeg fornøjelsen at stå i spidsen for udarbejdelsen af de nye danske retningslinjer for diabetisk øjenscreening[2], og det var selvfølgelig et krav, at screeningscenteret skulle leve op til de nye fordringer om at anvende individualiserede screeningsintervaller og inkludere OCT-scanning ved mistanke om DME.

Da jeg gjorde status over vores daværende screeningsindsats, kunne jeg glæde mig over en række forhold, men kunne samtidigt konstatere, at vi var udfordret på flere punkter. Eksempelvis gik der ofte flere uger mellem, at øjenfotoet blev foretaget på diabetesafdelingen, til vi fik beskrevet svaret på øjenafdelingen; dermed fik patienterne ofte først svar på øjenscreeningen ved næste diabeteskontrol mange måneder senere. Desuden havde vi en del patienter, som blev indkaldt til øjenafdelingen på mistanke om begyndende DME, hvor en efterfølgende OCT-scanning straks afkræftede dette. Dette gav i sagens natur anledning til flere måneders bekymring hos patienterne, som straks kunne have været afkræftet med en OCT-scanning.

Etablering af Graderingscenter SDCO

I sidste halvdel af 2018 gik arbejdet for alvor i gang. Det blev besluttet, at den nye øjenscreening skulle etableres som led i sammedagsscreeningen på SDCO og seks andre diabetesafdelinger

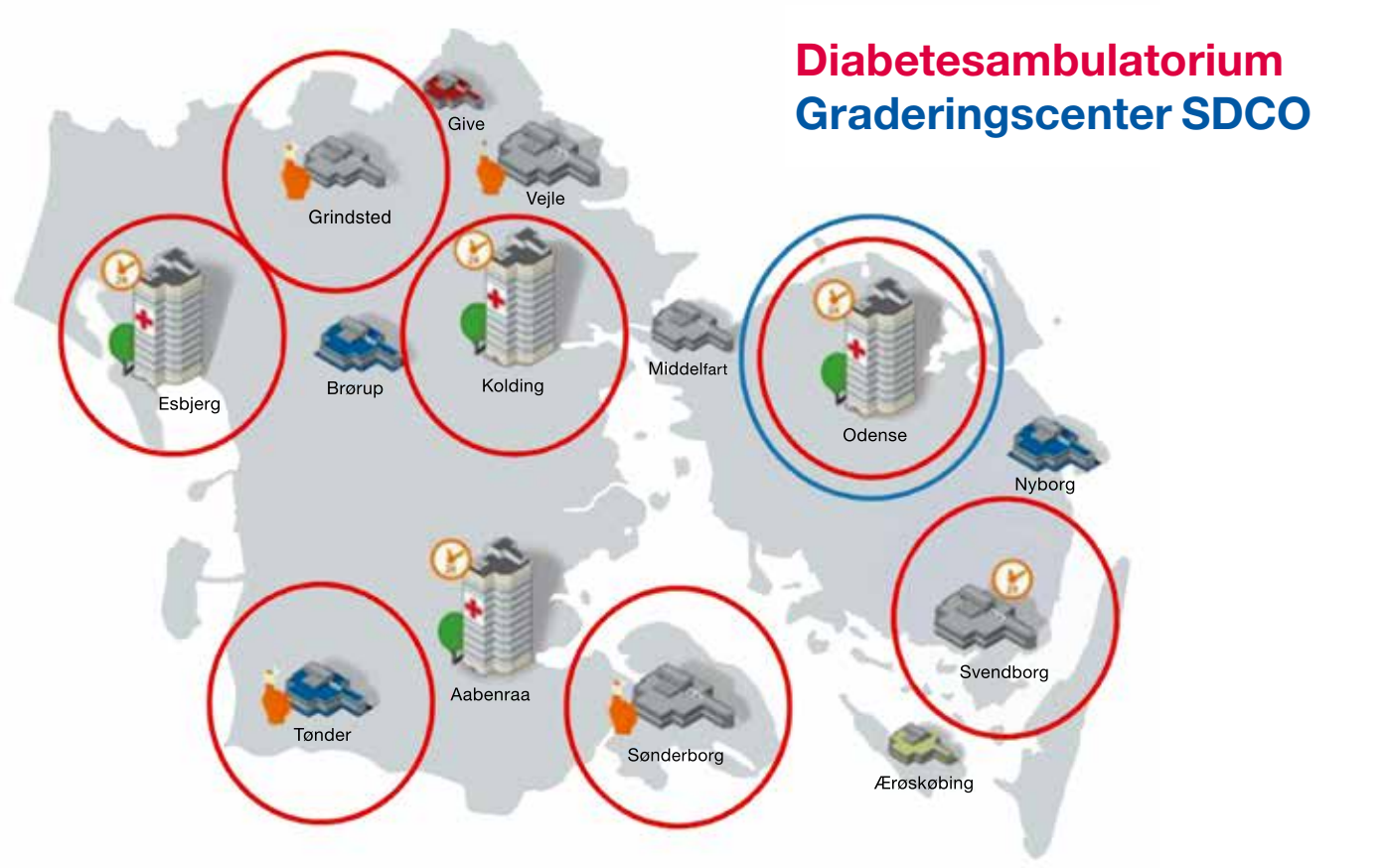
i Region Syddanmark (Figur 2). Der skulle etableres et graderingscenter på øjenafdelingen på OUH (Graderingscenter SDCO), som skulle vurdere øjenscreeninger fra de syv diabetesafdelinger, hvor patienterne mødte til sammedagsscreening. De syv screeningsstationer skulle således sende information om patienten (alder, køn, type og varighed af diabetes), langtidsblodsukker (HbA1c), blodtryk, visus, fundusfoto (6-felts mosaik) og evt. OCT (ved mistanke om DME). Herefter skulle undersøgelserne vurderes af en speciallæge i medicinsk retina, som i løbet af højst en time skulle sende svar og handleplan (forslag til nyt screeningsinterval eller indkaldelse til behandling på nærmeste øjenafdeling) retur (Figur 3+4). En arbejdsgruppe blev herefter nedsat, og der blev truffet aftale om indkøb af autorefraktorer (Topcon Auto Kerato-Refractometer KR-800) og funduskameraer med indbygget OCT (Topcon Triton Swept Source OCT).

Nu begyndte den spændende del af processen. Som led i screeningen skulle en række sygeplejersker, bioanalytikere og optikere fra de syv screeningsstationer oplæres i øjenscreening. Mange af disse havde aldrig tidligere beskæftiget sig med øjensygdomme, så en grundig oplæring var vigtig. Glæden var derfor stor, da 20 yderst motiverede kursister dukkede op til første øjenscreeningskursus i december 2018. Et intensivt 2-dages kursus blev afholdt med en kombination af teoretisk undervisning, praktiske kameraøvelser (Figur 5) og afsluttende certificeringstest (Figur 6).

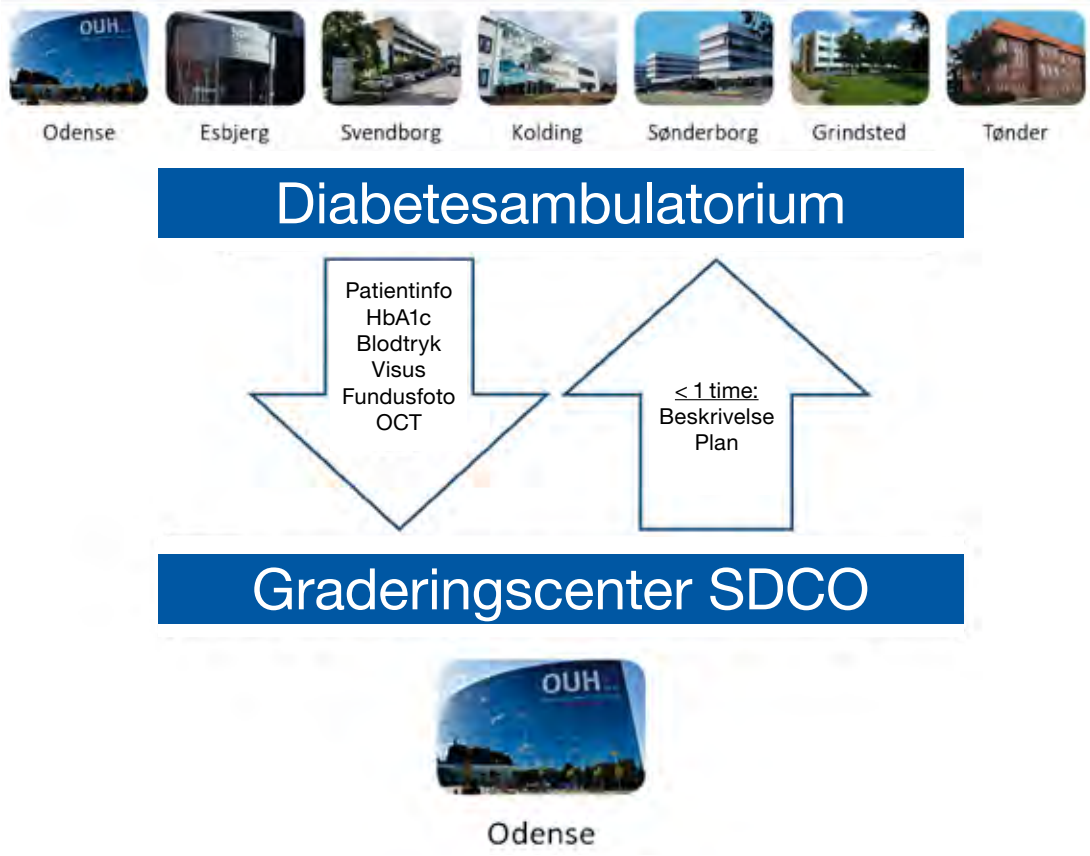
Jeg har valgt at skelne mellem to faggrupper (Figur 7). Faggruppe 1 er ansat på screeningsstationerne på de syv diabetesambulatorier. De er ansvarlige for patientundersøgelserne, men skal også foretage en indledende screening (Niveau 1 screening, Figur 8) for at afgøre, om der er DR på mindst ét øje, og om der skal foretages OCT scanning. Hos patienter uden DR (=grad 0) gives svaret direkte fra Faggruppe 1 til patienten (med efterfølgende verificering af prøvesvar på Graderingscenter SDCO), og patienten oplyses i dette tilfælde straks om, at der ikke ses diabetesforandringer i øjnene, og næste øjenscreening planlægges (oftest efter 24 måneder).

Faggruppe 2 er oftalmologiske speciallæger i medicinsk retina (Figur 7). De sidder på Graderingscenter SDCO og modtager herfra undersøgelserne fra de syv screeningsstationer. De har til opgave at fastsætte den eksakte grad af DR (Niveau 2 screening, Figur 1+8) og informere screeningsstationen om svaret og handlingsplanen. Alle modtagne billeder med DR (>grad 0) vurderes inden for en time, og ved resten (grad 0) verificeres Niveau 1 vurderingen, som er givet af Faggruppe 1.

Der er to formål med at indføre et todelt screeningssystem med Niveau 1 og 2 screening. For det første giver det mulighed for, at den sundhedsfaglige person i Faggruppe 1 kan give et umiddelbart svar til patienter uden



Figur 2: Øjenscreening på Steno Diabetes Center Odense (SDCO) med et centralt graderingscenter, som vurderer øjenscanninger fra syv diabetesafdelinger i Region Syddanmark.

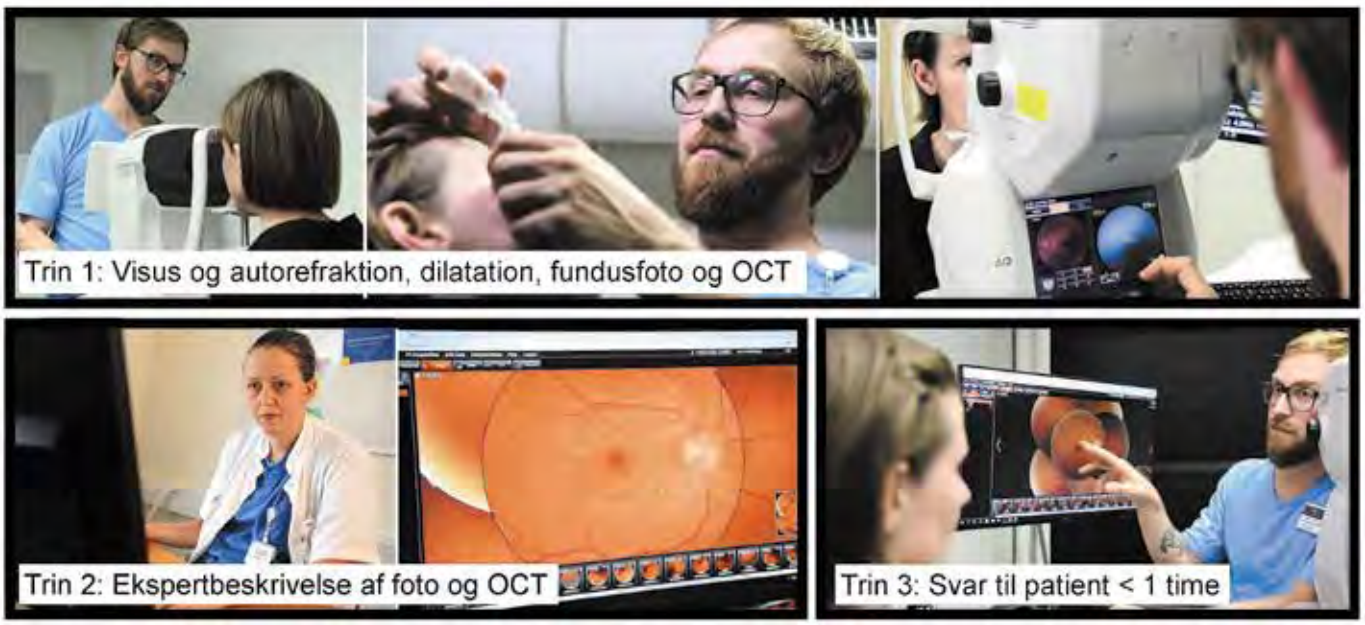


Figur 3: Arbejdsgang ved diabetisk øjenscreening på Steno Diabetes Center Odense. Øjenfotos og relevante oplysninger modtages på Graderingscenter SDCO, hvorefter resultatet returneres i løbet af en time, så patienten samme dag kan modtage svar og videre behandlingsplan på den lokale diabetesafdeling.

DR. Dette giver ofte anledning til en god snak med patienten om, hvordan man bedst minimerer risikoen for at udvikle synstruende DR. For det andet er det med til at øge involveringen af de sundhedsprofessionelle fra Faggruppe 1, så man ikke blot udfører en teknisk opgave, men også er medspiller i den sundhedsfaglige vurdering.

Det første år

Den nye øjenscreening blev startet op 1. marts 2019 og har således kunnet fejre sin første fødselsdag. Det store engagement fra alle sider har været

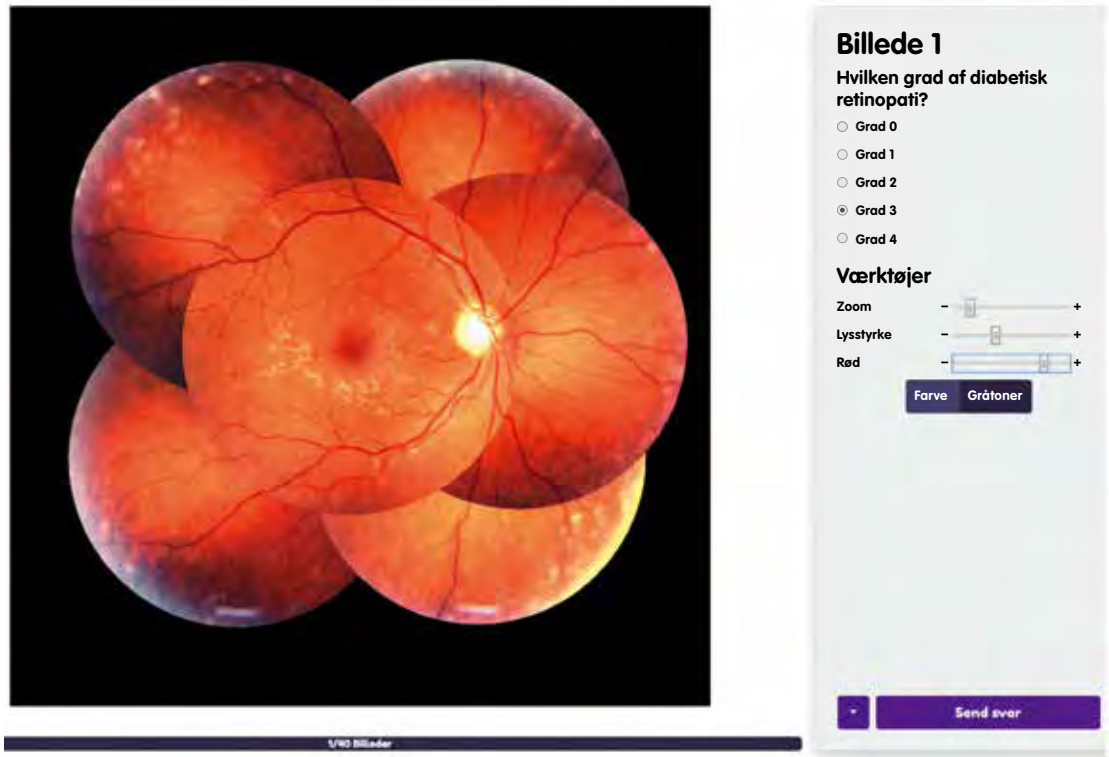


Figur 4: Arbejdsgang set med patienten øjne. Der foretages visusmåling og autorefraktion efterfulgt af pupildilatation og fundusfotografering. Ved behov suppleres med OCT. Når ekspertbeskrivelse er modtaget fra Graderingscenter SDCO, informeres patienten om behandlingssvar.

Figur 5: Demonstration af fundusfotografering ved optiker Martin Neumann, Steno Diabetes Center Odense.

med til at sikre, at vi heldigvis har været forskånet for store opstartsproblemer. Allerede første dag modtog vi således 23 øjenscreeninger af høj billedkvalitet.

Gennemsnittet af daglige scanninger lå de første måneder omkring 30, men i februar 2020 blev der sat ny rekord med et dagligt gennemsnit på 48,3 øjenscreeninger, og rekorden blev sat fredag 21. februar 2020, hvor 60 patienter blev screenet. Samlet har 7.200 personer



Figur 6: Computerbaseret certificeringstest med gradering af 40 billeder med diabetisk retinopati. Ved Niveau 2 certificering skal angives specifik grad af diabetisk retinopati, og ved billeder med grad 4 (proliferativ diabetisk retinopati) skal det anføres, om der er aktiv sygdom, som kræver henvisning til behandling.

Faggrupper	Faggruppe 1	Faggruppe 2
Faglig baggrund	Sygeplejerske Bioanalytiker Optiker	Medicinsk retina speciallæge
Ansættelsessted	Diabetesambulatorium (Odense, Svendborg, Kolding, Esbjerg, Sønderborg, Grindsted, Tønder)	Graderingscenter SDCO (Øjenafdelingen, Odense)
Faglig opgave ved øjenscreening i SDCO	Synsmåling Autorefraktion Fotografering OCT-scanning (ved behov) Niveau 1 screening	Niveau 2 screening

Figur 7: Arbejdsopgaver for de to faggrupper.

Screeningsniveau	Niveau 1	Niveau 2
Ansvarlig	Faggruppe 1	Faggruppe 2
Arbejdsbeskrivelse	Er der DR på mindst ét øje? Skal der foretages OCT?	Fastsætte endelig grad af DR ud fra ICDR skala. Fastsætte, hvorvidt der foreligger behandlingskrævende DME (hvis der er foretaget OCT). Konfirmere Niveau 1 vurdering og behandlingsplan

Figur 8: Beskrivelse af de to screeningsniveauer. Alle fotos vurderes således både af Faggruppe 1 og Faggruppe 2.

modtaget diabetisk øjenscreening på SDCO det første år.

Til at sikre rettidig vurdering af øjenscreeningerne er Graderingscenter SDCO bemandet alle hverdage kl. 8-15. Det er også muligt at komme i telefonisk kontakt med screeningsvagten på Graderingscenter SDCO, og denne mulighed er med til at sikre et godt samspil mellem Faggruppe 1 og 2.

De fleste erfaringer fra første år har været særdeles positive. For det første udtrykker langt de fleste patienter stor glæde over at kunne samle alle diabeteskontroller samme dag, og diabeteslægerne er ligeledes glade for at have en aktuel øjenstatus at kunne forholde sig til, når den diabetiske behandlingsplan skal lægges. For det andet har det været en sand fornøjelse at arbejde sammen med de mange dygtige og engagerede medarbejdere fra diabetesafdelingerne. Der udvises stor interesse og glæde over at være involveret i screeningen, og mange viser screeningsbillederne direkte til patienterne og sender gerne nysgerrige spørgsmål til mig, hvis de ser noget ukendt på billederne eller scanningerne. For det tredje er det også spændende, at vi som oftalmologer bliver mere inddraget i diabetesbehandlingen på diabetesambulatorierne. Jeg har i løbet af 2019 været rundt på de forskellige screeningsklinikker og er overalt blevet mødt med en stor nysgerrighed og interesse for at skabe stærkere patientforløb på tværs af faggrænserne.

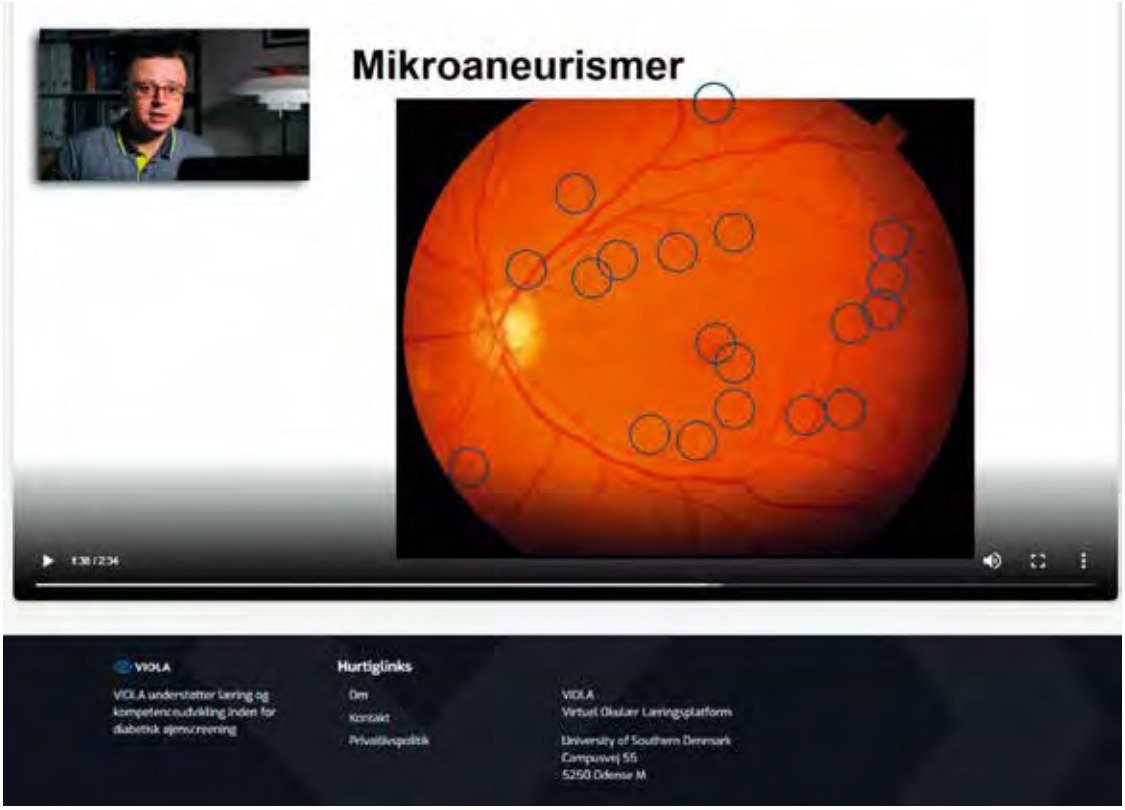
En af de største gevinster er muligheden for at udføre OCT hos patienter med centrale blødninger eller mikroaneurismer. Her er det sjældent muligt at afgøre, om der er DME ud fra et 2-dimensionelt fundusfoto[3,4]. Disse patienter skulle tidligere henvises til øjenafdelingen, men nu kan vi i stedet diagnosticere og følge dem i screeningsklinikken, hvis der kun er tale om et beskedent ødem, som ikke truer synet. Disse patienter ses igen tre måneder senere, hvor ødemet ofte er regredieret efter optimering af den glykæmiske regulation.

Det første år har naturligvis også budt på en række udfordringer, som vi løbende har måttet håndtere. Vi har for det første haft brug for at være tydelige i forhold til at informere patienterne om, at det er essentielt med livslang diabetisk øjenscreening, men at dette kun skal foretages ét sted. Typisk vil det være indiceret at fortsætte screeningen hos egen øjenlæge, hvis man har konkurrerende øjenlidelser (fx glaukom), som ikke kan håndteres i en øjenscreeningsklinik, som i sagens natur kun har til formål at vurdere DR. Omvendt er der mange patienter, som er rigtig glade for at gå til SDCO-screening, hvis de ikke fejler andet med øjnene. Dermed reduceres antallet af kontakter med sundhedsvæsenet, hvilket ofte har stor betydning for patienter med diabetes. Tilsvarende kan der frigøres ressourcer hos de praktiserende øjenlæger, hvor ledige tider ofte er en mangelvare.

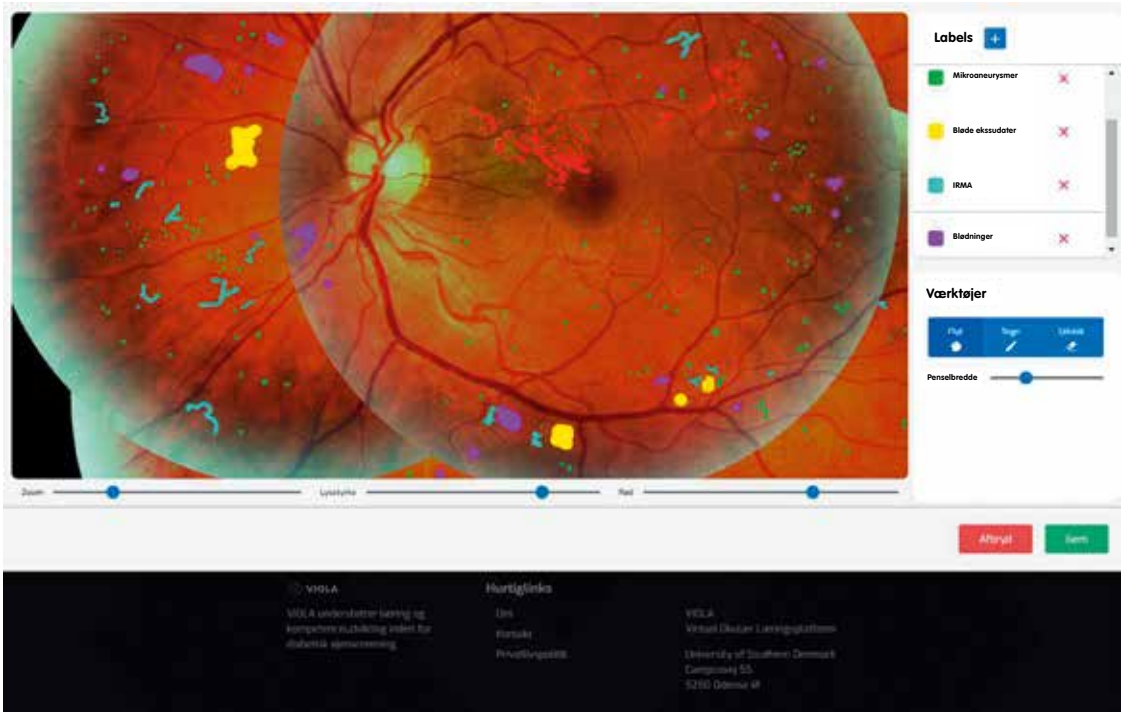
En anden udfordring har været det løbende personaleskift på diabetesafdelingerne. Vi har samlet trænet og certificeret 25 personer i Faggruppe 1, men der falder hele tiden nogle fra, og nye kommer til. Af samme årsag udbydes screeningskurset én gang årligt, og ved kurset i november 2019 deltog en blanding af 21 nye og gamle kursister (Figur 9).

Kommunikation har dog været den største udfordring. Det er især i Faggruppe 2, vi har skullet vænne os til at bruge meget præcise formuleringer i de prøvesvar, vi sender tilbage til Faggruppe 1. Det skal således fremgå tydeligt, hvilken information, der skal gives videre til patienten. Hvis der fx ses en glaukomsuspekt papil, skal det fremgå tydeligt, at patienten skal opsøge en praktiserende øjenlæge med henblik på glaukomvurdering med måling af synsfelt og øjentryk. Vi har gennem

Figur 9: Afholdelse af andet screeningskursus i november 2019.



Figur 10: Eksempel på videolektion om mikroaneurismer i VIOLA.



Figur 11: Ekspertvurderinger af forskellige diabeteslæsioner i VIOLA. Kursisten bliver præsenteret for det underliggende billede og skal herefter markere et antal læsioner, hvorefter disse sammenholdes med eksperternes vurdering. Til formålet udarbejdes et billedsæt på 300 fotomosaikker fordelt på alle grader af diabetisk retinopati.

årets løb haft fokus på at udvikle en stærk dialog mellem Faggruppe 1 og 2. Mange gange kan personer fra Faggruppe 1 være trygge ved at skulle informere patienten om at kontakte en praktiserende øjenlæge, hvis der udvikles kataraktbetinget synstab (fx ved slørede fotos), men andre gange kan det være svært at tage en snak med patienten om vitaminprofylakse ved tør AMD.

VIOLA – virtuel kompetenceudvikling

Den telemedicinske øjenscreening giver også andre muligheder for at udvikle virtuelle løsninger. Der er stor interesse for at foretage selvstændig kompetenceudvikling, og der har været stor efterspørgsel efter et virtuelt kursus i diabetisk øjenscreening. For at honorere dette er vi i tæt samarbejde med professor Thiusius Savarimuthus gruppe på Mærsk Mc-Kinney Møller Instituttet, Syddansk Universitet, ved at søsætte en virtuel okulær læringsplatform, VIOLA, som giver mulighed for virtuel oplæring i gradering af DR.

VIOLA opbygges af en række lektioner, som hver især svarer til en bestemt grad af DR. I hver lektion vil der være en indledende undervisningsvideo (Figur 10) efterfulgt af en række markeringsøvelser, hvor man skal identificere en række diabetiske øjenlæsioner som fx mikroaneurismer, hårde ekssudater, bløde ekssudater, blødninger, IRMA og proliferationer. Markeringen vil herefter blive sammenholdt med ekspertvurderinger (Figur 11) og en adaptiv læringsalgoritme sikrer, at øvelserne især fokuseres på de læsioner, som man har problemer med at identificere. Hver lektion inkluderer også en graderingstest, og hele kurset afsluttes med en certificeringstest, som alle i Faggruppe 1 og 2 skal igennem én gang årligt. Certificeringen er niveaudelt, så Faggruppe 1 blot skal kunne skelne grad 0 fra resten, hvorimod Faggruppe 2 skal kunne identificere den eksakte grad af DR og tage stilling til, om patienten skal henvises til behandling.

VIOLA forventes implementeret i september 2020 og skal efter planen også tilbydes til sundhedsprofessionelle uden for SDCO, som ønsker optræning og certificering i gradering af DR.

År 2 – i skyggen af COVID-19

Efter et godt første år, blev vi i marts 2020 udfordret af COVID-19-epidemien, som i skrivende stund har medført en betydelig nedgang i screeningskadencen. Vi ser frem til atter at tilbyde diabetisk øjenscreening i samme omfang som tidligere.

Tilsvarende screeningsinitiativer er ved at blive startet op i de andre regioner i Danmark, og det forventes således, at der i nærmere fremtid vil kunne tilbydes en forbedret hospitalsbaseret diabetisk øjenscreening, som forhåbentlig kan være med til at fastholde patienter med diabetes i livslange screeningsforløb, hvormed vi håber at kunne bidrage til at reducere antallet af personer med diabetesbetinget synstab.

Vi forventer i fremtiden at anvende diabetisk øjenscreening med kunstig intelligens. Dette tilbydes allerede enkelte steder i udlandet, men de nuværende systemer er desværre ikke egnet til danske forhold[5]. Det er derfor et klart forskningssatsningsområde hos SDCO at udvikle en screeningsalgoritme, som kan assistere i identifikationen af patienter med synstruende DR, som har behov for behandling for at forhindre irreversibelt synstab. Den nye screeningsklinik giver et godt grundlag for at udvikle og implementere en sådan forbedret øjenscreening.

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Erlend Christoffer Sommer Landsend, Senior Consultant and researcher at Department of Ophthalmology, Oslo University Hospital

Congenital **Aniridia**

Exploring Visual Disabling Manifestations in the Ocular Surface and Ocular Fundus through Clinical and Translational Approaches

Erlend Christoffer Sommer Landsend (M.D.) defended his doctoral thesis on February 13 this year at the Faculty of Medicine, University of Oslo. Congenital aniridia is a panocular disease, which is characterized by hypoplasia of the iris and the retinal fovea at birth. Foveal hypoplasia is the main cause of congenital reduced vision in aniridia. Most patients are born with low vision. Serious ocular complications may reduce the vision further in patients with aniridia. These include aniridia-associated keratopathy, which leads to progressive opacification of the cornea, pain, and often considerable visual impairment or blindness.

In his thesis, Landsend included 35 patients with aniridia and 21 healthy individuals. The participants were examined extensively regarding dry eye disease. Cytokine concentrations in the tear fluid were measured. Next, 14 of the 35 aniridia patients underwent autofluorescence imaging of the ocular fundus. The images were compared with 14 age- and gender-matched healthy individuals.

Landsend and colleagues detected more severe dry eye disease in aniridia patients than in healthy participants. Importantly, development of dry eye disease and keratopathy were interconnected. Aniridia patients showed more inflammation at the ocular surface in terms of increased levels of a number of pro-inflammatory tear cytokines. Higher cytokine concentrations were associated with more severe dry eye disease. Landsend found that autofluorescence imaging could be a useful tool in evaluation of foveal hypoplasia and give information that is not available through other clinical tools. Further, the findings give clues to the pathophysiology of foveal hypoplasia and to foveal development in general.


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COVID-19: Do's and Don'ts

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In December 2019, Wuhan, China, was faced with a new type of coronavirus, i.e. 2019 novel coronavirus (COVID-19).[1] Since then, the disease has affected most of the world by pushing healthcare systems to their breaking points, taking human lives, and causing financial losses. The aim of the present article is to provide an overview of the disease for eye health professionals and to provide strategies for protecting clinicians and patients.

Coronaviruses

Coronavirus (CoV) is a group of enveloped positive-strand RNA viruses for which there are four genera: a- and b-CoV, which typically cause infections in human and mammalian respiratory, gastrointestinal, and central nervous systems, and g- and d-CoV, which mainly infect birds.[2-6]

Previously, other types of coronavirus have affected the world, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) in 2003 and 2012, respectively.[7,8]

Spread of the disease, diagnosis, and the clinical features of patients

Despite the fact that SARS and MERS have much higher mortality rates than COVID-19,[9] the potential of spreading COVID-19 is much higher[10] and it can have fatal consequences, especially for at-risk patients, including the elderly and people with chronic diseases.[9] At this point, the spread of the disease is not well understood, but it is believed that the virus is transmitted through direct contact, indirect contact, or by droplets.[11] Indirect contact includes contact with different kinds of surfaces in the surroundings. Coronavirus has been shown to live for days on surfaces.[10]

Table 1. Personal protective equipment

COVID-19 diagnosis is confirmed with a positive real-time reverse transcriptase-polymerase chain reaction analyses of a mucous sample.[12] The sensitivity and specificity of the test are not well established, however; there might be up to 15-30% false negative results, causing problems in hospitals, as the test is typically used to decide whether or not to isolate patients or health workers.[13]

Diagnosis is important for lowering the risk of COVID-19 spread. A person infected with COVID-19 is likely to transmit the disease to 2.2 people, including men at increased risk of contracting the disease.[14] Ground-glass opacities are typical findings on chest X-rays and computed tomography (CT) scans, observed as a slight increase in lung density with sustained visibility of vascular structures and bronchial walls, and which is also observed in patients with lung cancer and diffuse pulmonary infiltrative disease.[15,16] The laboratory findings include lymphopenia (23.8%) and increased C-reactive protein (22.2%), and approximately one in every five patients admitted to hospital will need admission to the intensive care unit.[12] Currently, ongoing clinical trials are investigating potential treatment options, including chloroquine and antiviral drugs such as remdesivir, lopinavir, and ritonavir. However, it is important to emphasize that there are no evidence-based treatments at this time.[9,17,18]

Containing the disease

To contain the disease and protect individuals, the World Health Organization has issued recommendations for healthcare professionals that include postponing all non-urgent visits to the hospital and the use of personal protective equipment, including protective glasses, face masks, and disposable gloves (Table 1).[19,20] All patients presenting with COVID-19 symptoms (Table 2) are advised to stay home and self-isolate as long as symptoms have not progressed and put the patient at risk.[10] Early in the pandemic, Dr. Li Wenliang, a Chinese whistleblower and ophthalmologist, lost his life after treating a patient with glaucoma who was infected with COVID-19 but who did not present any symptoms.[11] This case emphasizes the fact that ophthalmologists are in close contact with patients and mucous membranes, and therefore ophthalmologists are prone to be infected by patients. More importantly, if doctors are infected, patients would be easily infected with COVID-19 as well.[11,21] To prevent doctors from spreading the disease to patients, health workers in the Capital Region of Denmark are offered testing to determine if they have developed antibodies against COVID-19. The test

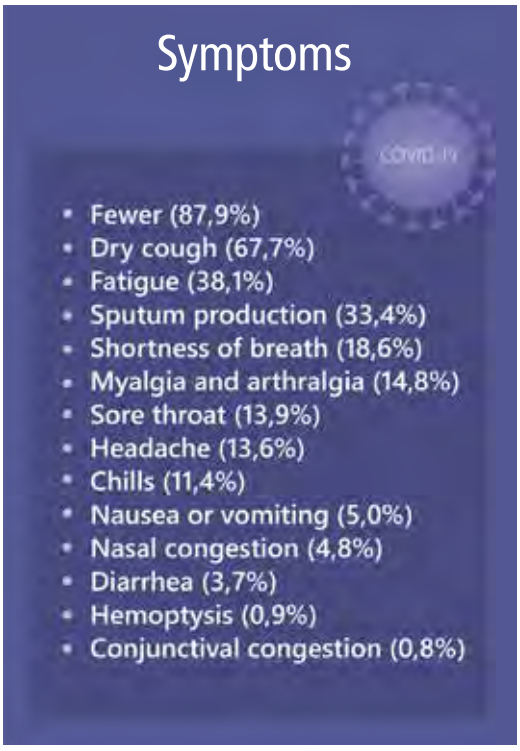

Table 2. Symptoms of COVID-19

Preclinical studies on previously identified coronaviruses

Animal species	Anatomical structure	Disease	Subgroup of coronavirus
Feline	Conjunctiva	Conjunctivitis	Feline infectious peritonitis virus
	Iris, ciliary body	Anterior uveitis	Feline infectious peritonitis virus
	Retina	Retinal vasculitis	Feline infectious peritonitis virus
	Retina	Choroiditis	Feline infectious peritonitis virus
Murine	Retina	Retinopathy	Mouse hepatitis virus – JHM virus
	Optic nerve	Optic neuritis	Mouse hepatitis virus – A59
Ferret	Multiple structures	Panophthalmitis	Feret systemic coronavirus

Table 3. Animal studies on previous coronaviruses

includes both immunoglobulin M, typically produced over weeks, and immunoglobulin G, typically produced over months.[22] However, the sensitivity and specificity of the test has not been evaluated.

In March 2020, a Hong Kong-based ophthalmologist published an article focusing on how to act responsibly during the crises. The article highlights that non-urgent visits must be postponed, which includes most cases in ophthalmology.[11] Previous experience from SARS and MERS further supports this statement, as the risk of contracting coronavirus is greatest during hospital visits.[14] Furthermore, the fact that most patients with eye disease are elderly, and thus more vulnerable to COVID-19, emphasizes that consultations with ophthalmologists should be postponed until further notice. [23,24] The main reason for avoiding the healthcare system is the risk of being infected by a COVID-19 carrier, who is possibly a doctor, a nurse, or other hospital staff, as healthcare workers maintain close human contact and pose a high risk of spreading the disease.

Eye disease induced by COVID-19

Preclinical studies

Animal studies have reported vision-threatening eye disease after infection with coronavirus subgroups. In this context, studies on cats (i.e., feline studies) have reported that coronavirus causes several ocular manifestations, including anterior uveitis, choroiditis, and retinal vasculitis, as part of the feline infectious peritonitis (FIP) complex, the term for coronavirus infection in cats.[25]

Figure 1. Slit-lamp examination of patients during COVID-19

Severe eye complications due to coronavirus have also been found in mice. Retinopathy and optic neuritis have been shown in mice infected with two coronaviruses: coronavirus mouse hepatitis virus JHM and A59, respectively.[26,27] Finally, a case report on a female ferret explained how a coronavirus infection, i.e., ferret systemic coronavirus, caused pyogranulomatous panophthalmitis in addition to other systemic manifestations.[28] Table 3 presents an overview of the existing animal studies.

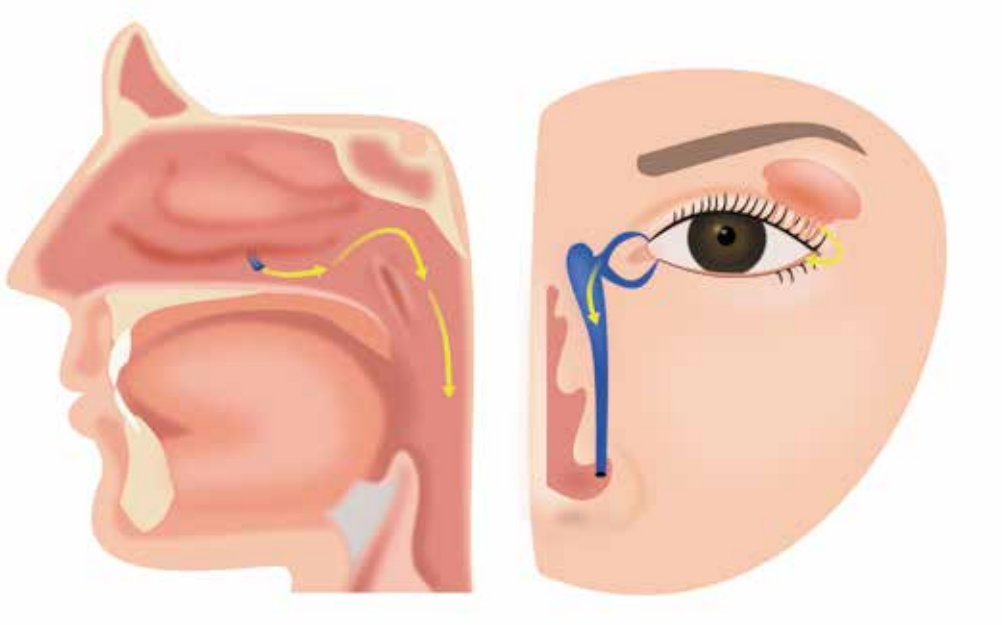

Figure 2. Spread of COVID-19 through the tear fluid drainage system

Clinical studies

Apart from conjunctivitis, there are, to our knowledge, no known COVID-19-induced eye diseases in humans. Among the less specific symptoms, eye pain has been reported. Currently, conjunctivitis caused by COVID-19 is a matter of dispute in the literature. However, this statement is supported by the American Academy of Ophthalmology and the European Society of Cataract & Refractive Surgeons.[29,30] Additionally, clinical cases support the possibility of COVID-19-induced conjunctivitis, as a healthcare professional who wore a face mask but not goggles while treating a patient infected with COVID-19 contracted the disease and reported conjunctivitis as the primary symptom.[31] In another study, the tear fluid of 30 patients with COVID-19 was analyzed. Among the 30 patients, only one patient complained of eye irritation. The tear fluid sample from this patient tested positive for COVID-19 bilaterally.

Apparently, COVID-19 enters the cell by interacting with the ACE2 (angiotensin I converting enzyme 2) receptor.[10,14,19] Compared to SARS and MERS, COVID-19 has a higher affinity for the receptor, which explains the aggressive behavior in the spread of the disease.[32] The ACE2 receptor has been found in the lower respiratory system but has not been identified in the oral or nasal cavity, which may be why patients rarely show upper respiratory system symptoms when infected with COVID-19 only.[33-35] Whether ACE2 receptors are found in the conjunctiva or cornea warrants further research.[36]

At present, we do not know whether COVID-19 can replicate in the conjunctival cells, and theoretically, COVID-19 can also spread to the upper and lower respiratory system through drainage of tear fluid (Figure 2).[19] Since conjunctivitis may be the first symptoms of COVID-19 and given the present knowledge gap, it is essential to wear personal protective equipment, including protective glasses. The American Academy of Ophthalmology has issued recommendations that are divided into "standard" and "transmission-based" precautions. Standard precautions include the use of face masks, disposable gloves, and protective glasses when examining a patient without COVID-19 symptoms in addition to cleaning and disinfecting environmental surfaces. When examining patients with symptoms of COVID-19 transmission-based precautions are recommended. In addition to standard precautions, these include equipping the patient with a surgical mask, appropriately positioning the patient unrelated to other people who are not properly equipped, limiting patient transport, and using of disposable or dedicated patient care equipment.[37] If aerosol producing procedures are performed, staff are advised to use special masks (N95 or better) instead of standard surgical masks, and pre-operative testing of asymptomatic patients are advised. Ophthalmologists should equip slit lamps with breath shields to prohibit speech during slit lamp examination and other close contact procedures.[38] In addition, the American Academy of Ophthalmology supports only urgent and emergent eye care during the crisis, which includes suspected or confirmed malignancy and sight- or life-threatening infections.[30]

In conclusion, COVID-19 has proven to be highly contagious and could have fatal consequences, especially for at-risk patients. The sensitivity and specificity of available testing methods have not been evaluated, and there may be up to 30% false negative results, leading to a false sense of security. To protect both clinicians and patients, the use of recommended protective personal equipment is advised, especially because we, as eye care professionals, are in close contact with patients who are typically elderly.

References: www.oftalmolog.com


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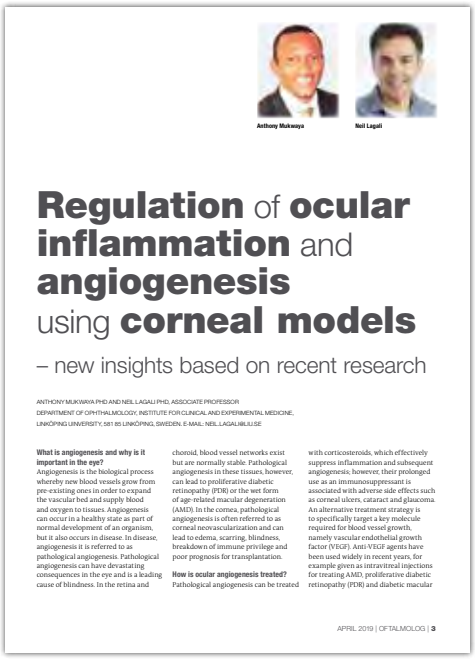
We are honored and deeply grateful to have our article selected to receive the Oftalmolog best paper award 2019. Ocular angiogenesis is a highly prevalent and serious condition and disease models are an important piece of the puzzle, helping us to identify underlying processes that we hope will one day lead to an improved understanding and treatment of vision-threatening neovascular disease.



Regulation of **ocular inflammation** and **angiogenesis** using **corneal models**

– new insights based on recent research

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What is angiogenesis and why is it important in the eye?
Angiogenesis is the biological process whereby new blood vessels grow from pre-existing ones in order to expand the vascular bed and supply blood and oxygen to tissues. Angiogenesis can occur in a healthy state as part of normal development of an organism, but it also occurs in disease. In disease, angiogenesis it is referred to as pathological angiogenesis. Pathological angiogenesis can have devastating consequences in the eye and is a leading cause of blindness. In the retina and choroid, blood vessel networks exist but are normally stable. Pathological angiogenesis in these tissues, however, can lead to proliferative diabetic retinopathy (PDR) or the wet form of age-related macular degeneration (AMD). In the cornea, pathological angiogenesis is often referred to as corneal neovascularization and can lead to edema, scarring, blindness, breakdown of immune privilege and poor prognosis for transplantation.

How is ocular angiogenesis treated?
Pathological angiogenesis can be treated with corticosteroids, which effectively suppress inflammation and subsequent angiogenesis; however, their prolonged use as an immunosuppressant is associated with adverse side effects such as corneal ulcers, cataract and glaucoma. An alternative treatment strategy is to specifically target a key molecule required for blood vessel growth, namely vascular endothelial growth factor (VEGF). Anti-VEGF agents have been used widely in recent years, for example given as intravitreal injections for treating AMD, proliferative diabetic retinopathy (PDR) and diabetic macular

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SILVER
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It gives me great pleasure to know that my personal perspective on Corneal Tissue Engineering published recently in Oftalmolog has won Silver! I have a great respect for Nordic ophthalmology, in particular their successes in corneal cell therapy. It is my hope that my own work in increasing our understanding of corneal biology and applying this to tissue engineering will further aid Nordic ophthalmologists and vision scientists in their endeavours to treat corneal blindness.

Oftalmologisk Selskap i Oslo

This article is a summary of the Oslo Society of Ophthalmology Honorary Lecture 2019 delivered by Professor Connon. Oslo Society of Ophthalmology, established in 1915, invites outstanding scientists four times a year to give lectures. Selected presentations are published in Oftalmolog.

Che John Connon

Corneal tissue engineering:
a personal perspective

CHE JOHN CONNON, PROFESSOR OF TISSUE ENGINEERING, NEWCASTLE UNIVERSITY, UNITED KINGDOM

There persists a growing and urgent need for engineered corneal tissue. We have taken an early lead on engineering cell-contrived corneal tissue i.e. controlling the inherent ability of corneal stromal cells to self-assemble and produce a collagen rich corneal stromal tissue - a mimic. We have dubbed this *in vitro* approach "tissue-templating". Central to this method is the axiom, 'where cells lead collagen follows'. Within this short article I will briefly outline the journey we have taken, key milestones and what the future may hold for corneal tissue engineering.

Within the field of corneal tissue engineering numerous attempts have been made to construct stromal tissue equivalents and with varying degrees of success, led by the seminal work of May Griffith et al[1] (and reviewed here[2]). These studies have previously focused on creating materials with appropriate levels of transparency, cell compatibility and mechanical strength. Despite the significance of these achievements few have yet addressed a critical quality - a cornea's shape and thereby its optical strength. An incorrectly shaped corneal construct would cause light to be focused either in front or behind the retina and thus the engineering of such a living tissue that can perform this function is, we believe, a key milestone in the development of a tissue engineered cornea.

The approach we have taken to create a functional tissue engineered cornea has been reductionist. We have endeavored, over the last 20 years, to build on the previous work of others and further improve our understanding of the biology of the cornea at a molecular, cellular and tissue level. We have taken this new understanding and looked to apply it in some novel manner in order to improve our tissue-engineering of a functional cornea.

For example, we have quantified the nanostructure of the cornea and related this arrangement to the preservation of corneal transparency[3,4], we subsequently applied these measurements to the design of new corneal biomaterials capable of supporting both corneal stromal and epithelial cell self-assembly, differentiation and growth[5]. More recently we have shown how cell-derived hierarchical collagen organisation can be modulated or prescribed by the precise spatio-temporal positioning of corneal stromal cells upon a 2D surface[6,7] (Figure 1). Further studies have shown that by controlling the amount of initial cell alignment collagenous tissues

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Goblet cells suffer from glaucoma treatment

Glaucoma is the most common cause of blindness worldwide. The disease is a result of increased intraocular pressure (IOP), which is caused by an impaired balance between the production and drainage of aqueous liquid produced by nonpigmented epithelial cells of the ciliary body.[1]

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With time, the increased IOP will lead to loss of the inner retinal nerve cells, the retinal ganglion cells,[2-4] and therefore the aim of glaucoma treatment is reduction of the IOP.

The most common glaucoma treatment comprises pressure-lowering eye drops.[5] The commercially available eye drops consist of prostaglandin analogues, beta-blockers, alpha-2-receptor-agonists, and muscarinic agonists.[6-8] However, a common complication of the chronic use of anti-glaucomatous eye drops is ocular surface disease, which often leads to decreased quality of life and impaired compliance in patients with glaucoma.[9]

Ocular surface disease is caused by increased tear osmolarity, the accumulation of inflammatory cells, disruption of the ocular surface, and alterations in the tear film.[10-13]

The pathogenesis of ocular surface disease has increasingly been ascribed to damage of the conjunctival goblet cells.[14] The conjunctival goblet cells contribute to the immune system of the ocular surface and produce mucins, MUC5AC in particular, which is an important component of the tear film.[15]

The tear film is composed of three layers (Figure 1): A superficial lipid layer originating from the meibomian gland; a middle aqueous layer containing water, electrolytes, proteins, peptides, and glycopeptides; and the innermost

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This award contributes to a much-needed focus on improving quality of life in patients who are undergoing treatment for glaucoma. We are very grateful to be nominated for this fine award among the many brilliant articles published in Oftalmolog during 2019.

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