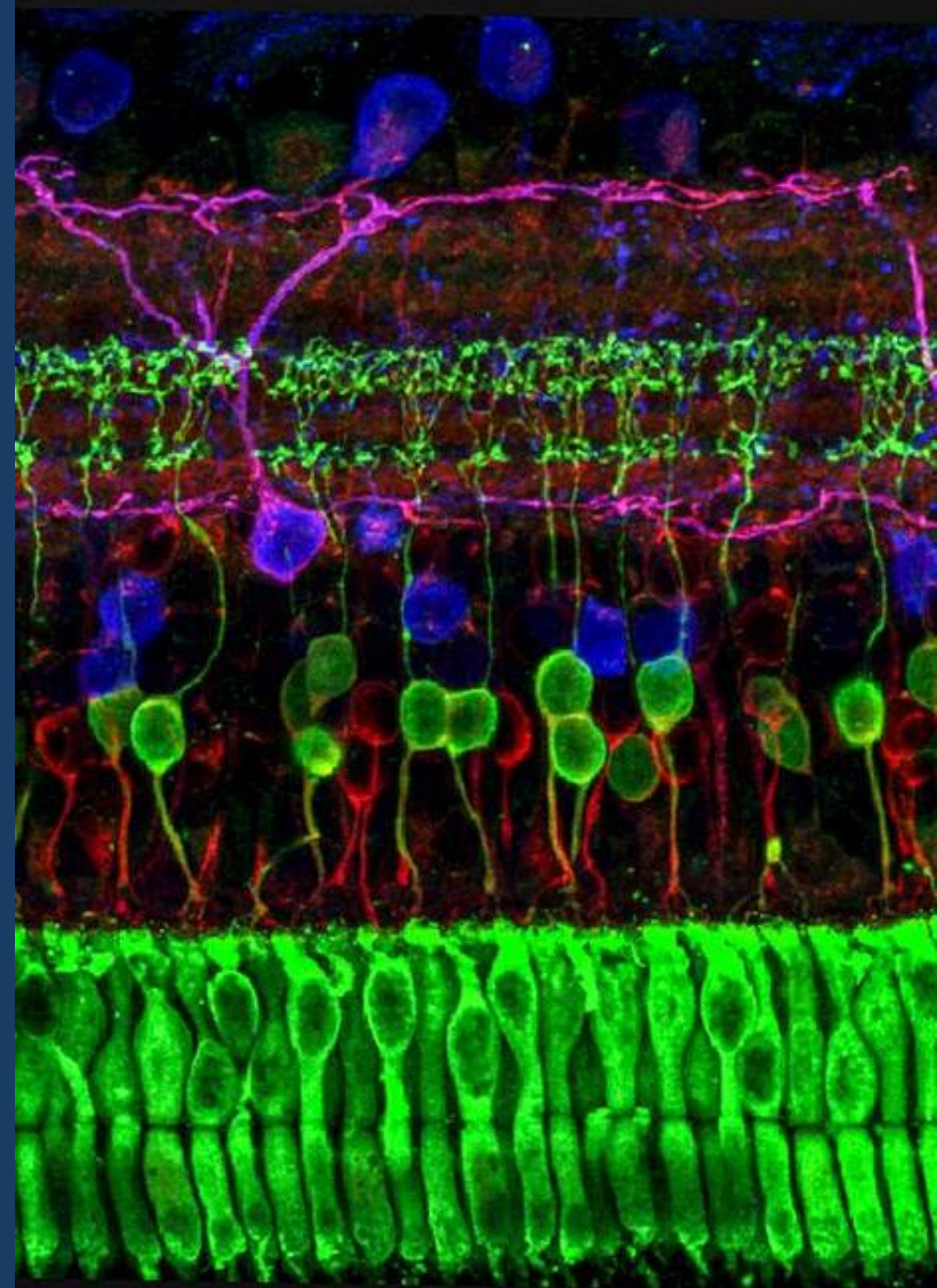


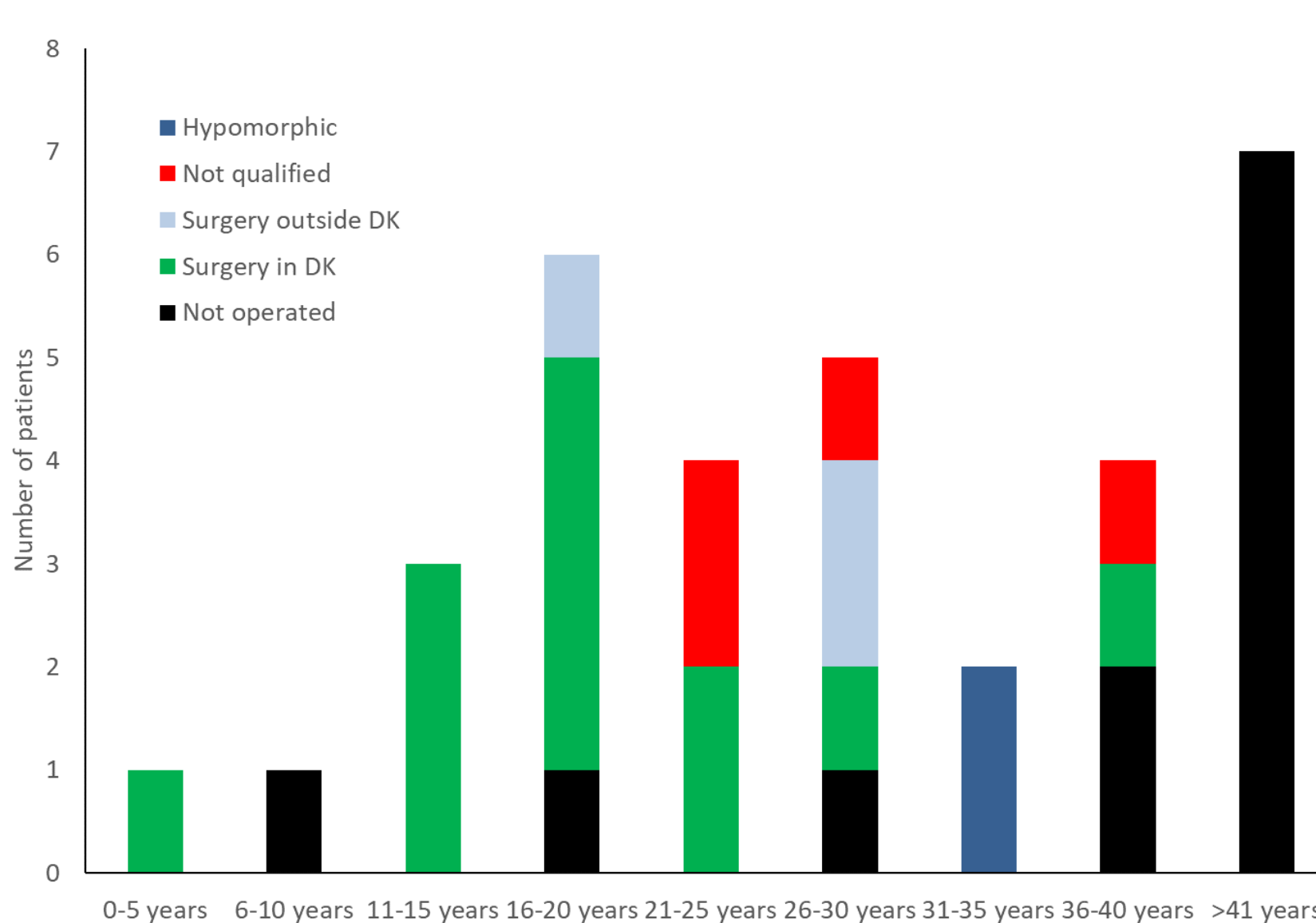
Genterapi – erfaringer fra den virkelige verden og hvad fremtiden bringer

Kristian Klemp

Overlæge, klinisk lektor, PhD



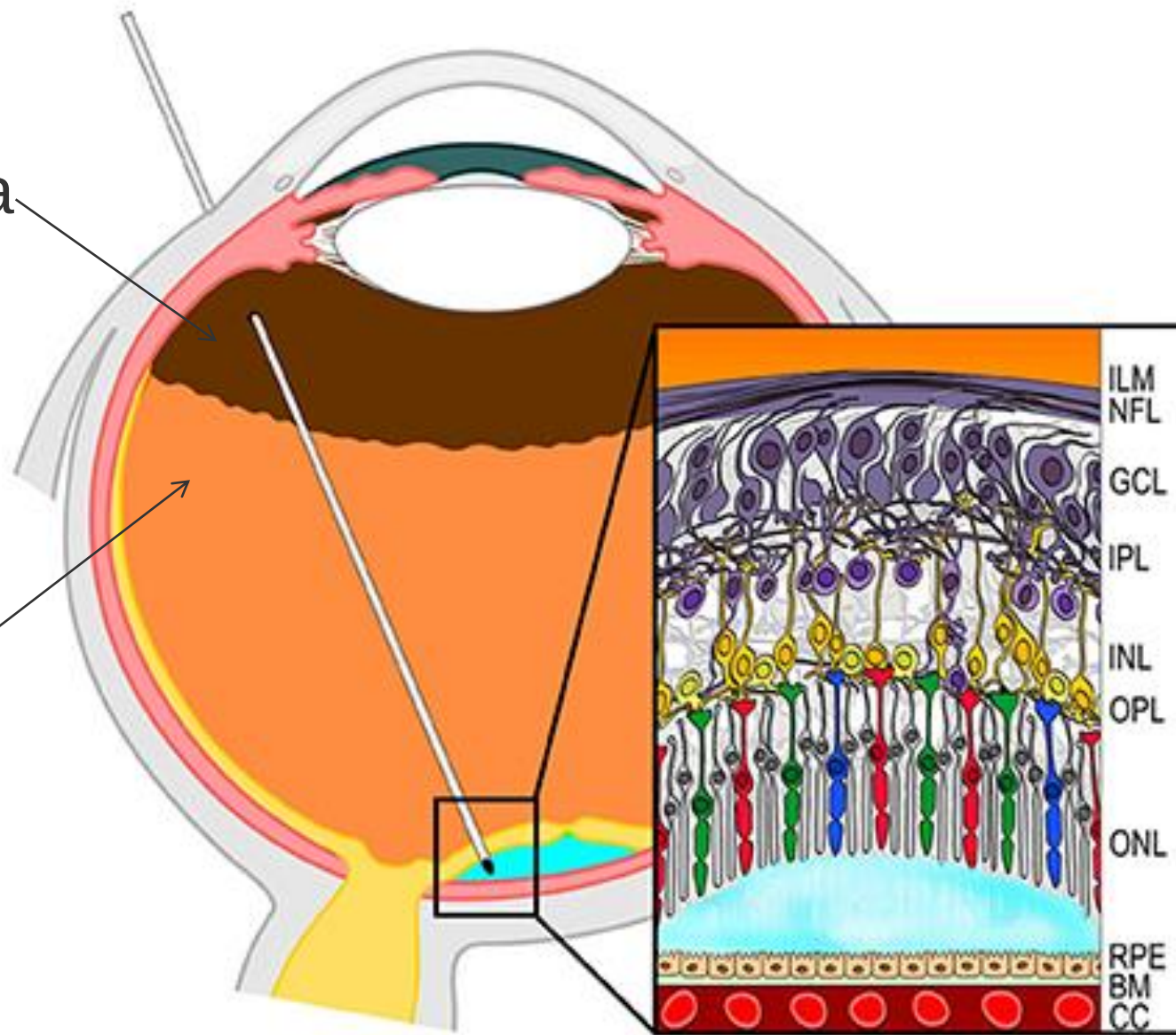
Danske RPE65 patienter



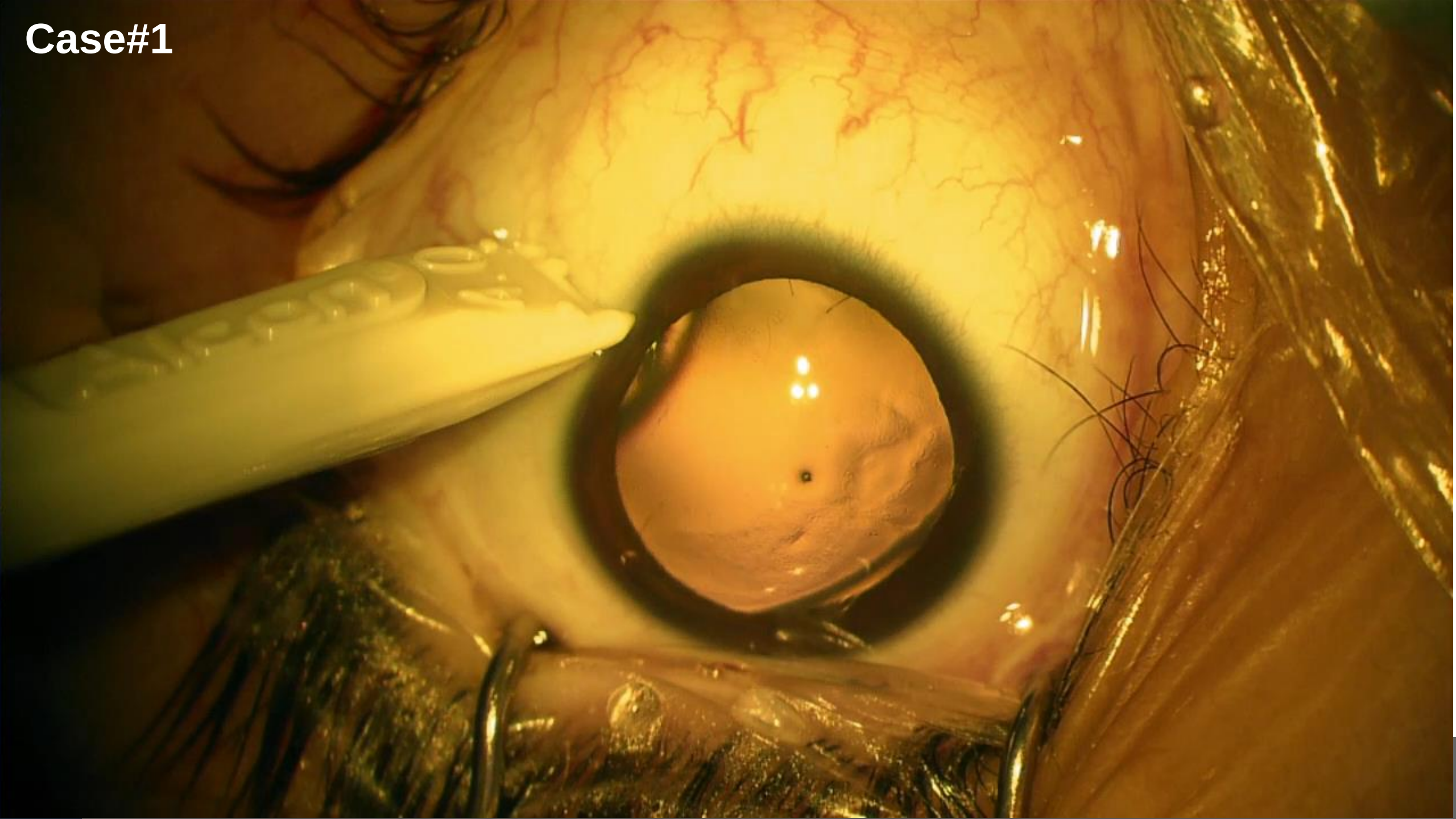
- 12 patienter er behandlet (23 øjne)
- 4-38 år
- Follow-up op til 2 år

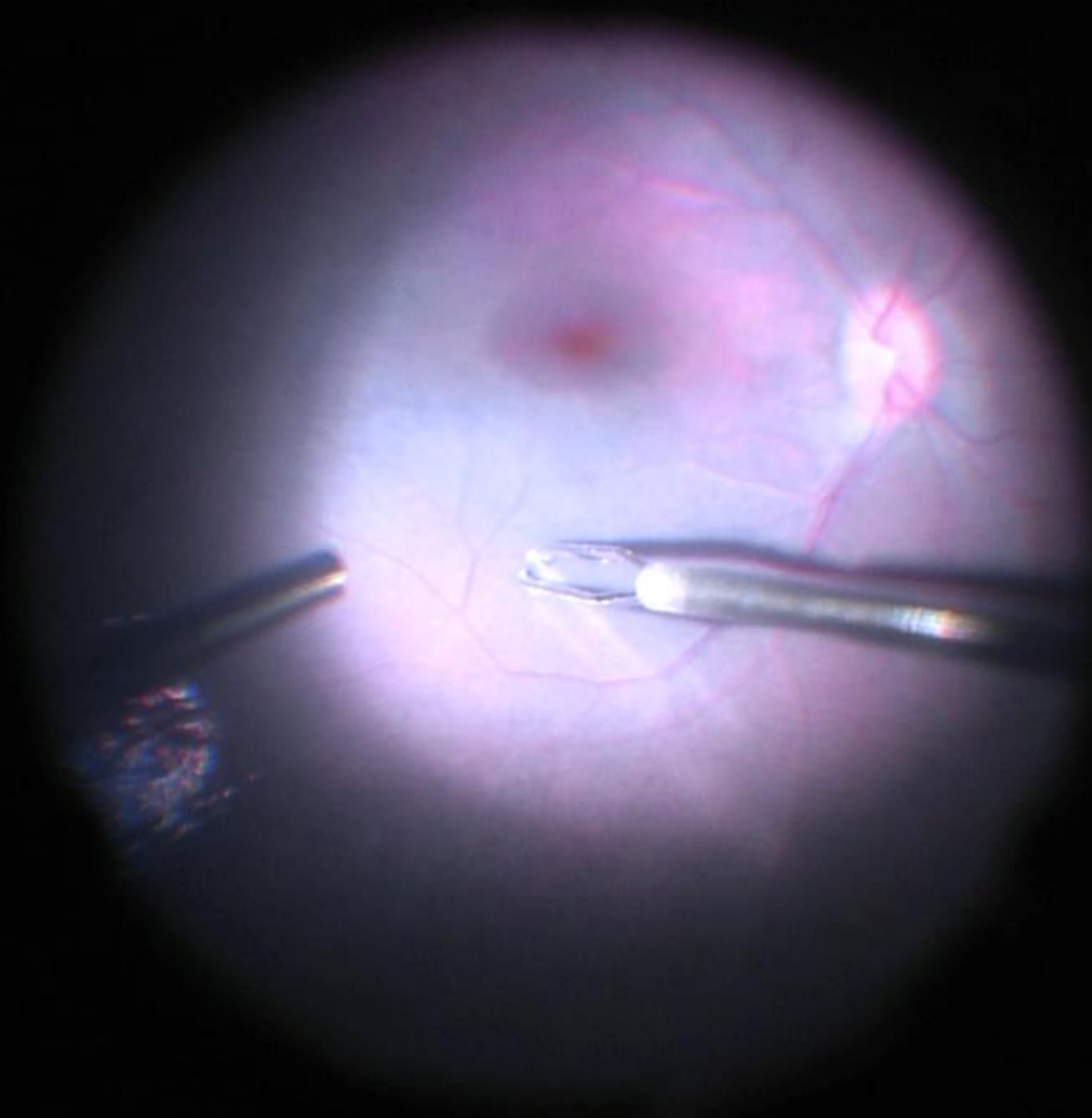
Pars plana

Nethinden

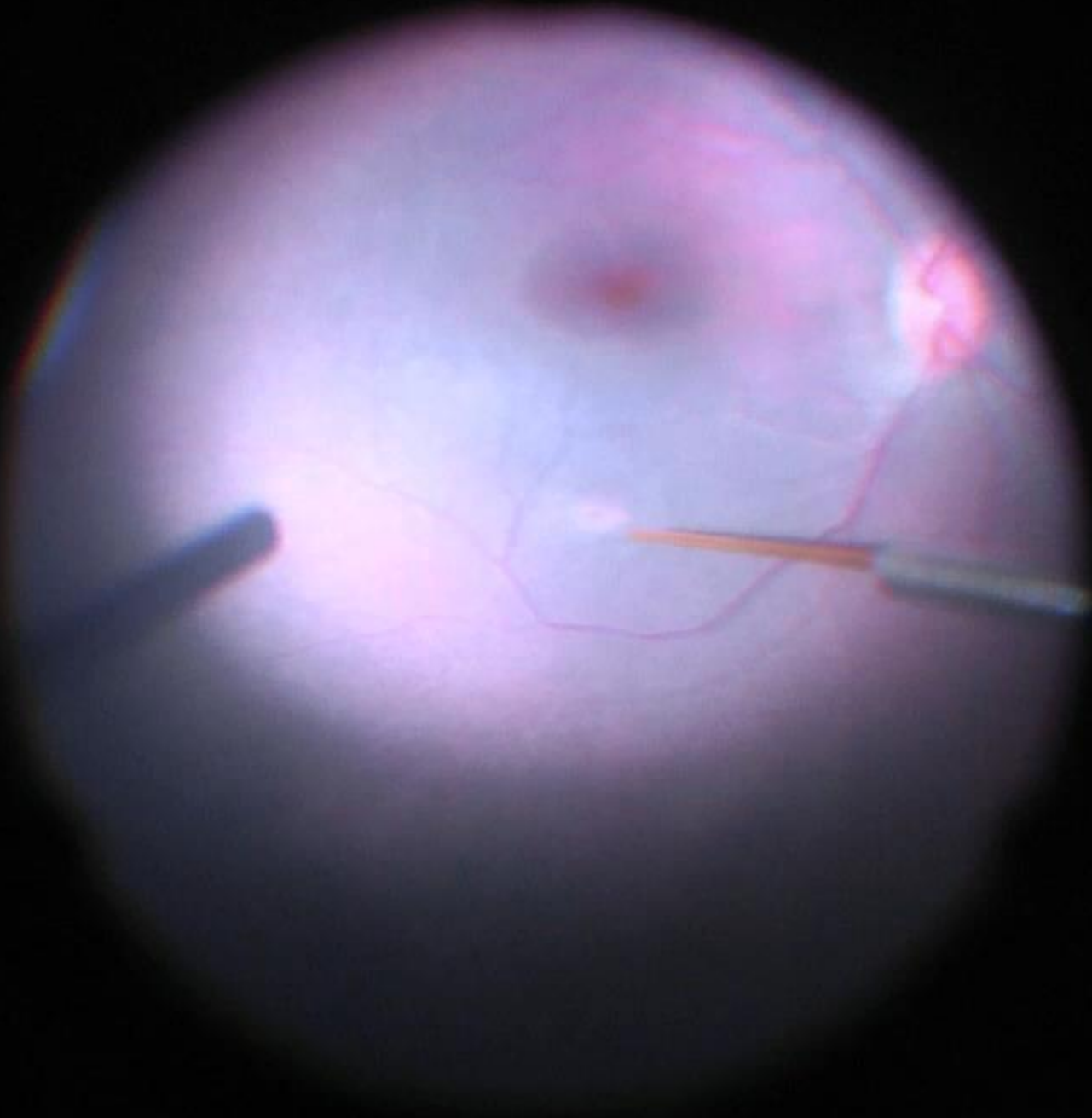


Case#1





Venstre øje



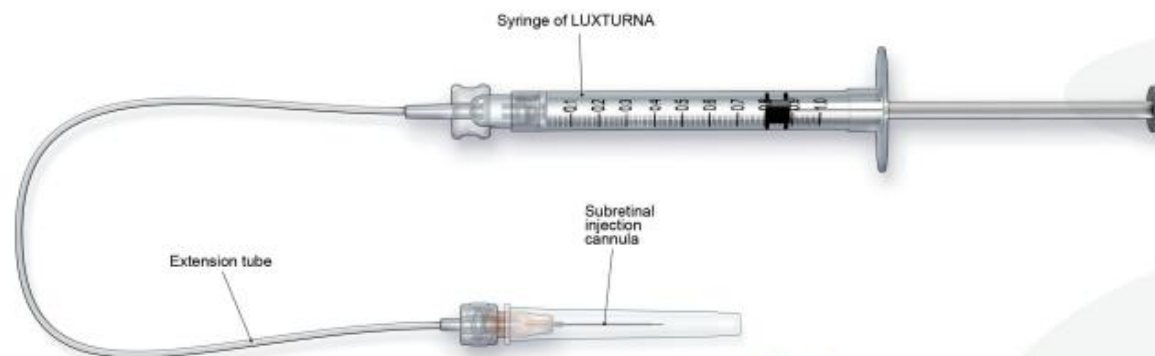


Figure 5. Injection apparatus assembly.

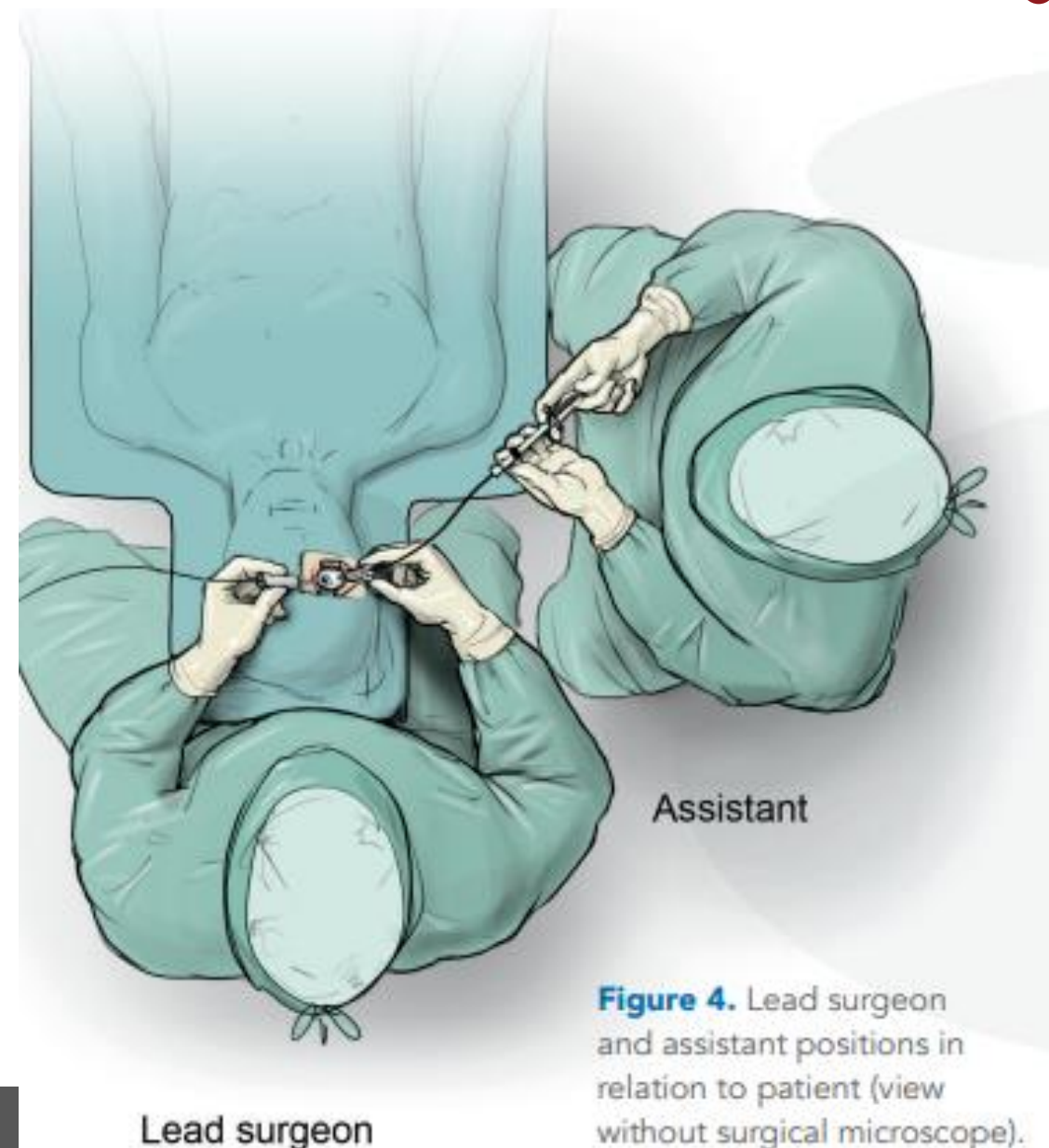
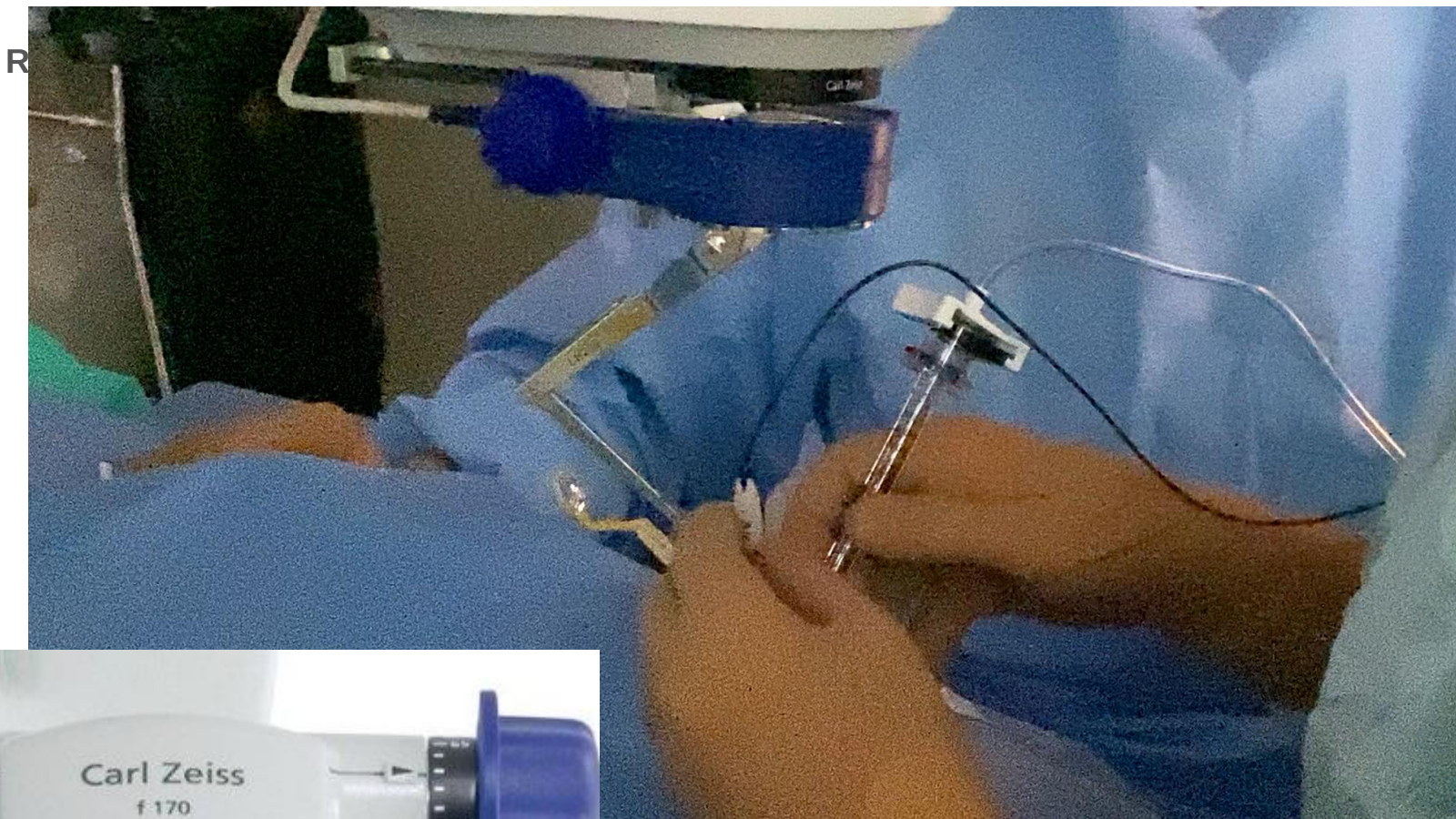
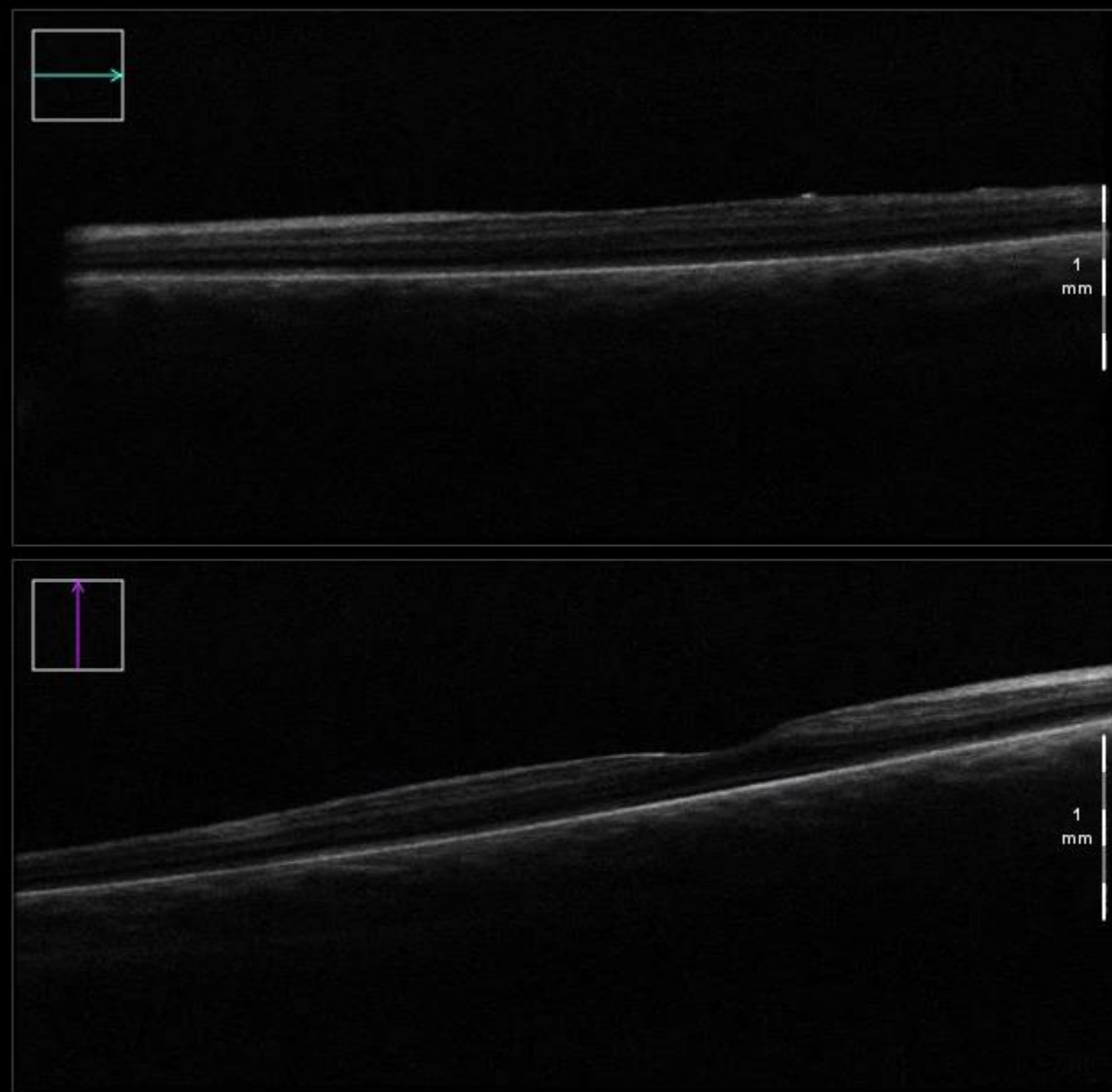
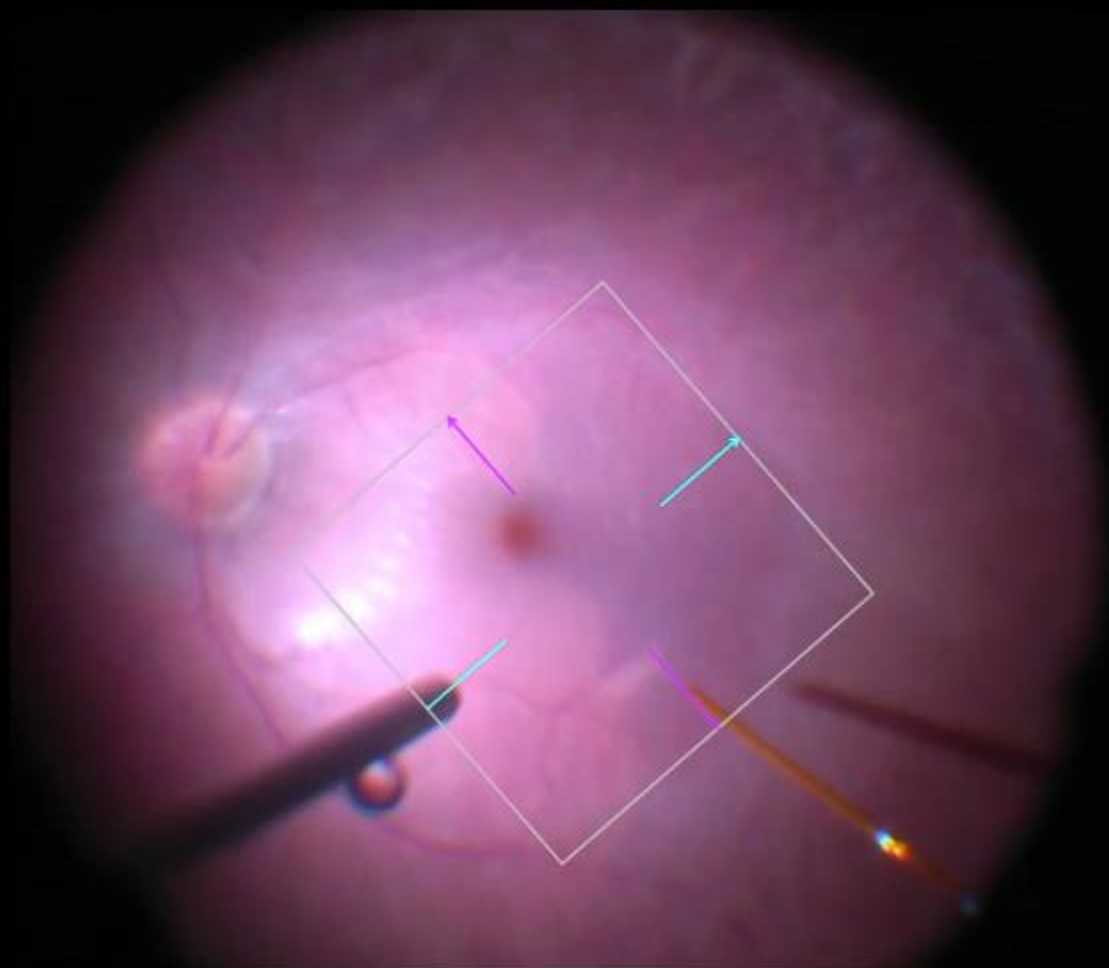


Figure 4. Lead surgeon and assistant positions in relation to patient (view without surgical microscope).

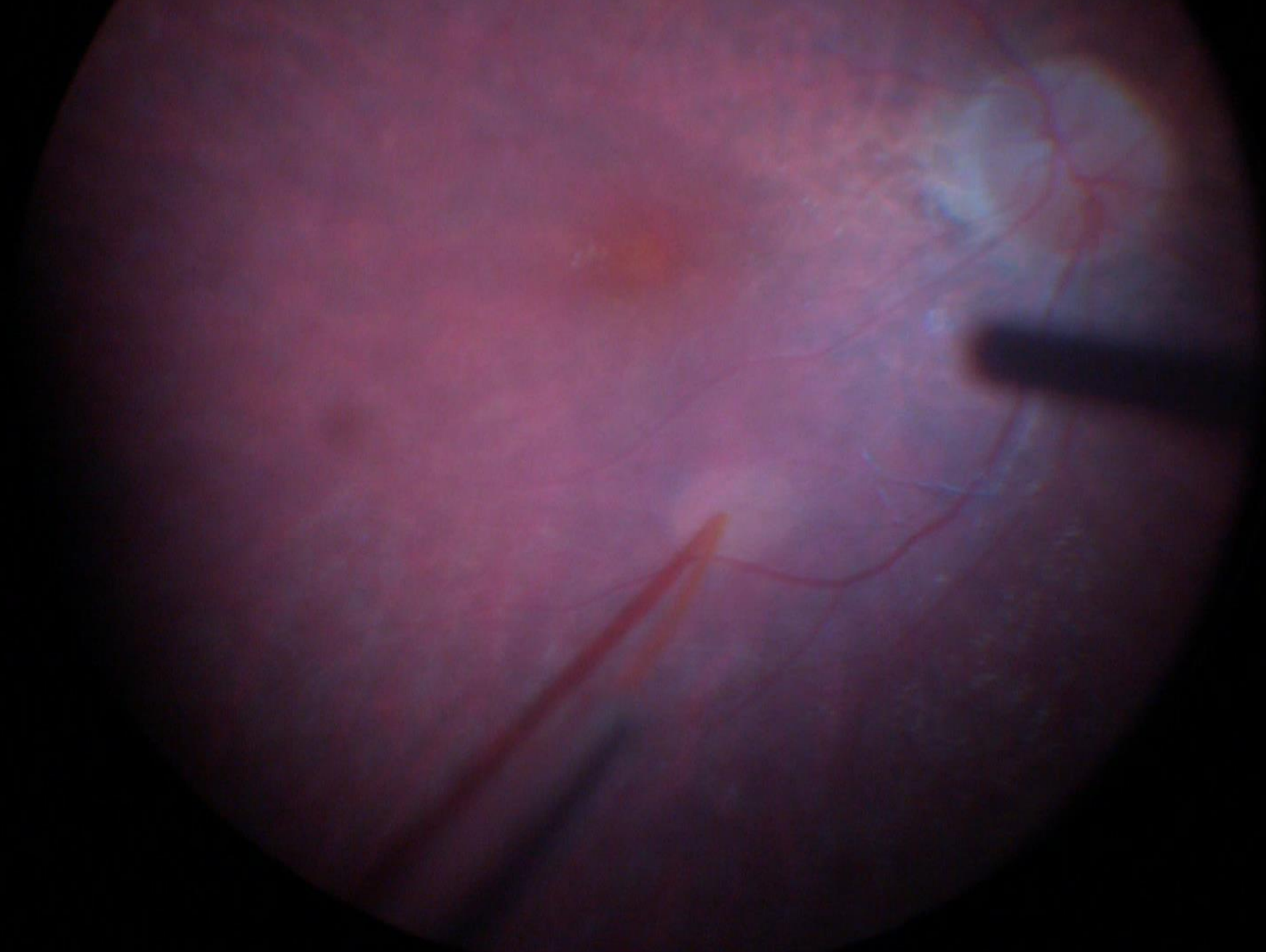


S
T



Case#2

Venstre øje





Follow-up

3 mdr: "Det går hele tiden fremad, hele tiden nye små oplevelser, af at patienten har bedre og bedre syn. Har eks kunnet hælde kaffe op i mørk bil da de kørte herover kl 3 i nat. Falder ikke længere eller går ind i ting."

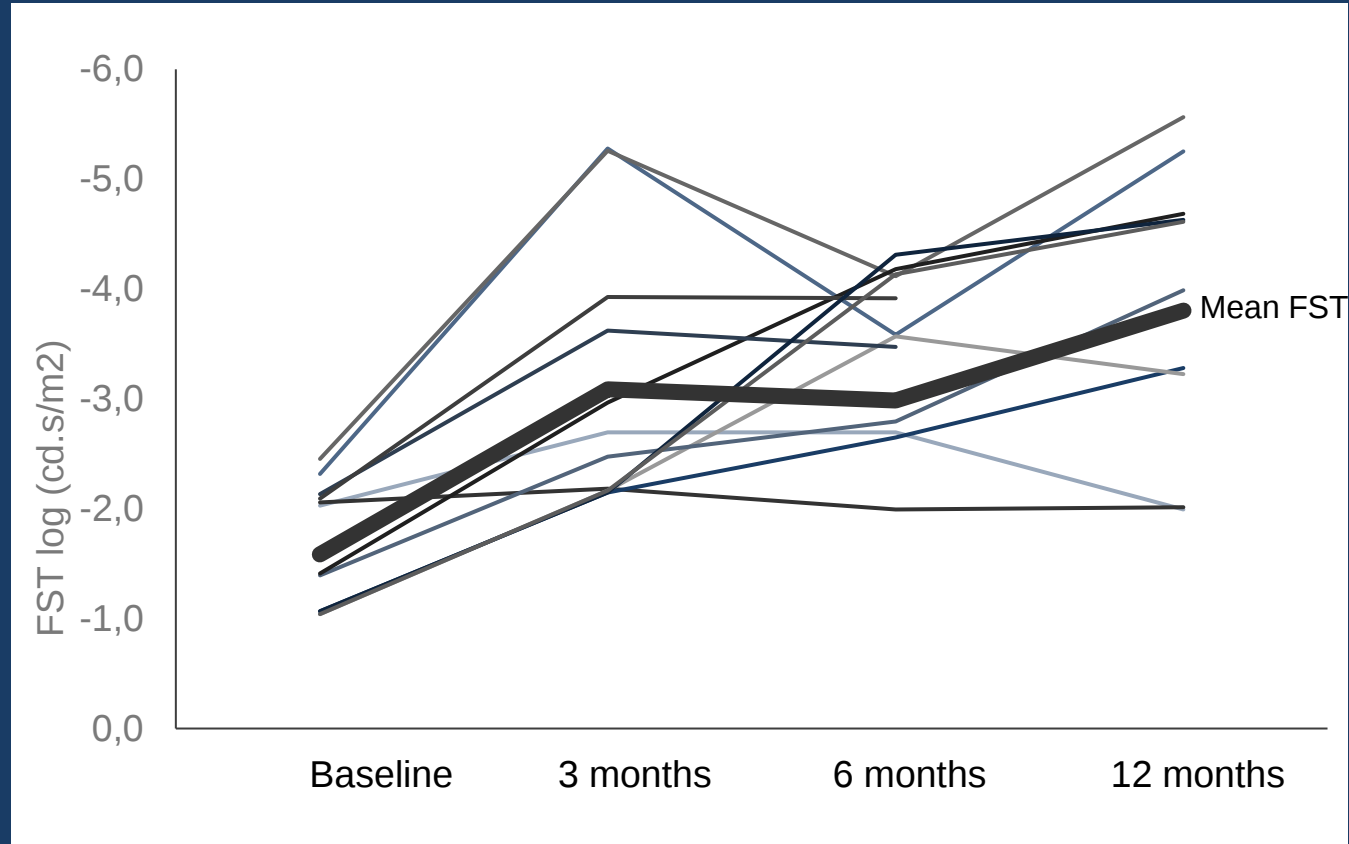
6 mdr: " Oplever stadig nye ting ved synet, er begyndt at lave mere komplicerede retter, hvor patienten lige efter operationen for første gang kunne lave mad, men simpel mad, så bliver det mere og mere avanceret. Har taget toget hjem fra Ribe for første gang og det gik rigtig godt, kan orientere sig i mørke, ukendte omgivelser"

12 mdr: "Det går simpelthen så godt, ser supergodt i mørke, kan se stjerner og har rigtig mange gode synsoplevelser, som hun ikke har haft tidligere."

18 mdr: Patienten er ved at begynde at lede efter et almindeligt arbejde, vil gerne arbejde med udsatte børn/unge.

Outcome

FST – et mål for lyssensitivitet



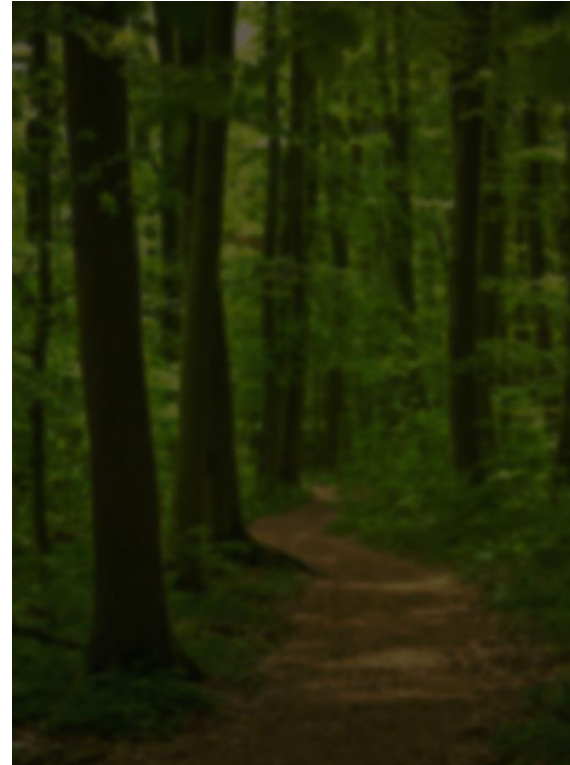


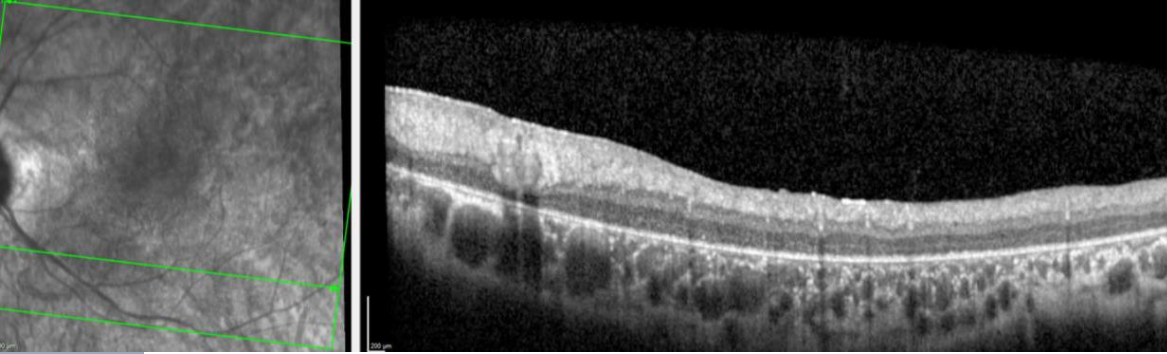
Andre patienters subjektive oplevelser

- "Mor du har forskellige nuancer i dit hår"
- "Jeg er så glad – jeg har selv handlet ind og lavet aftensmad for første gang i mit liv"
- "Vi hører aldrig hunden mere, før peb den altid, når vores barn faldt over den"
- "Før skulle jeg vente ved hoveddøren på mine klassekammerater, som fulgte mig i skole. Nu går jeg selv, hvis de er sent på den"
- "Jeg kunne selv finde hen til covidtest centret"

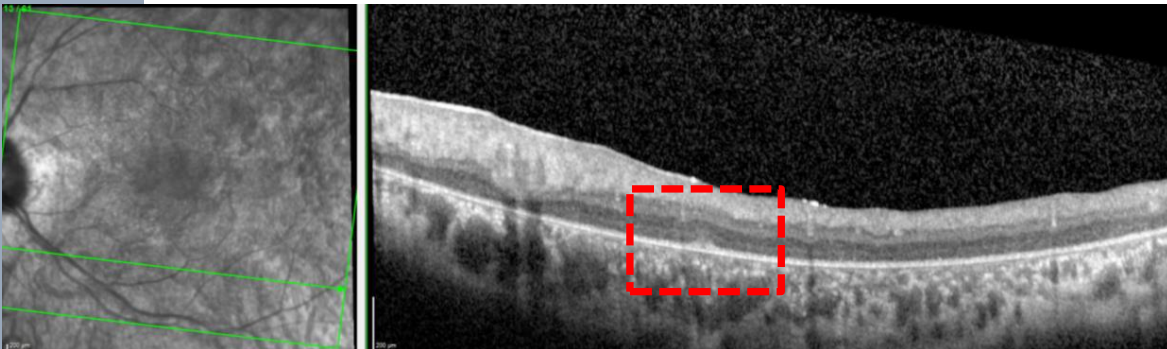
Outcome

- Langt de fleste har fået subjektiv fremgang i et omfang, hvor det er livsændrende
- Selv efter 1 år oplever patienterne synsfremgang
- Bivirkninger i forventeligt niveau
- Ingen alvorlige komplikationer til kirurgi (nethindeløsning, blødning, infektion)

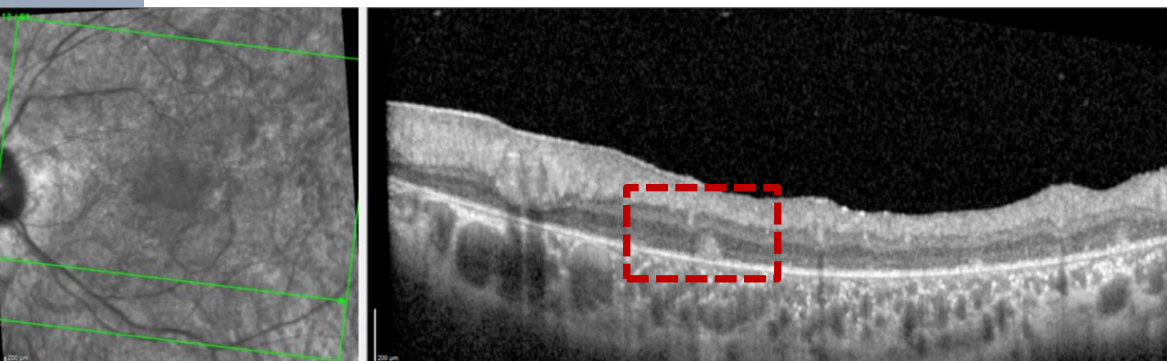




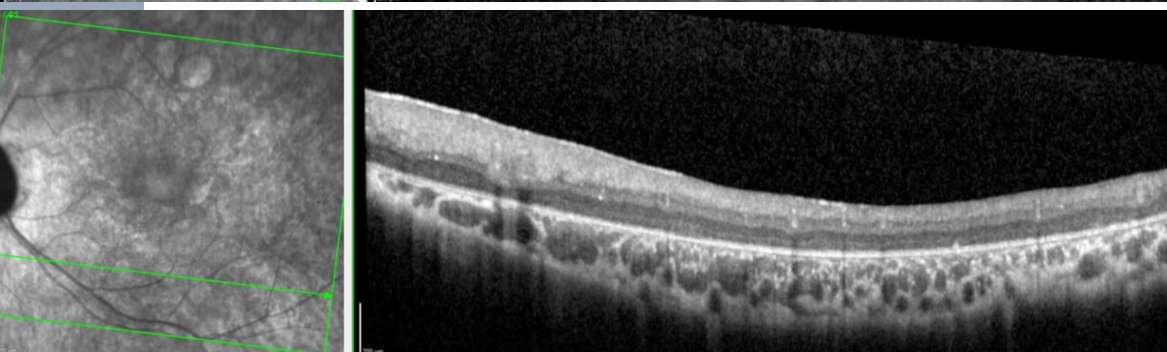
Præ-op



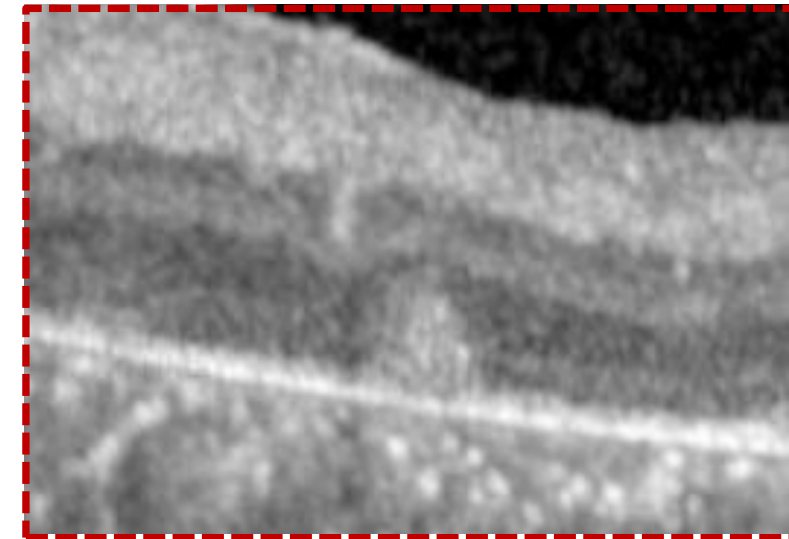
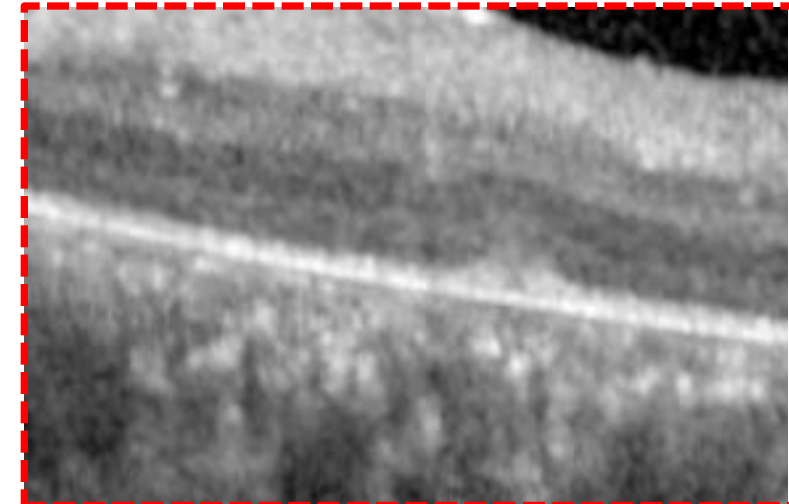
2½ mdr post-op
Oral prednisolon



3½ mdr post-op
Sub-tenonTA



6 mdr post-op



Hvad har vi lært?

- Udviklet skånsom og præcis injektionsteknik vha pneumatisk fodpumpe og peroperativ OCT
 - Single surgeon procedure
 - Mindre risiko for retinal skade
 - Præcis dosering
- Udviklet ILM peeling teknik
 - Letter subretinal administration betydeligt
 - Nedsætter vektor load i øjet over nethinden og dermed risiko for inflammation og synstab
- At erkende tegn på intraokulær inflammation meget tidligt og at behandle den effektivt
 - Eliminerer synstab pga inflammation



Inflammation after Voretigene Neparovect Administration in Patients with RPE65-Related Retinal Dystrophy

Line Kessel, PhD,^{1,2} Ulrik Correll Christensen, PhD,¹ Kristian Klemp, PhD¹

Purpose: To report on the prevalence of intraocular inflammation after subretinal voretigene neparovect (VN) administration.

Design: Retrospective review of medical files.

Participants: All patients receiving VN in Denmark.

Methods: Twelve patients received VN gene therapy as standard of care for biallelic RPE65-related retinal disease. Bilateral treatment was performed in 11 patients and unilateral treatment in 1 patient. Patients were followed clinically before and after VN administration using functional measurements (visual acuity, full-field scotopic threshold test, visual fields) and structural evaluations (fundus imaging [color and autofluorescence], OCT, slit-lamp).

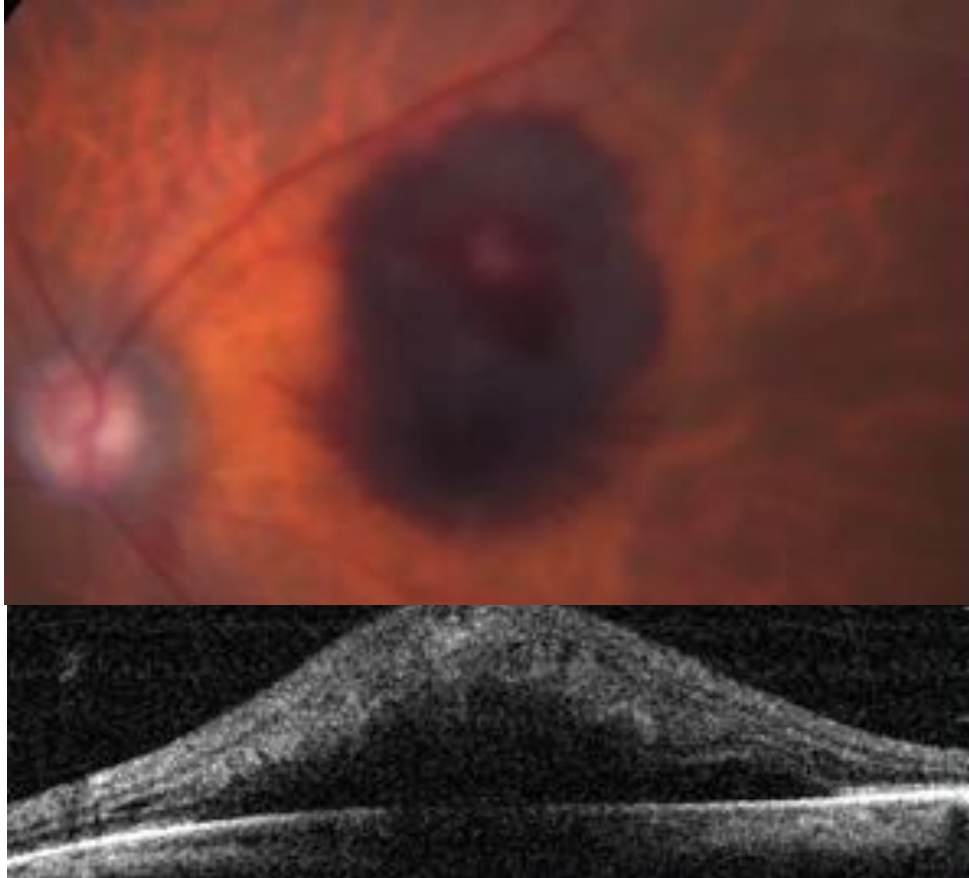
Main Outcome Measures: Signs of intraocular inflammation, including vitritis and outer retinal infiltrates.

Results: Vitritis was observed in 9 of 23 eyes receiving VN. The median time to resolution of vitritis from the time of treatment was 89 days. Four eyes also presented with outer retinal infiltrates at the time of vitritis. Inflammation subsided on immunosuppressant therapy. The presence of inflammation did not adversely affect visual outcome after VN therapy. In 1 eye, outer retinal infiltrates were demonstrated to precede later development of atrophy.

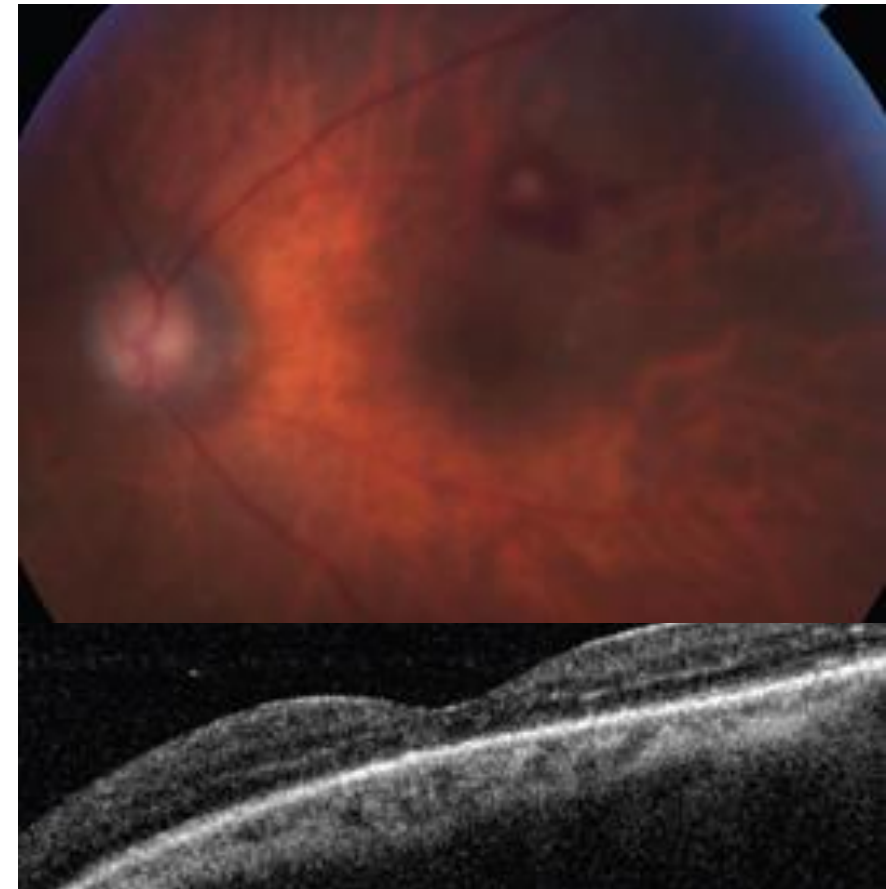
Conclusions: Patients undergoing subretinal gene therapy need to be closely monitored for signs of inflammation. Although we did not observe a detrimental effect on visual function in eyes with inflammation, it seems wise to treat it appropriately because it may lead to atrophy of the retinal pigment epithelium and outer retina. Also, it seems advisable to reduce the inflammatory load, such as using a surgical technique that minimizes residual viral vectors in the vitreous body. *Ophthalmology* 2022;■:1–7 © 2022 by the American Academy of Ophthalmology

Spin-off for andre patientergrupper

Submakulær blødning
(våd AMD, makroaneurismer)



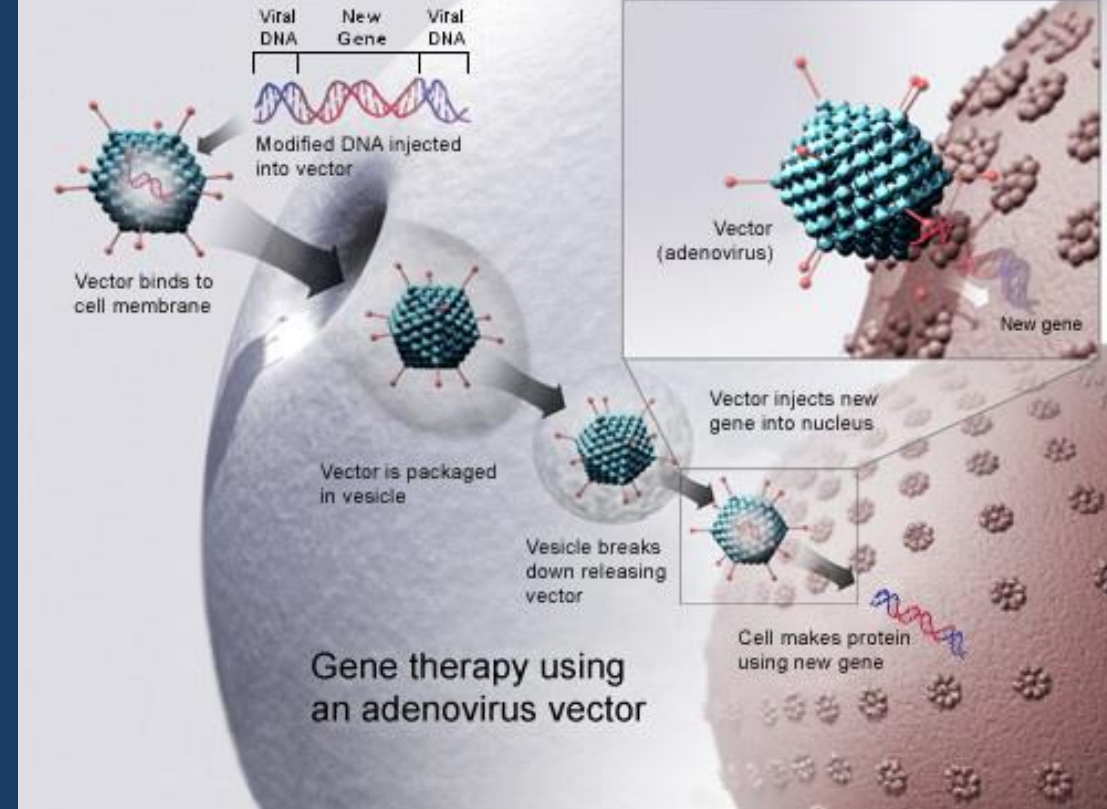
6 uger efter subretinal tPA injektion
(Actilyse)



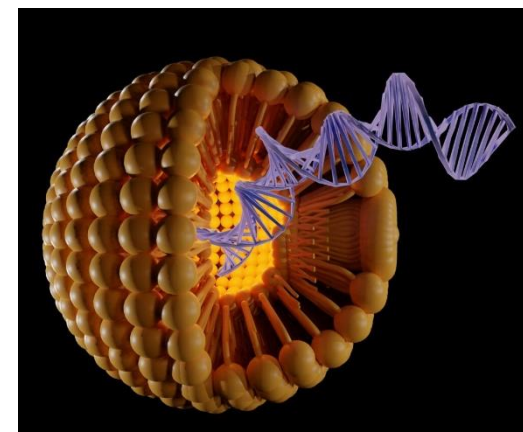
Hvad bringer fremtiden....

Genterapi

- For andre arvelige nethindelidelser
- Biofactory approach (ekspression af lægemidler i nethinden (f.eks. anti-VEGF))



- Genterapi leveret i syntetiske nanopartikler for at undgå inflammation udløst af virusvektorer

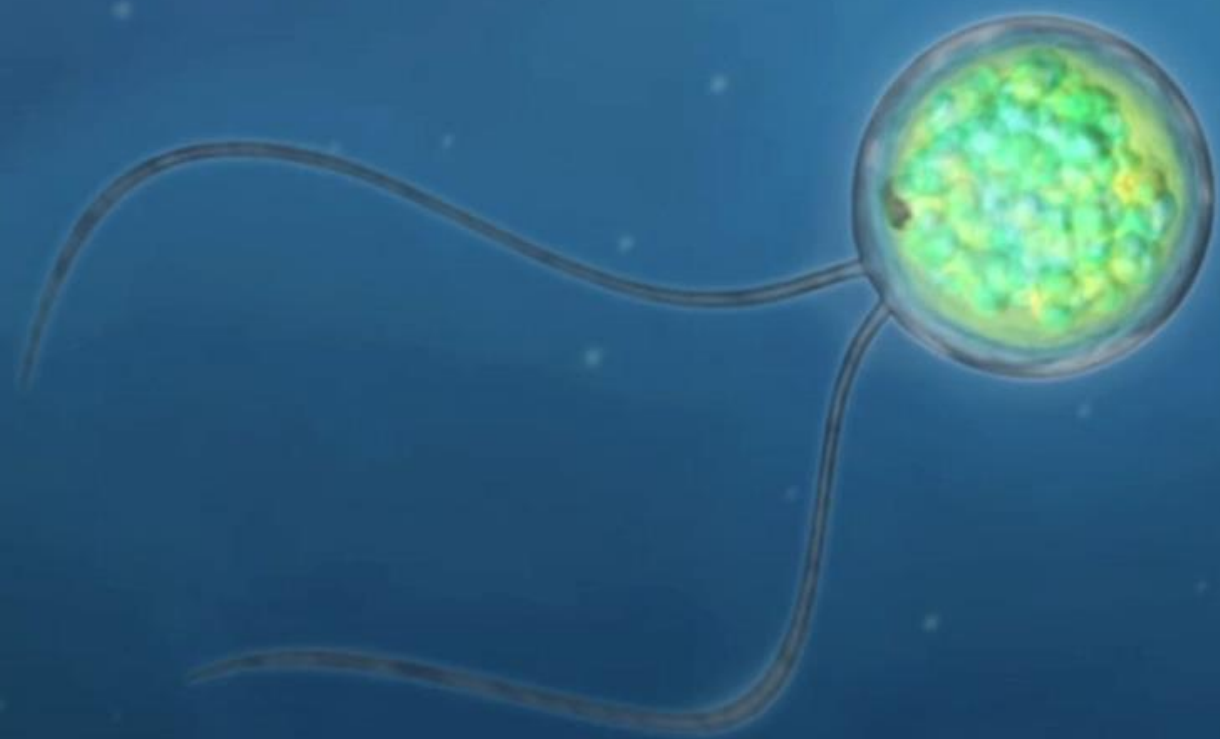


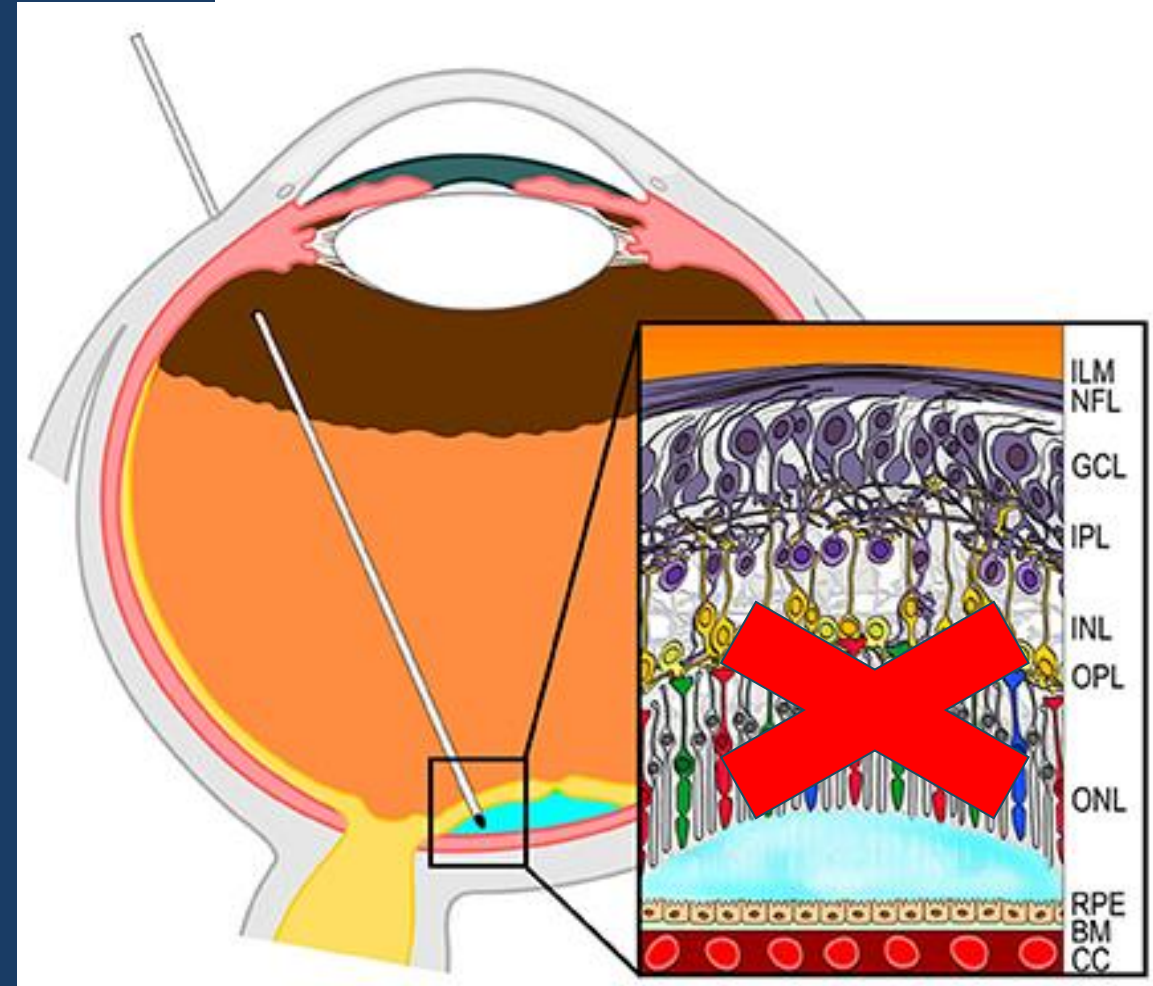
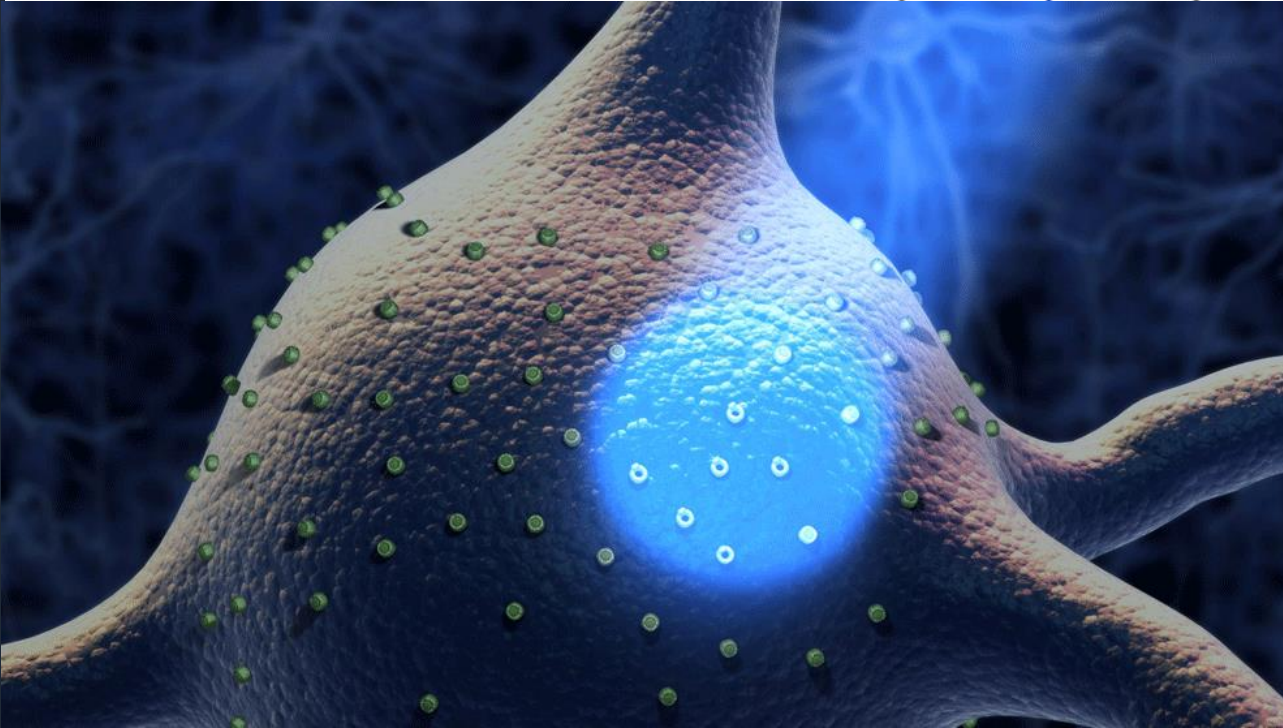
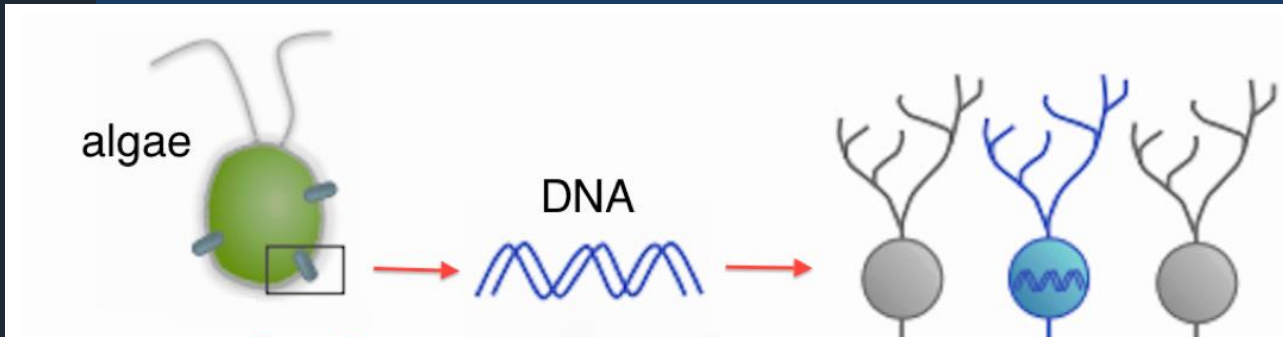


Aktive trials indenfor hereditære nethindesygdomme

Øjensygdom	Fase 1/2	Fase 3
Retinitis pigmentosa (Incidens 50-100 pr år i DK)	11	6*
Lebers congenitte amaurose (non-RPE65)	3	
Choroideremia	2	1
Akromatopsi	3	
Lebers Hereditære Opticus Neuropati	1	1
Retinoskise	2	

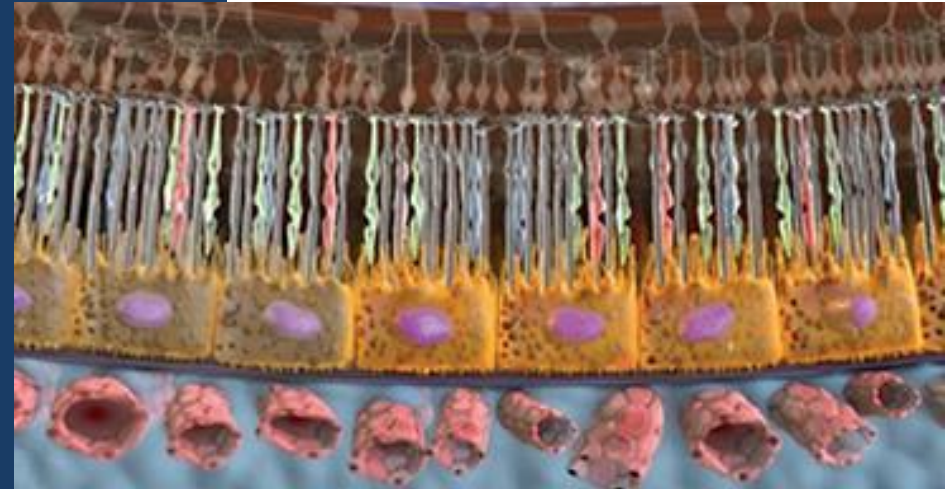
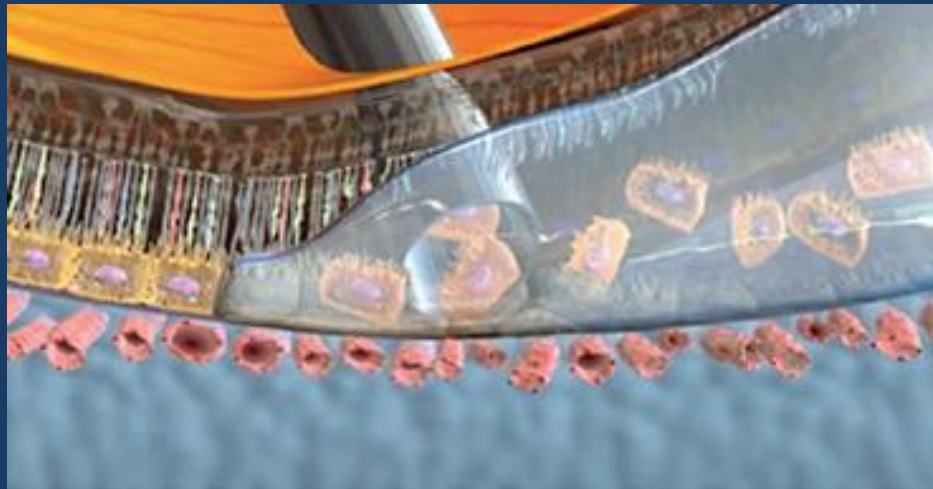
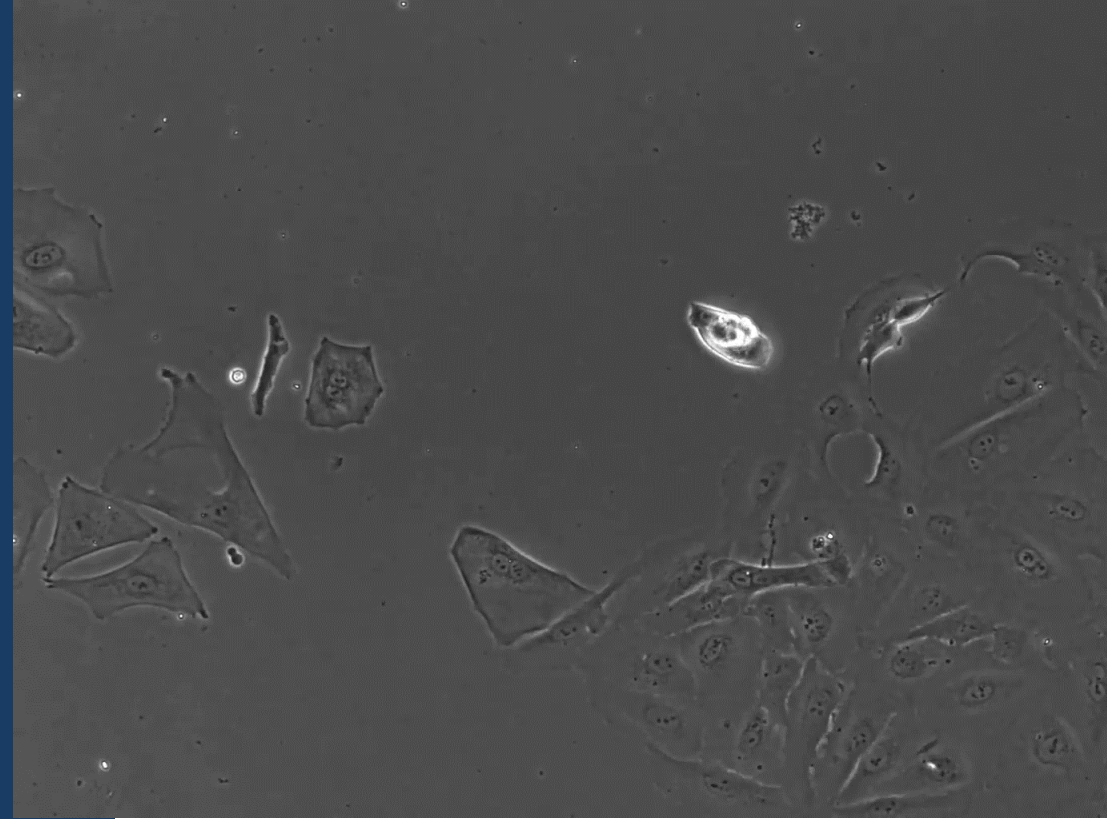
* Lumeos Trial. Genterapi for x-linked Retinitis pigmentosa, bl.a. på Rigshospitalet.





Stamcelleterapi

Transplantation af nye fotoreceptorer
og RPE celler ved f.eks. tør AMD



Tak til ALLE involverede!



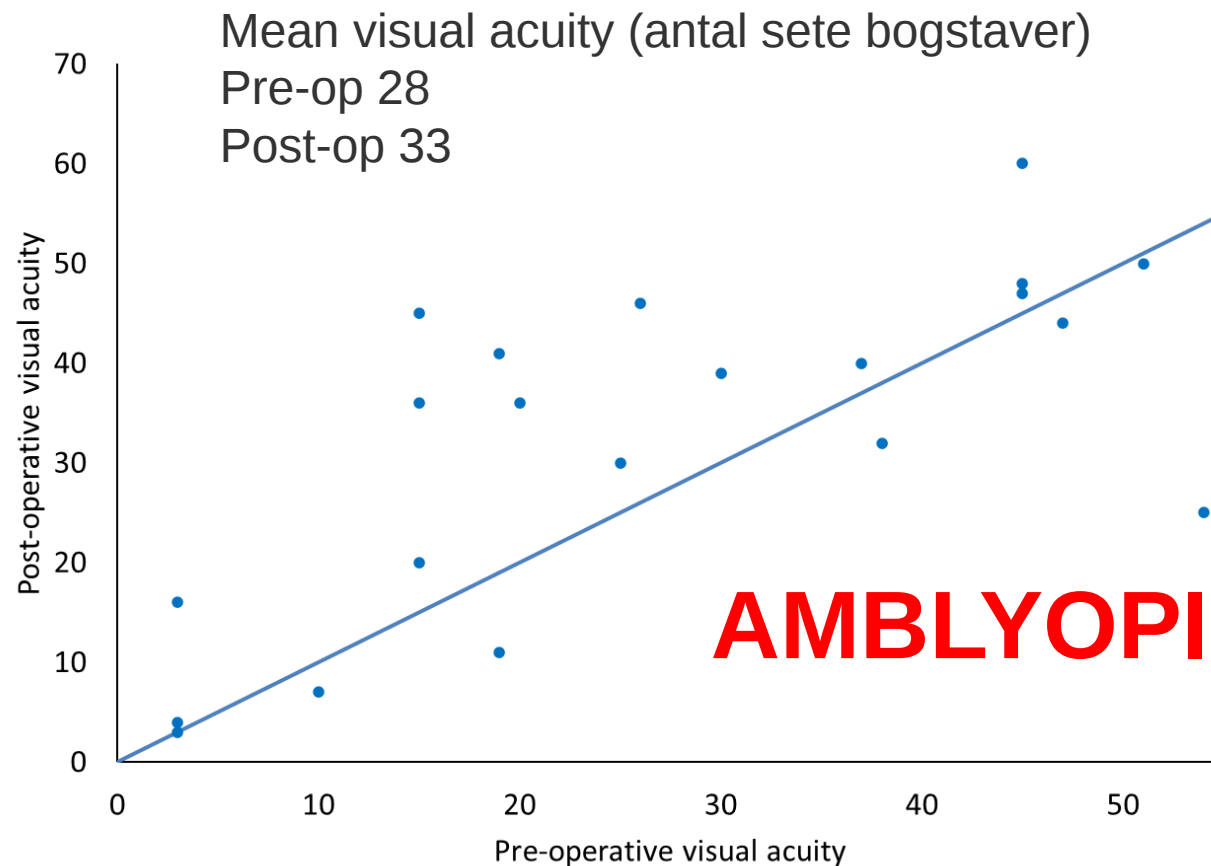
Ulrik Christensen



Line Kessel



Synsstyrke – et dårligt mål for effekt hos RPE65 patienter



VA pre-op
19/20



VA post-op
30/35





Præoperativ synsstyrke: 0,04 (4%) 0,16 (16%)

Postoperativ synsstyrke: 0,16 (16%) 0,32 (32%)

Follow-up

1 mdr: "Det går godt, fantastisk fremgang visuelt. Kan finde lejetøj på mørke steder"

3 mdr: "Fortsat synsfremgang"

10 mdr: "Er synsmæssigt meget bedre end før"