



CENTRE FOR  
Eye Research  
Australia



# A clinician's experience of conducting first in human device trials in Australia

## Med Tech Forum

## Robyn Guymer



THE UNIVERSITY OF  
MELBOURNE

Saving sight. Changing lives.

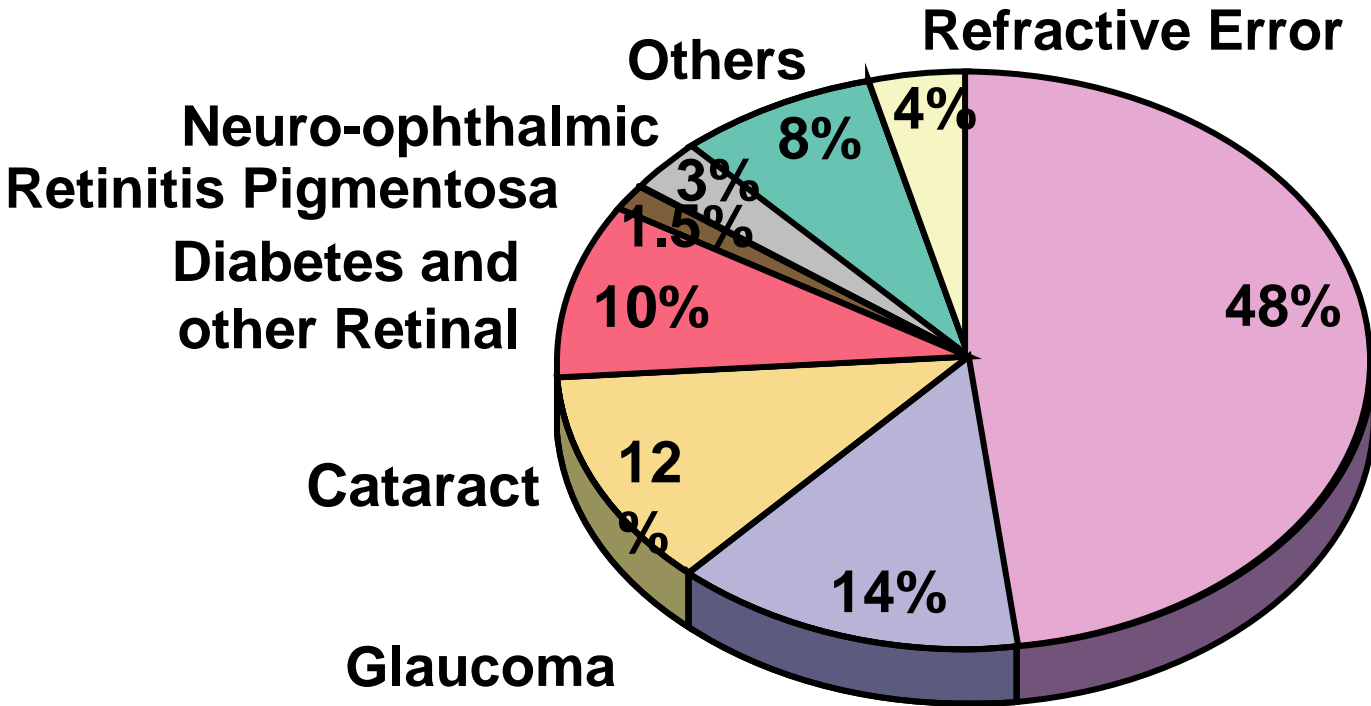
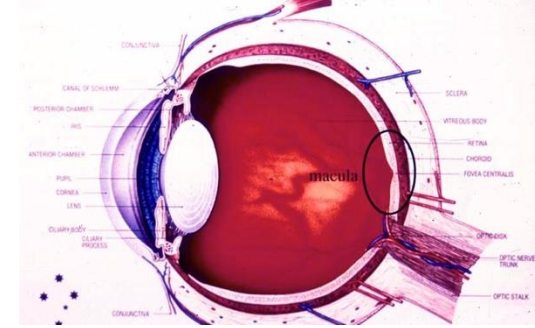
Centre for  
Eye Research Australia Limited  
University of Melbourne  
Department of Ophthalmology



Deputy director  
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Professor of Ophthalmology  
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NHMRC Principal Research Fellow  
Medical retinal consultant RVEEH  
Private practice- medical retinal diseases

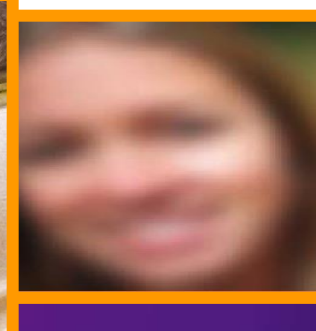
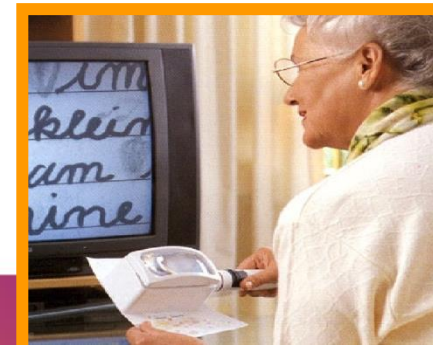


# Age-related macular degeneration (AMD)



**Age related  
Macular  
Degeneration**

- Its common
- Its increasing
- Its expensive
- Affects driving, reading, recognizing faces

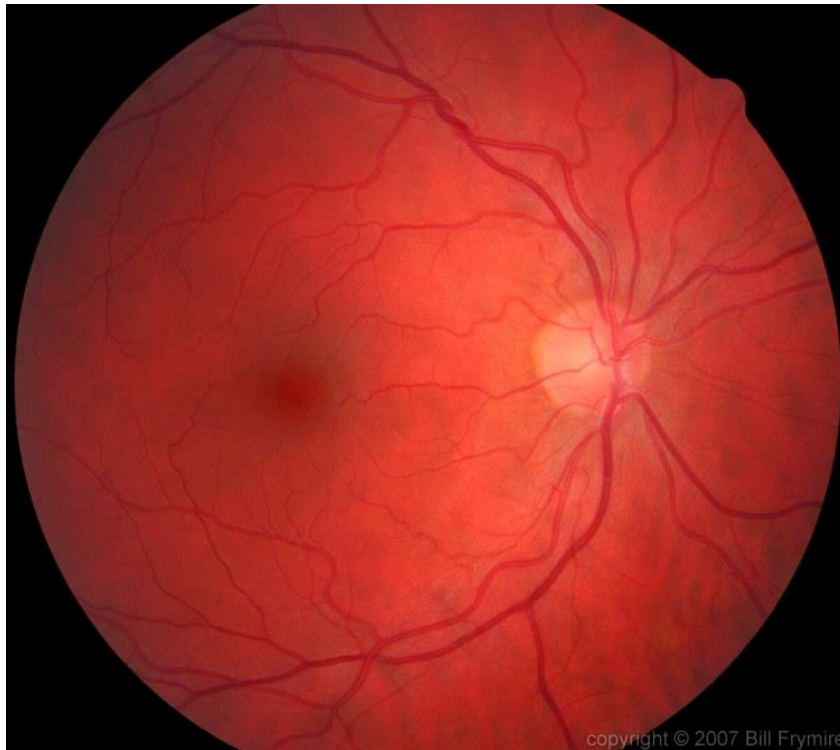




# Age related macular degeneration

-early stages are asymptomatic

-accumulation of debris

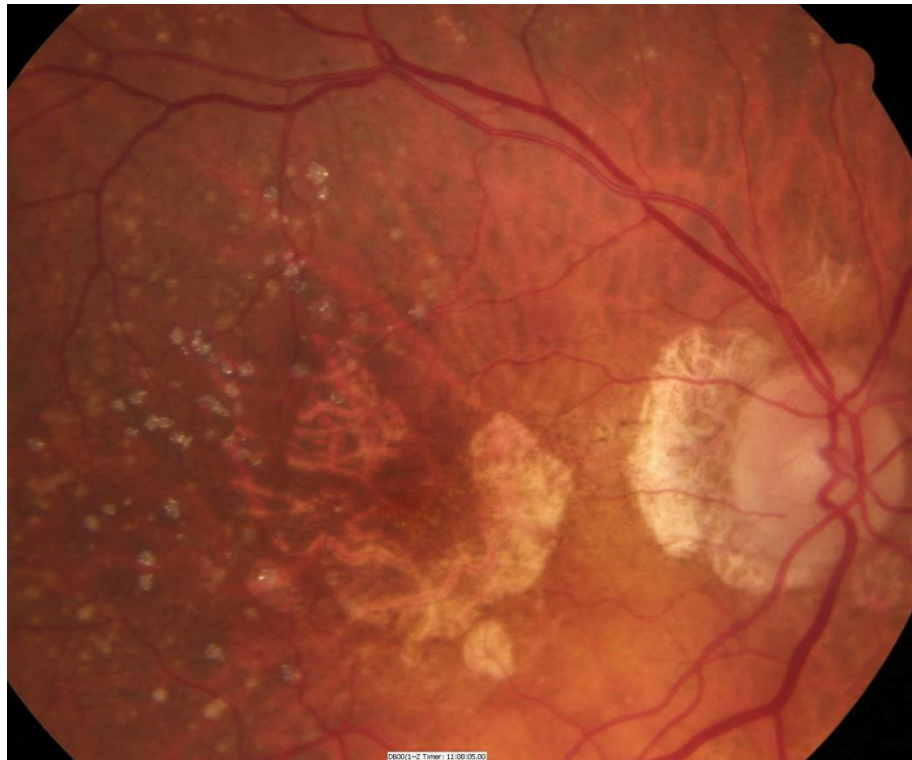


Normal macula



Early stages of AMD-drusen and pigmentary changes

# Age related macular degeneration late AMD threatens vision



Geographic atrophy “dry”



neovascular AMD “wet”



# Age related macular degeneration (AMD)



Late stage disease results in legal blindness  $< 6/60$



MRU: translational. Basic science to novel interventions

30 Phase 2 or 3 international intervention RCT as site PI

- 1 phase 1b/2a,

7 IIT RCT as PI

- 3 laser studies

- photodynamic therapy

- Bionic eye implant (co PI)

- post approval. Changing the way clinicians use the drug

- different indication of approved drug

# Eye offers a unique opportunity for novel interventions

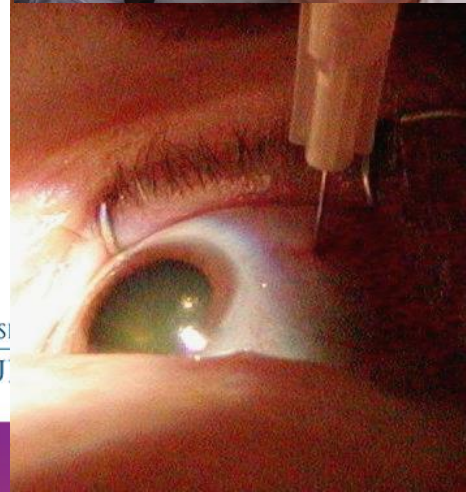
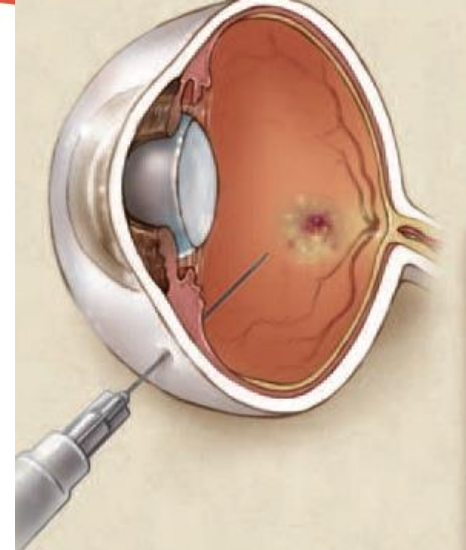
- **Small organ, relatively isolated**
  - Less drug needs to be made and purified
  - Less risk of systemic side effects

First medical treatment for neovascular AMD approved 2006

Anti- VEGF: now the biggest cost on PBS

Ranibizumab: monoclonal antibody fragment

Aflibercept: recombinant fusion protein of VEGF receptor and fused Fc portion IgG





# Incidence rates of legal blindness from AMD

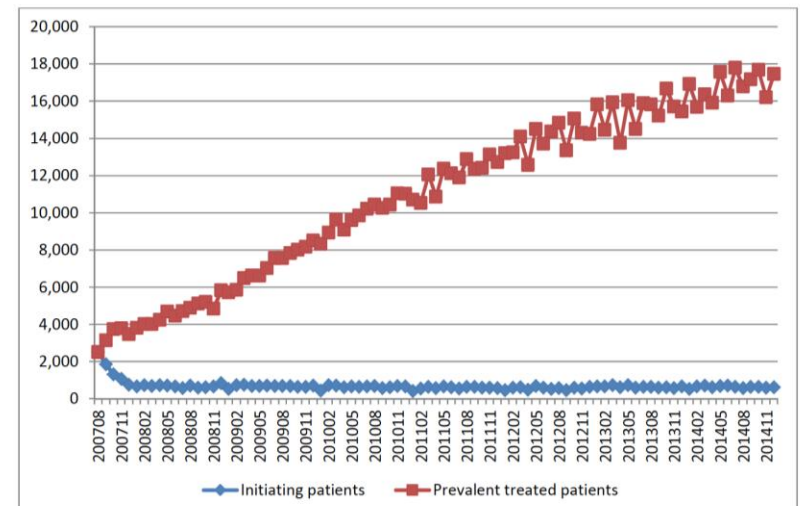
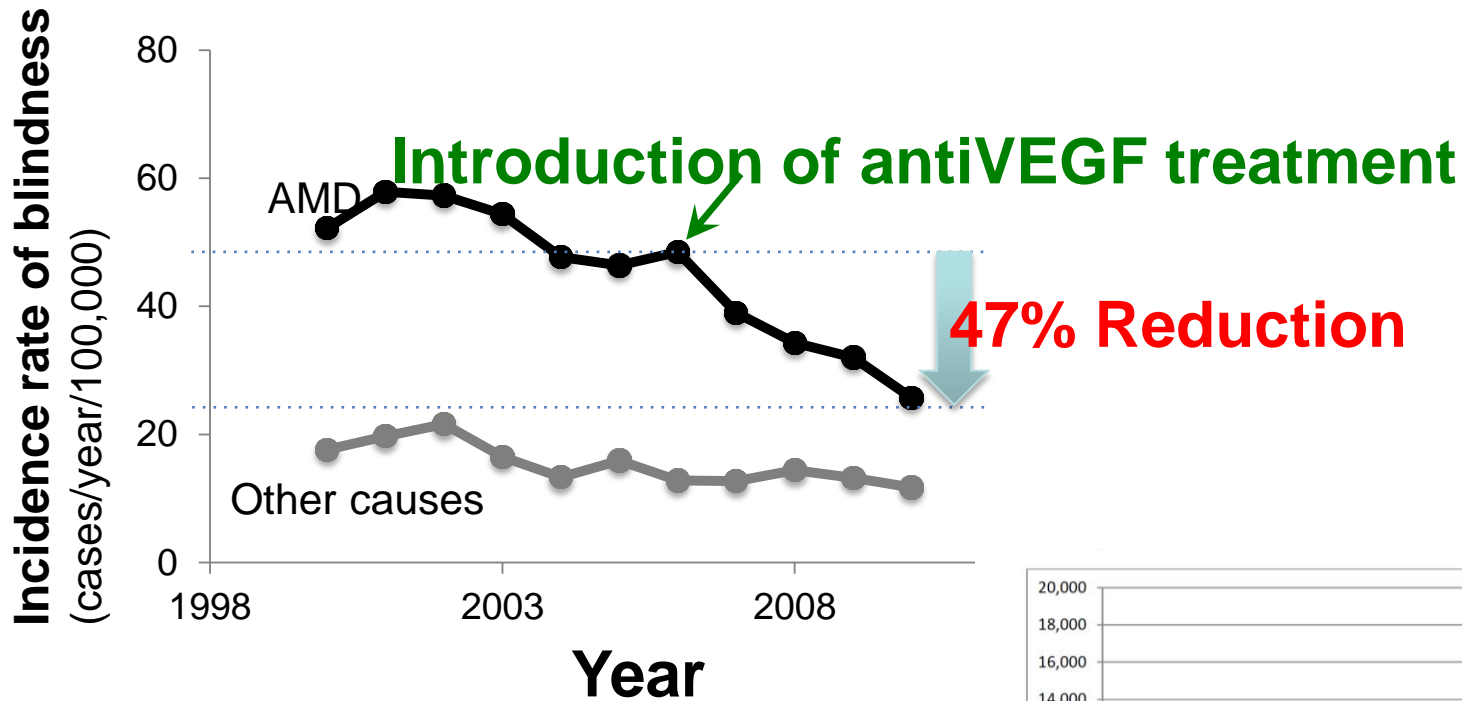
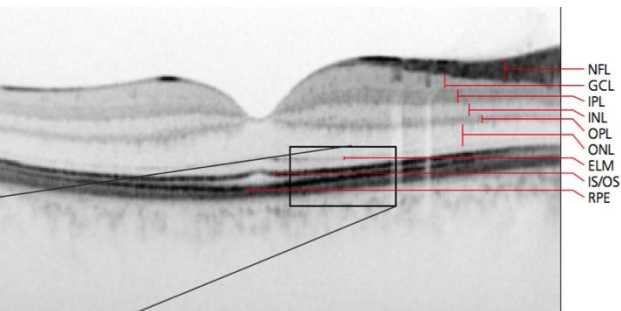


Figure 1: Number of initial patients and all patients treated each month from August 2007 to December 2014

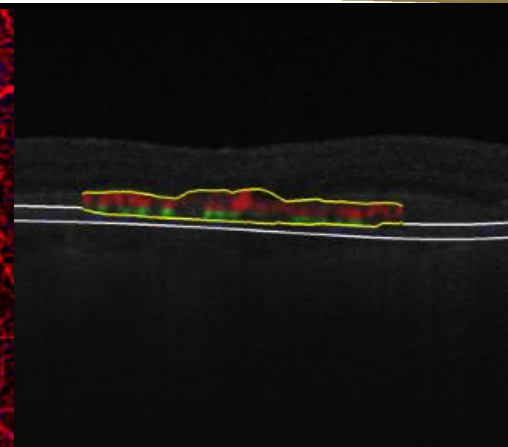
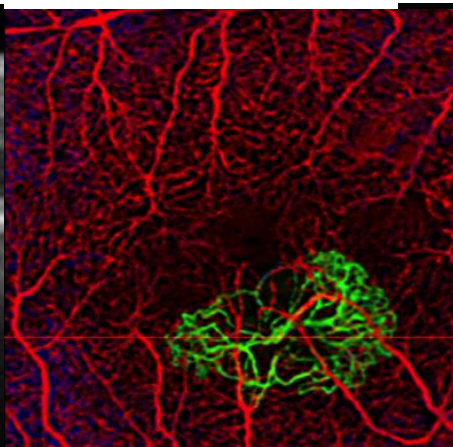
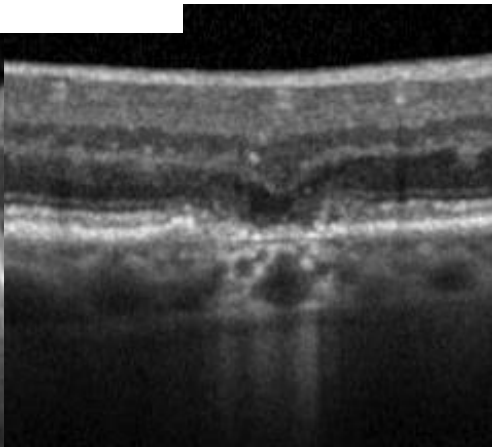
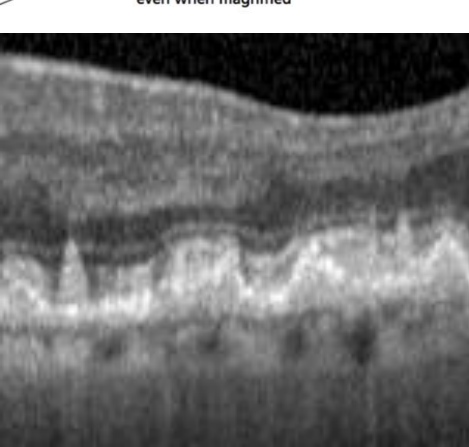
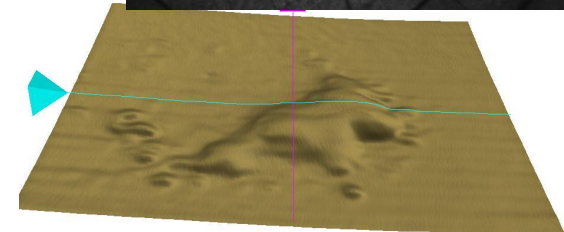
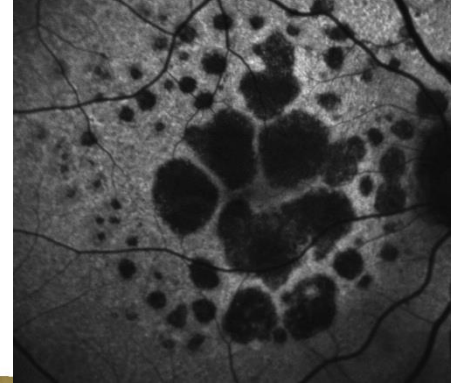
Source: DHS Medicare Pharmacy Claims database, accessed April 2015

# Eye offers a unique opportunity for novel interventions

- **Can see what is going on directly**
  - Can directly see pathology, blood vessels , nerves
  - Imaging the retina has become extraordinary
  - testing the function is improving

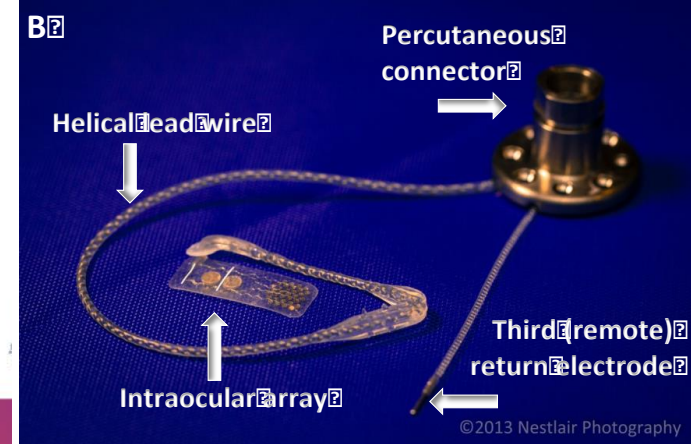
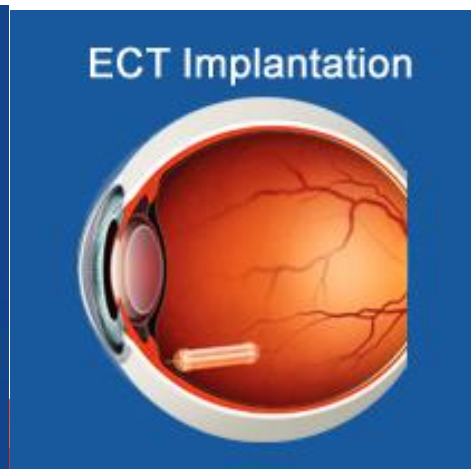
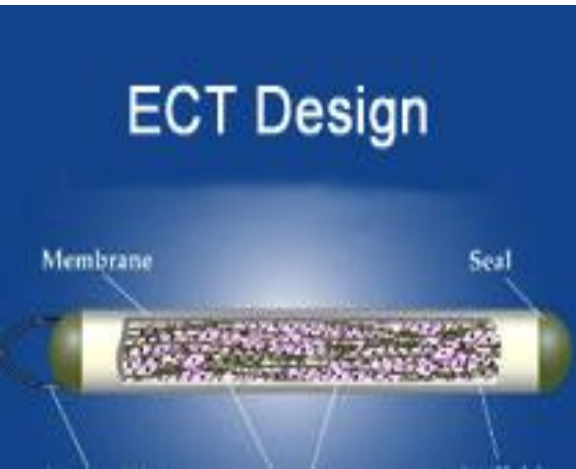
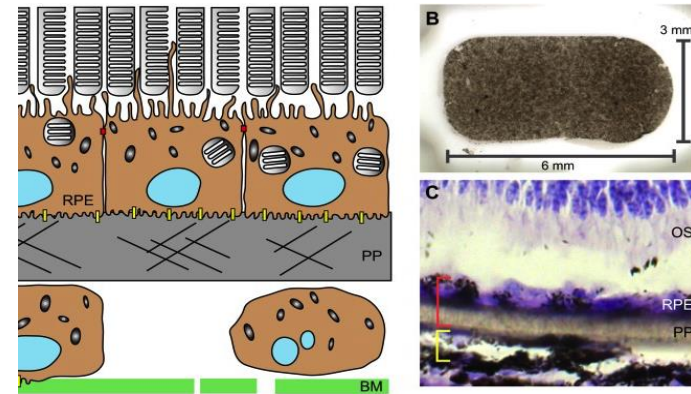
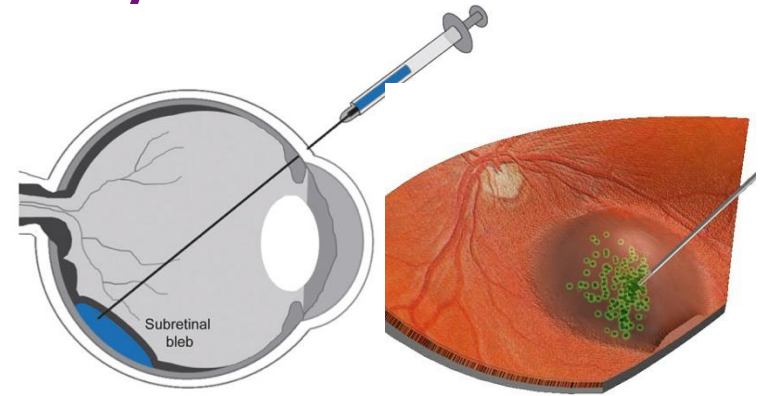


Enhanced detail enables fine layer identification, even when magnified



# Eye offers a unique opportunity for novel interventions

- Ophthalmology often lead the way
- Gene replacement therapy
- Stem cells trials
- Encapsulated technology-CNTF
- bionics





# Bionic Vision Australia (BVA)

a partnership of world leading Australian research institutes,



**UNSW**  
THE UNIVERSITY OF NEW SOUTH WALES



The Bionic Ear Institute



Centre for Eye Research Australia



**NICTA**

Core partners  
Since 2007

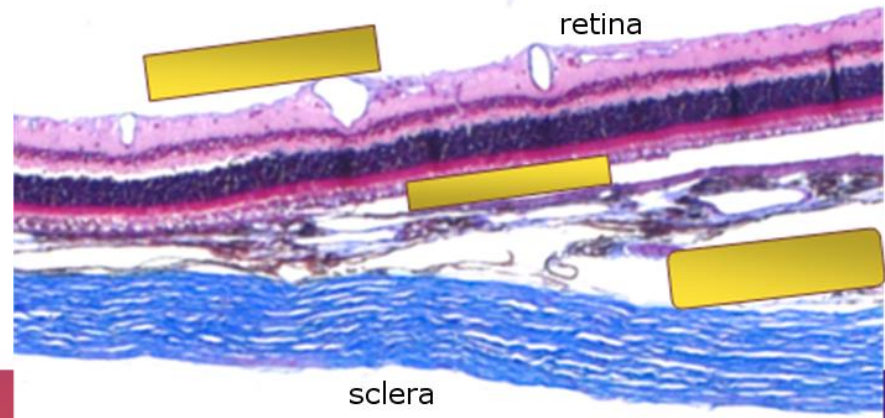
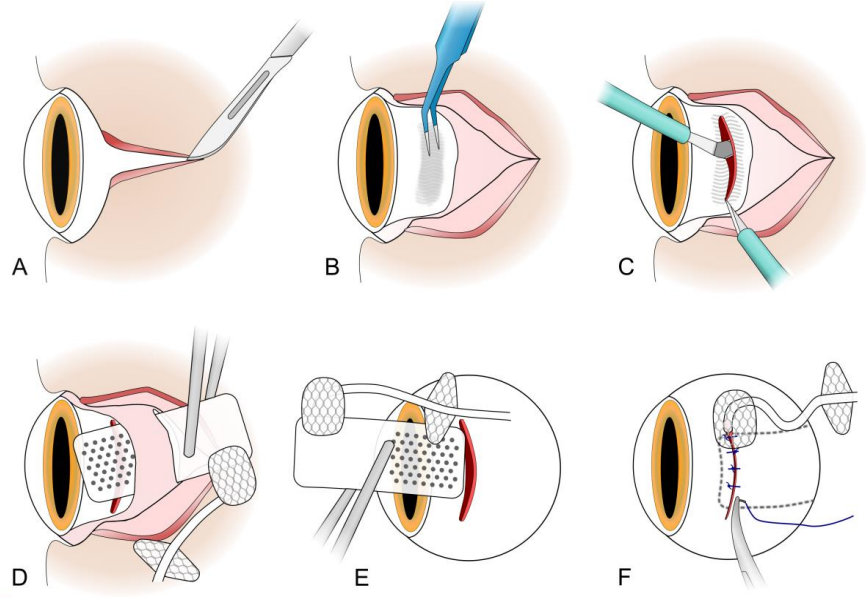
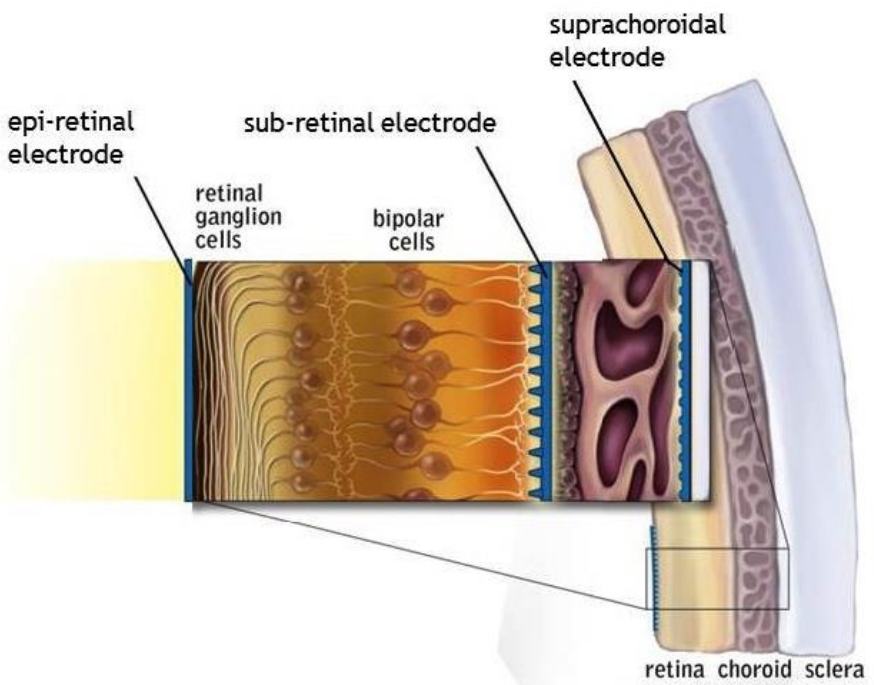
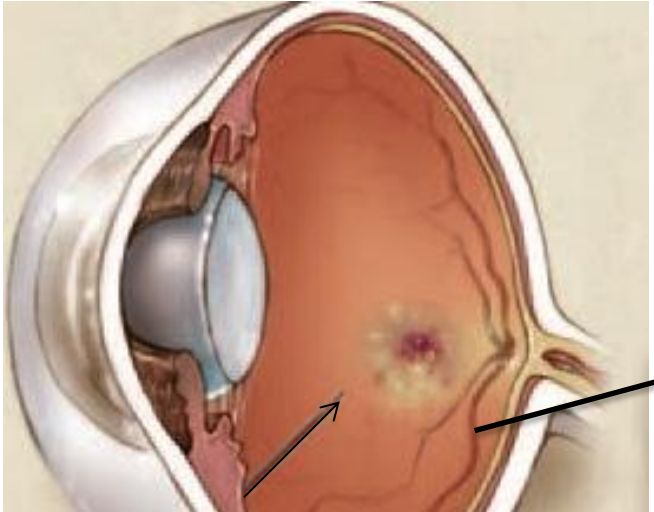


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CENTRE FOR  
Eye Research  
Australia

# Retinal Prosthesis: unique location, easier surgery



# Multi-discipline team



Surgeons and engineers in theatre and meetings together





# First in human device trials

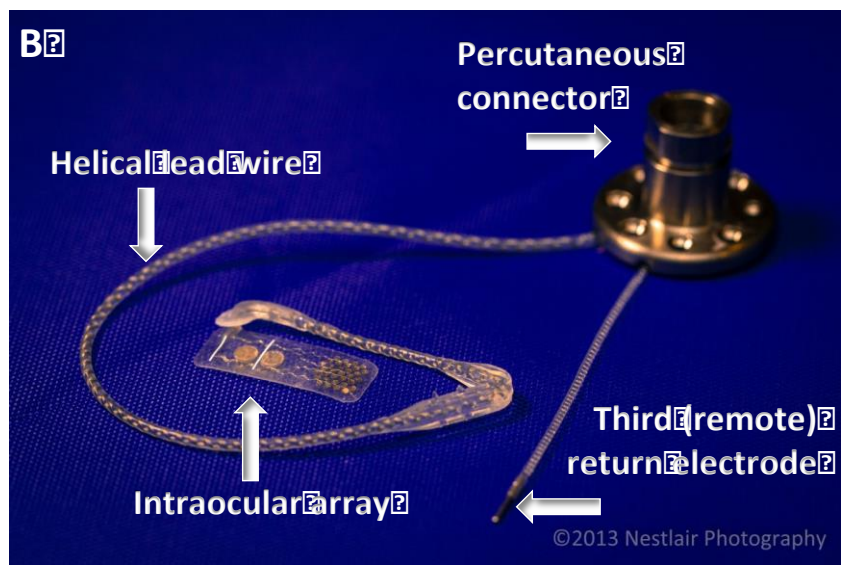
## Getting started is a problem

- Multiple parties, multiple institutes, universities, industry
  - IP issues
  - It is an industry trial or an investigator initiated study
  - Clinical trial agreements- what templates?
    - Compared to new drug trials
  - Devices less help on regulatory front compared to drugs
  - Not clear what to do if a device and a drug, (delivery of drug)
  - Sponsor
  - Indemnity

# Bionic Vision Australia: Participants

- First in human studies need to find willing participants- ultraistic
- So when planning the protocol need to understand that hard to find patients
- Stem cell first in human study had half of the people who put their hand up end up in placebo group to try and look at efficacy as well as safety. Waste of the few willing people to not end up not in active arm of study
- Device; what happens when study finishes,
  - who looks after the device? The company might not exist into the future
  - Might be different components no longer supported
- BVA , not only were participants blind, we were giving back vision for the study, but we were then taking out the device as only prototype. So making them blind again!







## Key to our success;

- de-risking the procedure
  - extensive preclinical testing
- Exhaustive selection process
  - including psychological testing
- A full and frank discussion and consent process
- Fully involving the participants in the research process

Finalist the Eureka award for multi-discipline teams



# Bionic Vision Technologies



**Next Bionic eye clinical trial of 3 patients.**

**New fully implantable take home device**

- BVT is a commercial entity with funds to help run the clinical trial
- NHMRC grant also to conduct the trial ( not sufficient funds)
- Our Institute regards the study as commercial as some funds coming from industry.
- Commercial entity regard it as a IIT so want us to sponsor and indemnity as cheaper on costs and ethics costs
  - IP contracts, CTA, costs of trial
- **Researchers are ready, just want to get started**- delays mean
  - Competition in other restorative approaches- stem cells and gene therapy starting
  - Competition for the researcher expertise – needed for other projects
  - Competition for the patients- not exclusive to one study, limited resource







# ELLEX nanosecond laser



A potential  
“cure” for AMD



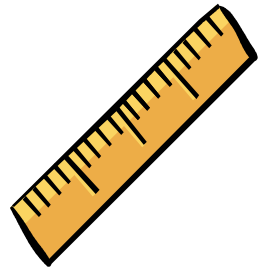


In 2RT  
3ns = 1m

# Ellex 2RT



If 2RT laser  
treatment energy =  
your height



0.000000003 seconds  
33 million times shorter! than 0.1 sec

**2RT laser pulse has no  
time to create thermal  
damage**

500 – 1000 times less energy  
than thermal laser

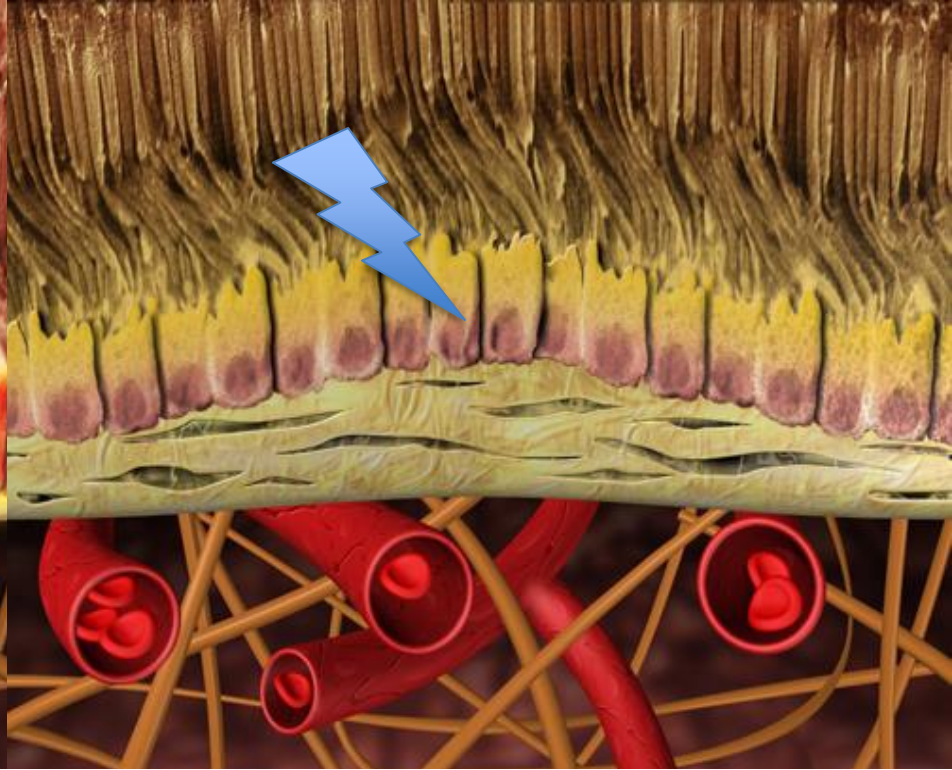
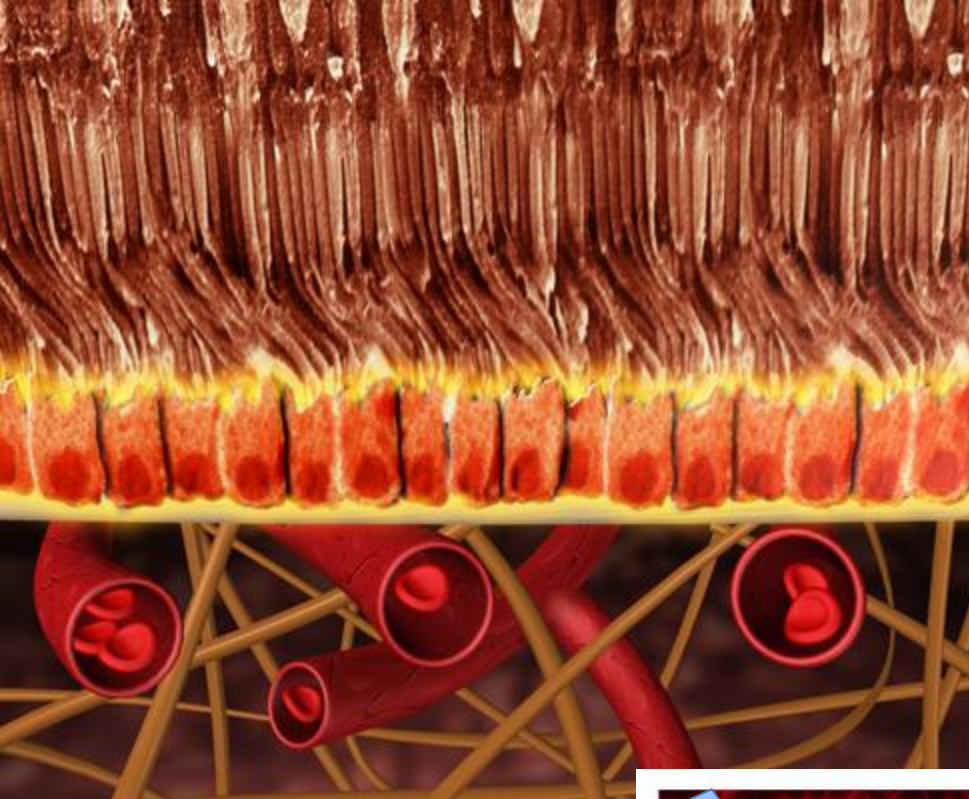


2RT laser produces completely  
different, non-thermal effects in the  
RPE  
100,000 Watts with every pulse!  
But over 0.000000003 seconds  
VERY good at producing small  
bubbles (boiling) around very small  
pigments.

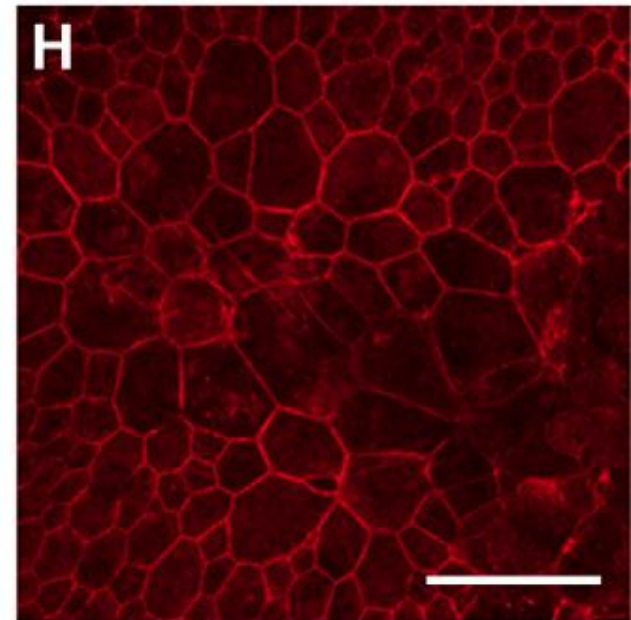
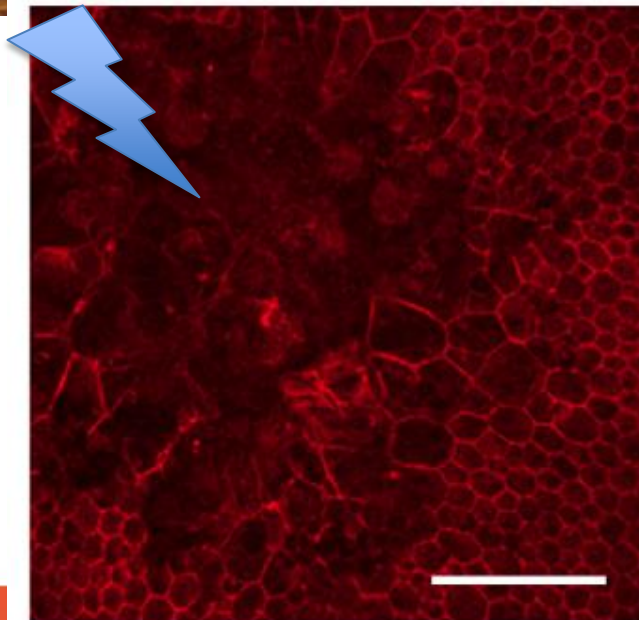
standard  
photocoagulator  
energy =  
**4 x height of  
Empire State  
building**

Then 0.1sec =  
**CIRCUMFERENCE OF  
THE EARTH**





Ellex laser:  
2RT laser  
Retinal  
Rejuvenation  
therapy



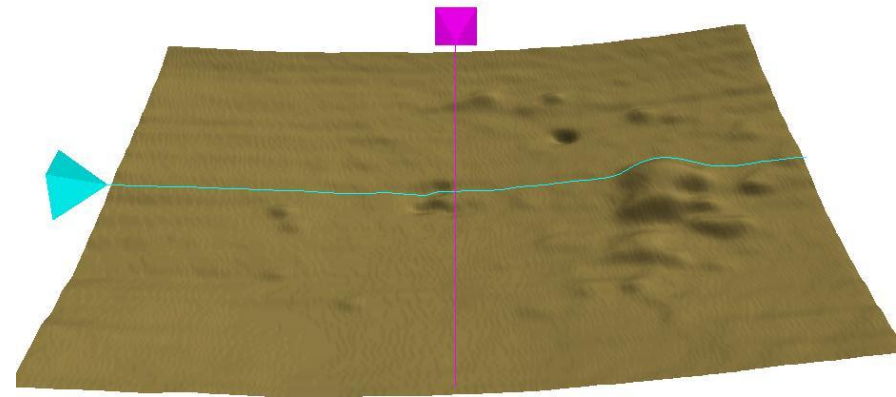
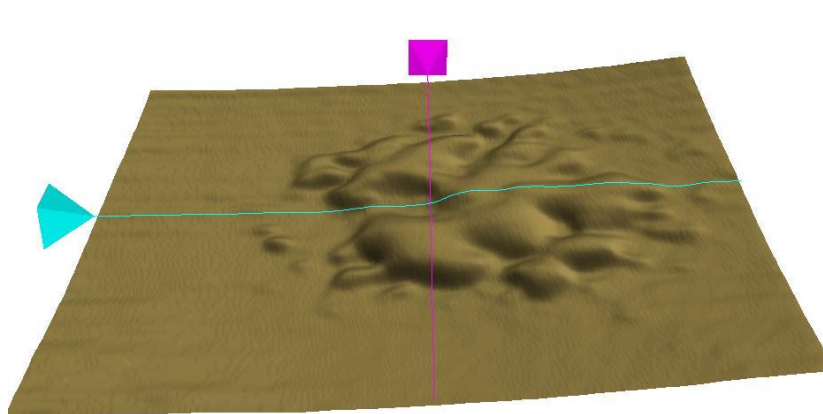
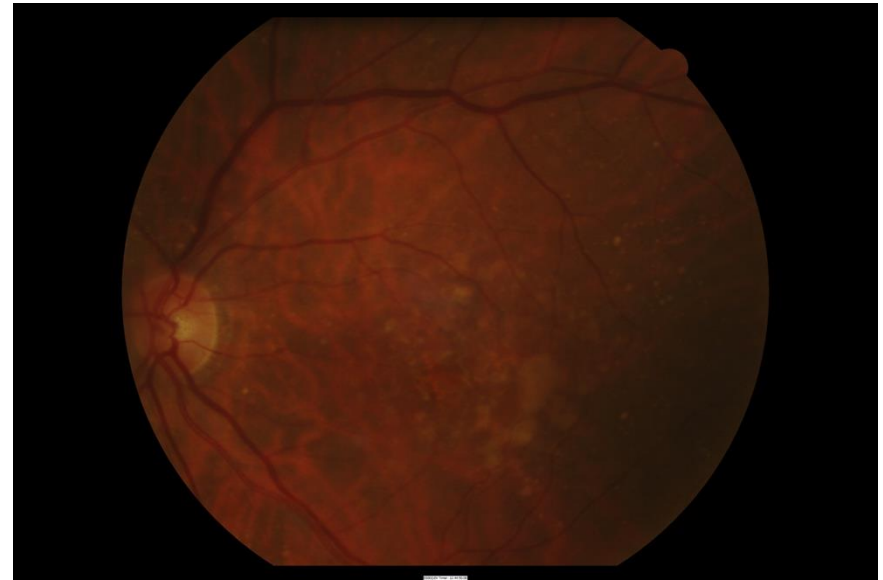


2RT aims to be the only treatment that slows progression to vision loss by clearing debris

Pre laser

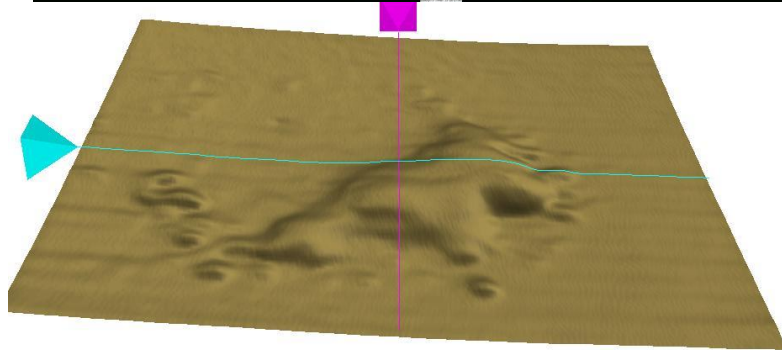


3 months post laser

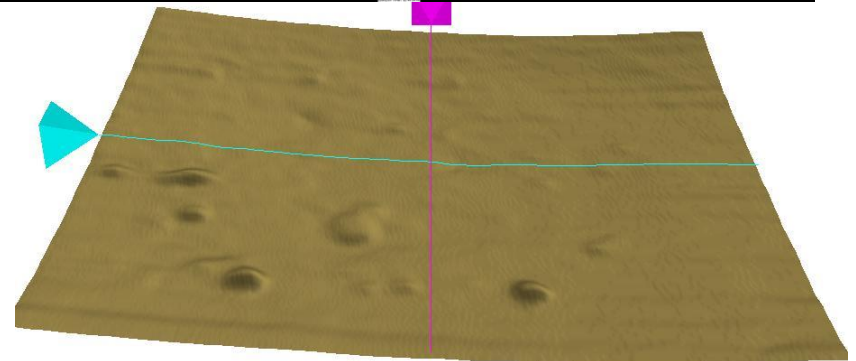
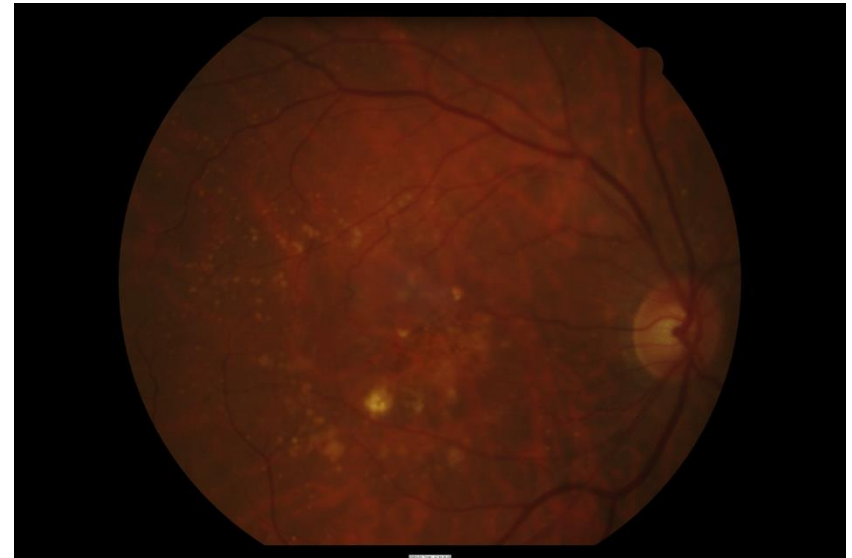




# Baseline



# 3 months



ch

# Outpatients at RVEEH: no place for early disease

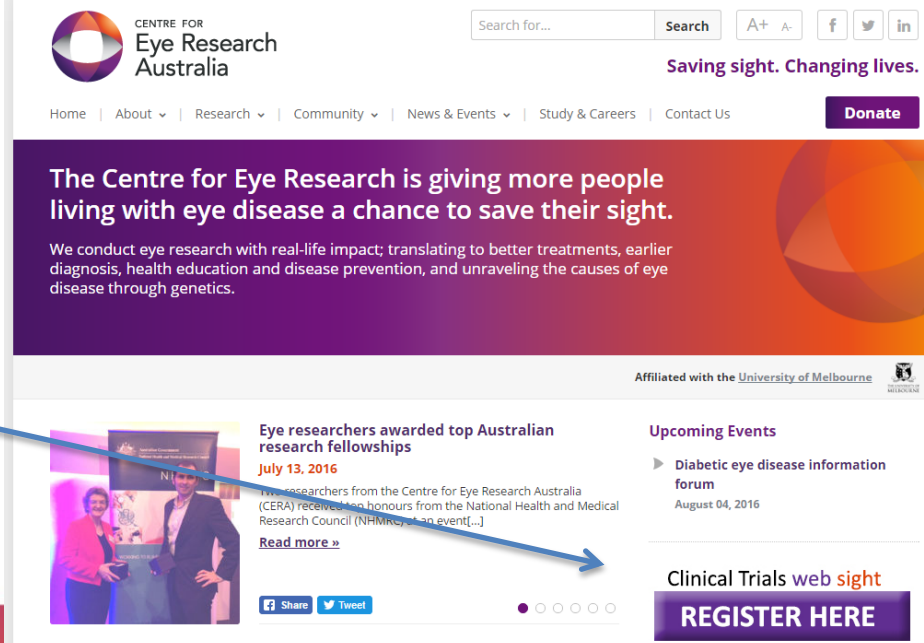
## Patient recruitment

- Early disease is not found in a tertiary referral hospital
- No EMR for outpatient services
- No registry of disease
- Most common cause of poor vision in people over 50 yet we cant find them



# Patient recruitment

- Go to the media
  - 3000 calls for all sorts of disease
  - 6 months to get back to everyone
- Steps to be ready for next time
  - Website self registration
  - Crowd sourcing Registry “web sight”





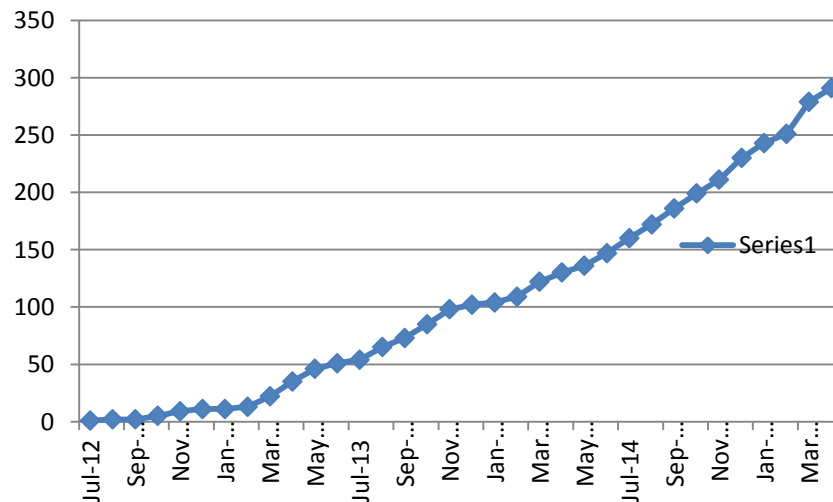
# First patient in the world to receive nanosecond rejuvenating laser therapy



# LEAD

## (Laser intervention in Early Age-related Macular Degeneration)

- 289 people, 3 years follow up (6 sites) fully recruited
- FIRST TRIAL OF NANOSECOND LASER IN AMD- slow progression to VA loss
- BUT ALSO FIRST TRIAL TO:
- NEW INCLUSION/EXCLUSION CRITERIA
- NEW ENDPOINTS



## LEAD study: all the cohort has reached 2 years

- We set out to try and run the trial as if it were a big pharma trial. for registration
- Trying to do to regulatory requirements but not resourced
- We employed one person to get us up and going- ethics TGA, protocols, DSMC
- But now it is the team on the cleaning data, chasing sites
- Because we didn't have enough money to pay sites properly, people were doing for the "love of science"
- So now hard to ask them to do more than they through they agreed to, chasing up queries, photocopying data book, for validation of the laser dose.
- We are trying to keep company at arms length so we are not perceived to have compromised the results



# Small Biotechs

- At least one company a month come to my office
- They like us because the researchers are good at what they do
- We like the concept so are keen to help
- So now what do we do?
  - They want to know what pre-clinical data do they need before we would consider doing a human trial
  - Then they want to know ballpark costs of the trial?
  - Usually once you tell them they go away and try to find it cheaper then come back
- We try to provide a one stop shop for eye trials but we are too small so working to work in partnership with Neuroscience trials Australia



## Reliability of rod and cone sensitivity measurements using a novel dark-adapted chromatic perimeter

Shoaib, S., Patel, P.J., Xing, W., Bunce, C., Egan, C., Tufail, A.T., et al. Test-Retest Variability of Microperimetry Using the Nidek MP1 in Patients with Macular Disease. Invest Ophthalmol Vis Sci. 2019;60(7):3464-72.

### AIMS:

The dark-adapted chromatic perimeter (DACP) was designed to measure dark-adapted retinal sensitivity with a large dynamic range, allowing the ability to study dark adaptation kinetics at multiple retinal locations simultaneously. This study investigated the intra-session repeatability of retinal sensitivities using the 505nm and 620nm stimuli in cases with non-neovascular age-related macular degeneration (AMD) and in subjects with normal fundus appearance.

### METHODS:

Retinal sensitivities were measured in one eye of 31 AMD and 16 control subjects after 20 and 30 minutes of dark adaptation. To determine the effect of learning on the test performance, a subset of participants (6 cases and 14 controls) attended a second visit (4 ± 2 weeks from the initial visit) and measurements of retinal sensitivity were repeated. The intra-session point wise sensitivity (PWS) coefficient of repeatability (CoR) of each visit was determined and compared between the control and AMD group. The DACP testing parameters are shown in Figure 1.

DACP	PARAMETERS	505 nm	620 nm
Dynamic Range		0 - 75 dB	0 - 50 dB
Stimulus Size		Goldmann V	
Threshold		4 - 2 staircase	
Stimulus Length of Each Test		3 - 5 minutes	
Stimulus Grid (28 points)			

Figure 1. DACP testing parameters for measuring retinal sensitivity using 505nm (cyan) and 620nm (red) stimuli. \* - rod - mediated sensitivity predominantly measured in normal eye \*\* - cone - mediated sensitivity predominantly measured in normal eye

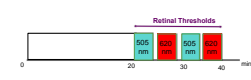


Figure 2. Testing protocol for the first visit and second visit tested 4 ± 2 weeks after.

### RESULTS:

The differences in mean sensitivity between the first and second test for both visits were significant for 505 nm stimulus ( $p \leq 0.01$ ) but not for 620 nm stimulus ( $p \geq 0.07$ ) in both cases and controls. Thus the intra-session repeatability of the DACP was determined only for the 620 nm stimulus. The CoR for 28 cone test points of the first visit ranged from 2.82 - 6.35 dB for controls and 4.10 - 12.13 dB for AMD subjects. The CoR of the second visit ranged from 2.41 - 12.35 dB for controls and from 2.02 - 10.42 dB for AMD cases. Outliers were detected in 1.2% of the data points. The PWS CoR for control and AMD subjects are shown in Figure 3.

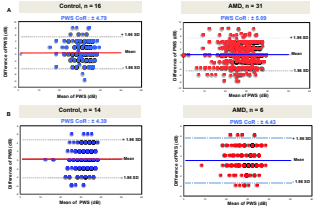


Figure 3. The Bland-Altman plots of the first (A) and second (B) visit for controls and cases using 620nm stimuli after outliers were excluded. The intra-session CoR of the 2 groups was similar.

### CONCLUSIONS:

- The intra-session CoR for 620 nm stimulus did not seem to be worse with the presence of pathology.
- There was a slight improvement in CoR in the second visit.
- When testing retinal sensitivity using rod predominantly 505 nm stimulus, it was apparent that rod adaptation still occurring after 20 minutes of DA, even in control subjects.

### DISCUSSION:

- There was an improvement in rod sensitivity, but not with the cone sensitivity, in control and AMD groups on the first and second intra-session tests after 20 minutes of DA, suggesting that the rod dark adaptation is still on going rather than the process of learning.
- This is an important finding when one is considering using rod sensitivity as a marker of disease severity in clinical trials.
- Ceiling and floor effects were not found with the broad stimulus intensity availability on DACP.
- DACP is recommended to evaluate macular function in clinical use. PWS CoR of DACP for the first ( $\pm 5.09$  dB) and second ( $\pm 4.43$  dB) intra-session tests in AMD group, which were similar with other microperimeters, such as Nidek MP1 ( $\pm 5.56$  dB) and MAIA ( $\pm 4.37$  dB).

### REFERENCES:

- Chen FK, Patel PJ, Xing W, Bunce C, Egan C, Tufail AT, et al. Test-Retest Variability of Microperimetry Using the Nidek MP1 in Patients with Macular Disease. Invest Ophthalmol Vis Sci. 2019;60(7):3464-72.
- Wu ZC, Ajjan LN, Guymer RW, Luo CD. Intra-Session Test-Retest Variability of Microperimetry in Age-Related Macular Degeneration. Invest Ophthalmol Vis Sci. 2013;54(12):7378-85.

### ACKNOWLEDGEMENTS:

This research was supported by Australia Awards Scholarship (AAS) and Macular Disease Foundation Australia (MDFA)

# Launch of the International Task Force

Aim: agreed testing protocols for restorative interventions





# International Classification of Atrophy meeting: -agree on our endpoints for the laser study



# Clinical trial setting: ideally looks professional.

Dream is an Academic Eye Centre but current reality is ...





# Happy patients- but we could do so much more if properly resourced

