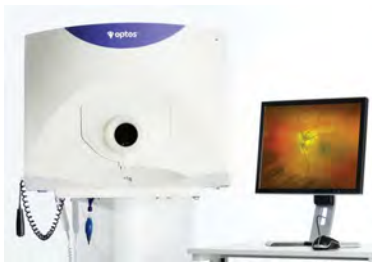




# Connecting the dots in diabetic retinopathy: what has changed?

Paula Katalinic

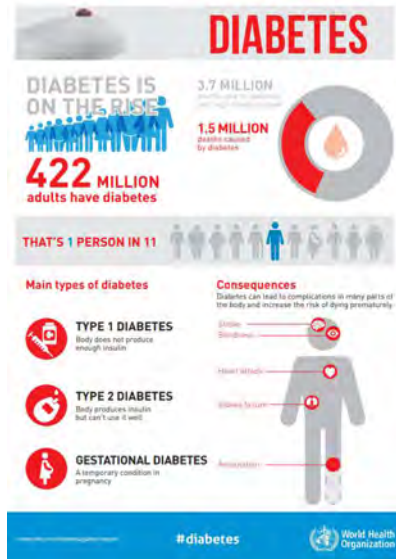
Principal Staff Optometrist & Lead Clinician (Diabetes)



## Aims of my talk



## Diabetes: a global health crisis



- Diabetes affects 1 in 11 people worldwide\*
  - In 2012, it caused 1.2 million deaths
- Approx. 6% of Australians >18 years of age#
- Approx. 6.5% of NZ >18 years of age with diagnosed diabetes~
  - >240,000 diagnosed & 100,000 undiagnosed^

\*World Health Organisation  
#Australian Bureau of Statistics  
^ NZ Ministry of Health  
~ Derived from Stats NZ

## Diabetic retinopathy A worldwide snapshot

- A leading cause of preventable vision loss in working age adults
- Most frequent cause of *new blindness* in those aged 20-74 years in developed countries
- **Global prevalence of retinopathy ~34.6%\***  
→ 1 in 10 had vision threatening DR

\*pooled meta-analysis involving 35 studies worldwide -Yau, Diabetes Care, 2012



# Diabetic Retinopathy in Australia

## Blue Mountains Eye Study (1992-1994)



Of the participants >49 years with diabetes:

- 32.4% had DR
- **4.3% had macular oedema**
- **1.6% had PDR**

# Diabetic Retinopathy in NZ



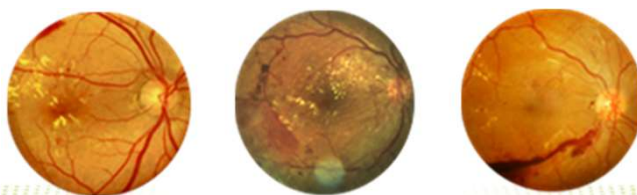
	Wellington region	Northland region
Study	Chang, Lee and Sue, NZ Med J (2017)	Papali'i Curtain & Dalziel, NZ Med J (2013)
Any DR	22.5%	19%
Sight threatening DR	2.3%*	1.8%*
PDR		0.4%
Treatable maculopathy	1	1.4%
# Participants	17508 people (first screening) <b>88.9%</b>	7098 screenings from 5647 people; <b>79%</b>
Ethnicity	NZ European (56.6%); NZ Māori (13%), PI (10.5%), Asian (11.7%)	~77% New Zealand European (56.5%) and Māori (39.3%)

\* Different grading scales were used in each of the regions

# Broad rule of thumb

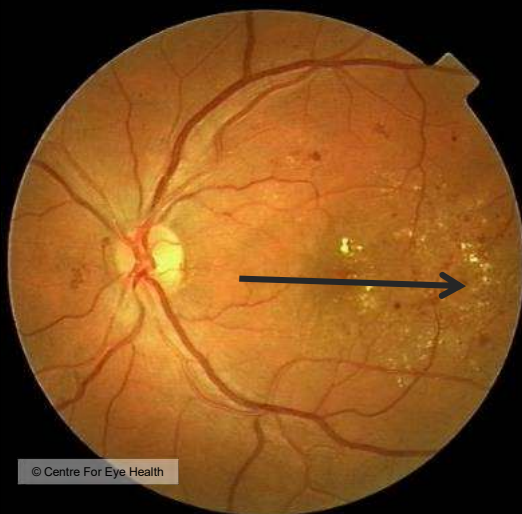


**1/3 have DR**  
**1/3 of those have vision threatening DR**

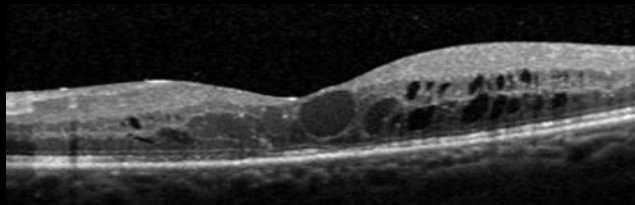


An initiative of Guide Dogs NSW/ACT and The University of New South Wales

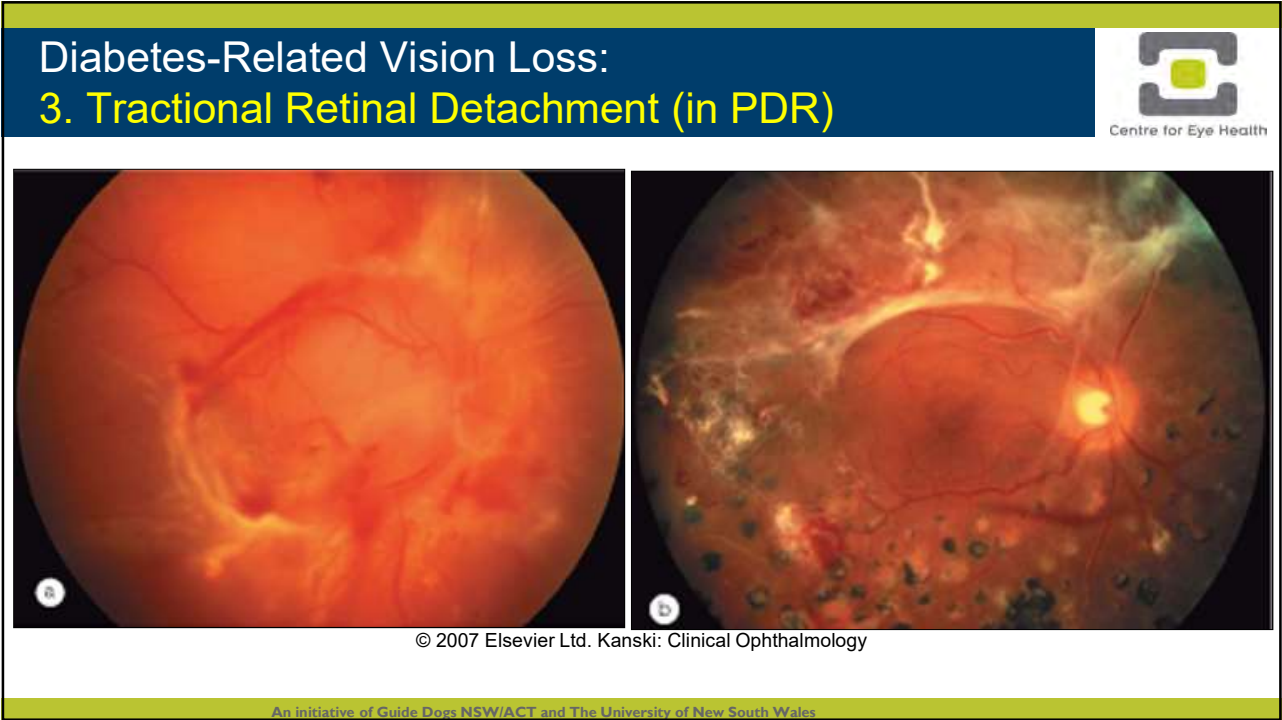
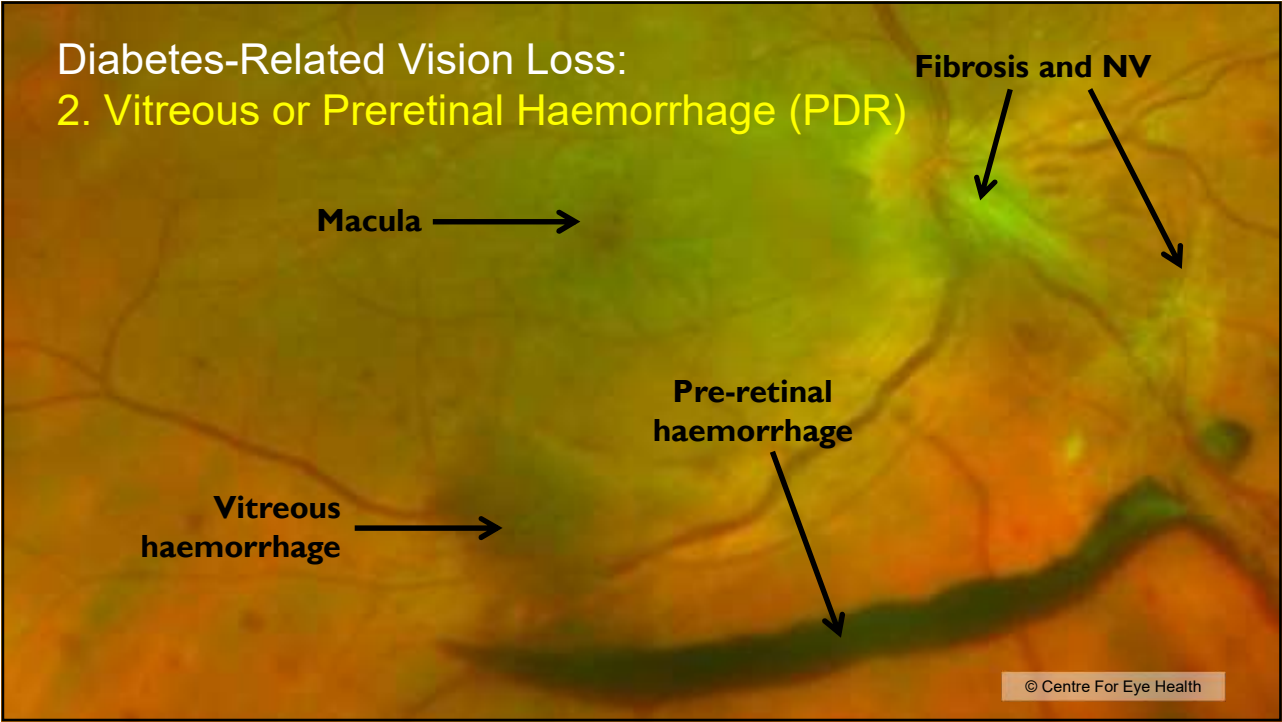
## Diabetes-Related Vision Loss: 1. Diabetic Macular Oedema



© Centre For Eye Health



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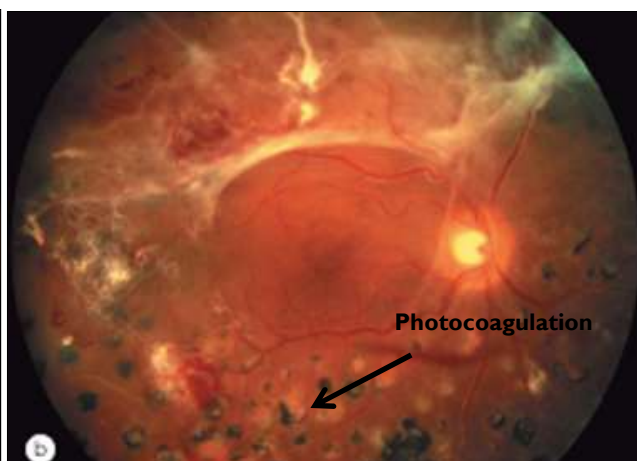
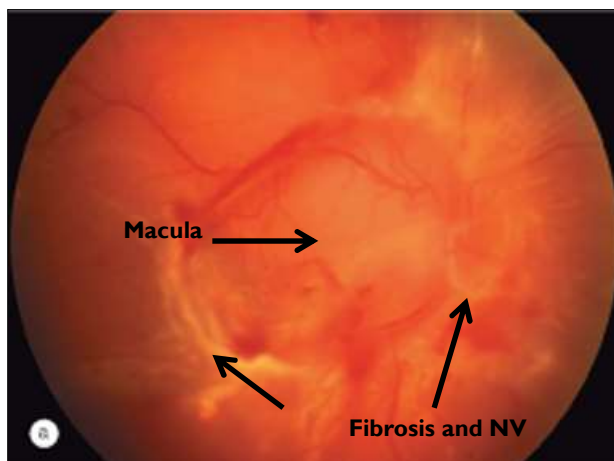


## Diabetes-Related Vision Loss:

### 3. Tractional Retinal Detachment (in PDR)



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Post vitrectomy and endolaser

© 2007 Elsevier Ltd. Kanski: Clinical Ophthalmology

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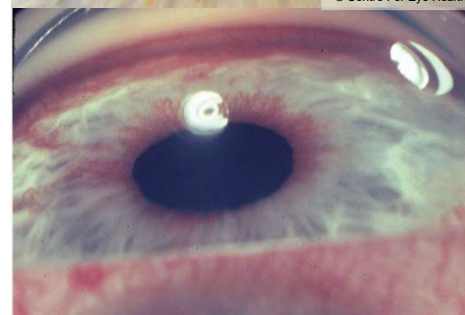
## Diabetes-Related Vision Loss:

### 4. Neovascular Glaucoma

- Fibrovascular network of vessels grows over angle structures
- IOP  $\uparrow$  and secondary glaucoma
- Iris rubeosis usually seen first at pupil margin
  - NV may infiltrate angle without any vessels visible on slit lamp exam
  - Gonioscopy when IOP is raised



© Centre For Eye Health



Source: Review of Optometry [http://www.revophth.com/index.asp?page=1\\_13859.htm](http://www.revophth.com/index.asp?page=1_13859.htm)

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Diabetes-Related Vision Loss:  
5. Diabetic macular ischaemia (DMI)

- VA loss can occur in cases of moderate to severe DMI
- Difficult to detect with fundoscopy
- Historically, fluorescein angiography was used in cases of unexplained VA loss

OCT Angiography enables optometrists to quickly & non-invasively assess for DMI

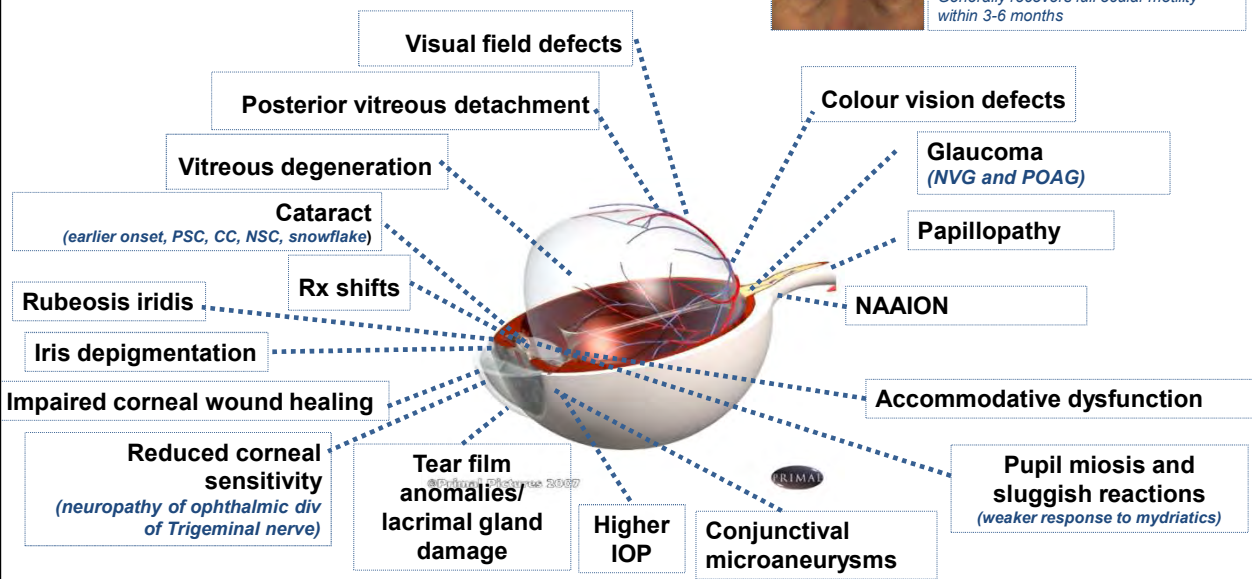
Enlargement of the foveal avascular zone (FAZ)

Paramacular capillary non-perfusion



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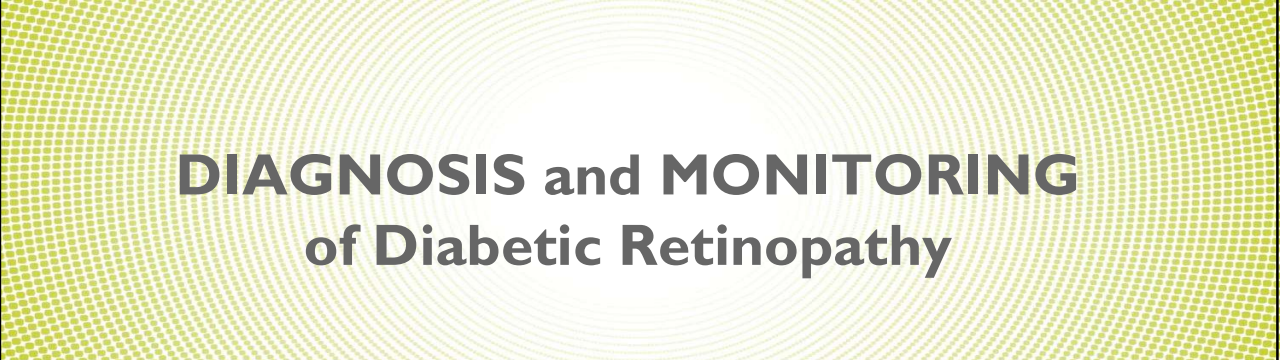
Other effects of diabetes





Up to **98%** of severe vision loss is **preventable**  
with **early detection & treatment\***

\*Early Treatment Diabetic Retinopathy Study



**DIAGNOSIS and MONITORING**  
**of Diabetic Retinopathy**



## Gold standard for detection and classification of DR



Centre for Eye Health

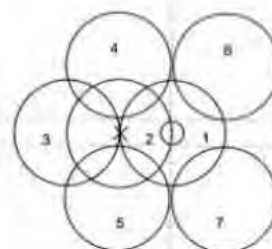
### ETDRS 7 standard field stereoscopic photography

- Labour intensive (15 images per eye)
- Requires skilled photographers
- Used in clinical trials

**MODIFIED AIRIE CLASSIFICATION** uses 7 standard photographic fields to detect neovascularisation.

#### RIGHT EYE

- Field 1 - Disc
- Field 2 - Macula
- Field 3 - Temporal to macula
- Field 4 - Superior-temporal
- Field 5 - Inferior-temporal
- Field 6 - Superior-nasal
- Field 7 - Inferior-nasal



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## In clinical practice.... Slit lamp funduscopy



Centre for Eye Health

The clinical gold standard remains dilated stereoscopic slit lamp funduscopy



### LIMITATIONS

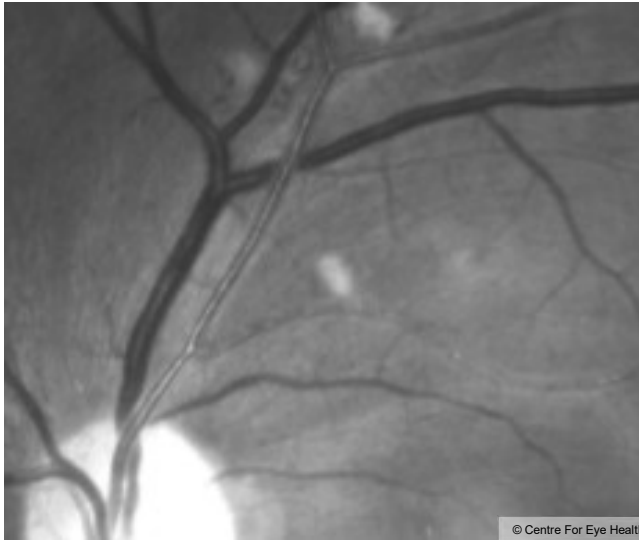
- Photosensitivity - particularly when assessing macula
- Pupil often dilates poorly in DM
- Small field of view
- Eye movements
- Media opacities
- Difficult to appreciate subtle retinal oedema

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## Retinal photography



Centre for Eye Health



© Centre For Eye Health

### LIMITATIONS

- Availability of stereoscopic imaging options
- Field of view and resolution
- Artefacts: pupil size, media opacities, exposure, vignetting
- Difficult to discriminate:
  - Between IRMA and NVE
  - Macular thickening

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Advanced  
imaging in  
diabetes



## OCT in diabetic retinopathy



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- OCT is now fundamental in the diagnosis of DME & measuring response to treatment
- Rapidly becoming the standard of care



### Benefits in diabetes

- Detection of retinal thickening & CME
- Precise measurement of macular thickness & changes over time
- May assist discriminating between IRMA & NV
- Can image through cataract and small pupils

### Limitations

- Small field of view
- Diffuse thickening is not obvious in line scans

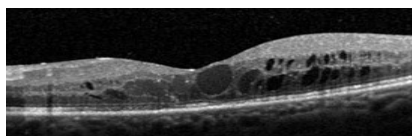
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## Detection of macular oedema



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- Wang et. al. (*JAMA Ophthal*, 2016) compared single field fundus photography to OCT
- 26.9%-32.7% of eyes with DME on OCT were diagnosed as having no DME on fundus photography alone
- Up to 58% false positives from fundus photography depending on grading scale



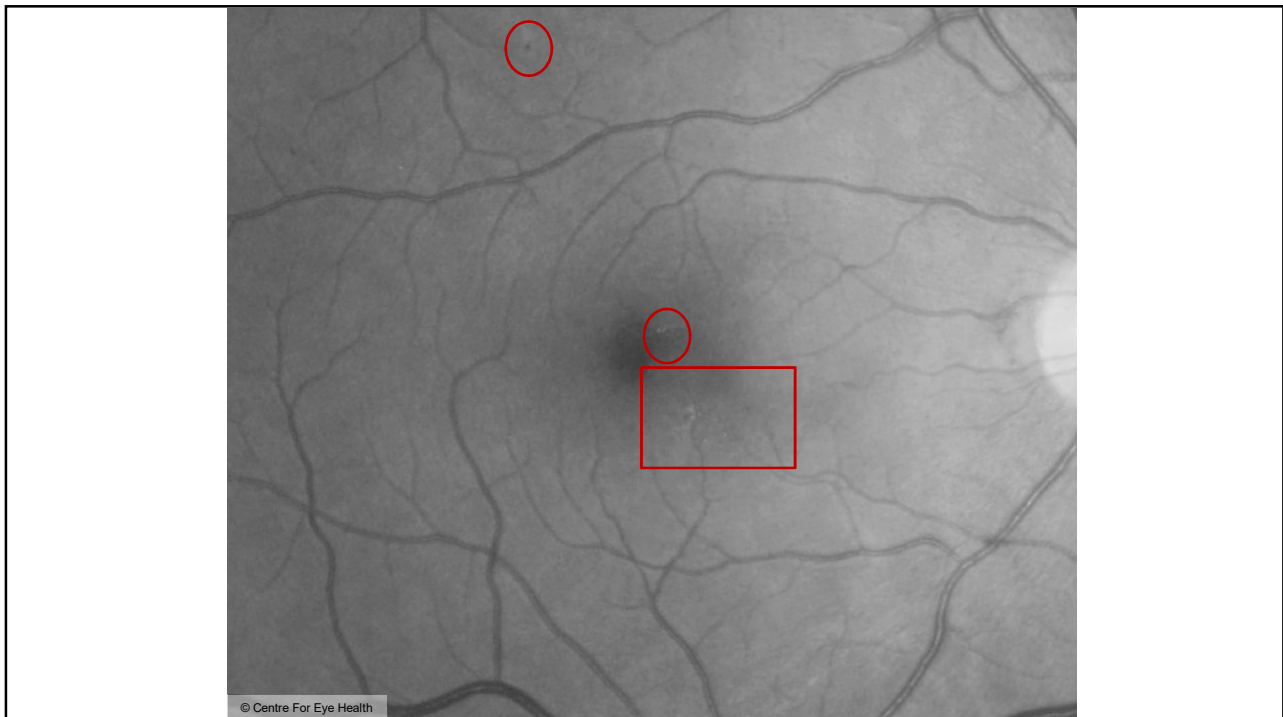
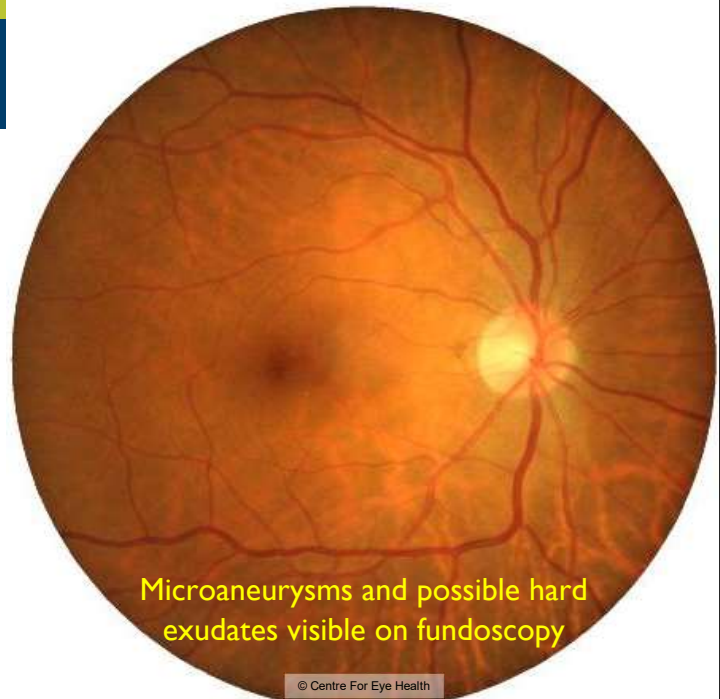
OCT can enhance detection of diabetic macula oedema

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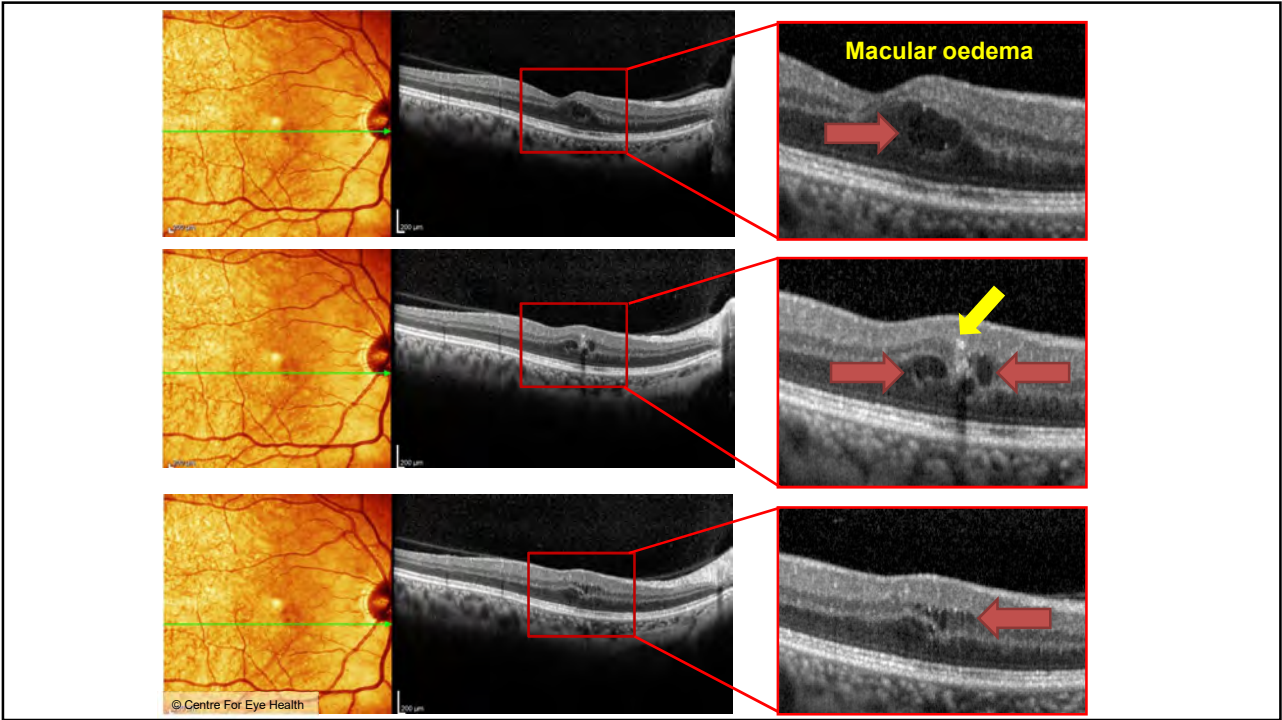
## Case 1

51 year old Caucasian female

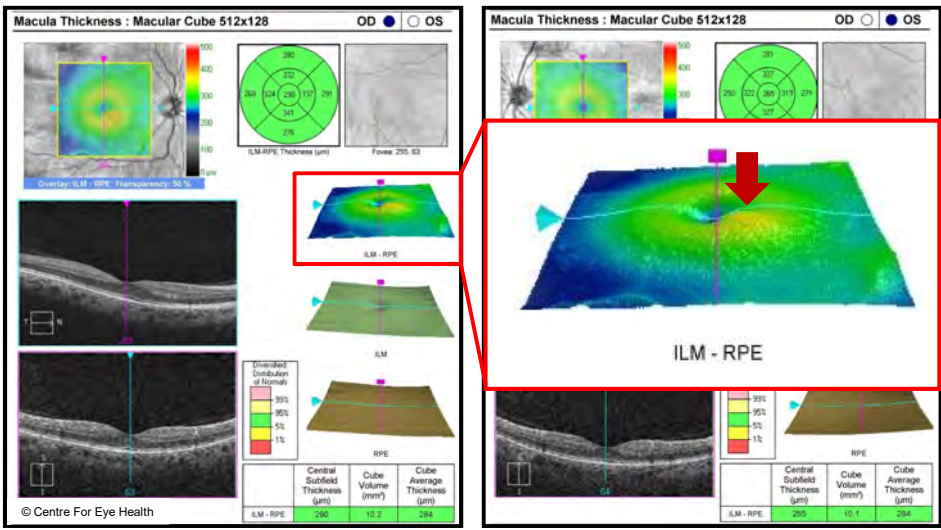
- DM since age 16 (genetic)
- No history of DR
- Aided VA: R: 6/7.6-1 L: 6/6-2
- Early PSC OU
- No Retinopathy OS



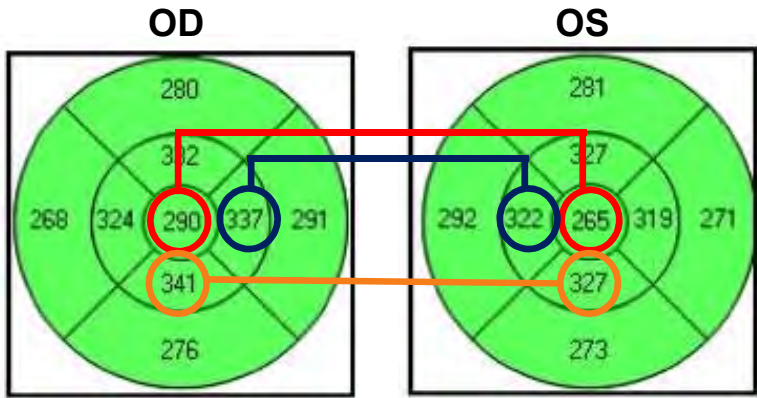




# Cirrus OCT Macular Thickness



Cirrus OCT (ETDRS grids)



Relative thickening in the central, inner nasal subfield and inner inferior subfield OD

?

International Diabetic Retinopathy and Diabetic Macular Oedema Disease Severity Scales

DIABETIC RETINOPATHY	
No apparent retinopathy	No abnormalities
Mild nonproliferative DR (NPDR)	Microaneurysms only
Moderate NPDR	More than just microaneurysms but less than severe NPDR
Severe NPDR	No signs of PDR, with any of the following: <ul style="list-style-type: none"><li>• &gt;20 intraretinal haemorrhages in each of 4 quadrants</li><li>• Definite VB in ≥ 2 quadrants</li><li>• Prominent IRMA in ≥ 1 quadrant</li></ul>
Proliferative diabetic retinopathy (PDR)	One or both of the following: Neovascularization, Vitreous/pre-retinal haemorrhage
MACULAR OEDEMA	
DME apparently absent	No apparent retinal thickening or HEx in posterior pole
Mild DME	Some retinal thickening or HEx in posterior pole, but distant from centre of the macula
Moderate DME	Retinal thickening or HEx approaching, but not involving, the centre of the macula
Severe DME	Retinal thickening or HE involving the centre of the macula

## International Disease Severity Scale: Diabetic macular oedema



- **Absent:** no retinal thickening or hard exudates in posterior pole
- **Mild:** Thickening or hard exudates (Th/Hex) in posterior pole but *distant from the centre of the macula*
- **Moderate:** Th/HEx *approaching the centre of the macula*
- **Severe:** Th/HEx *involving centre of the macula*



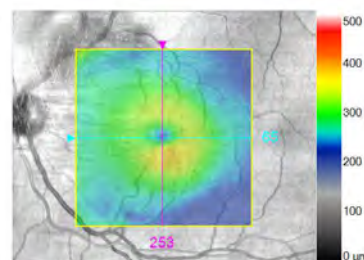
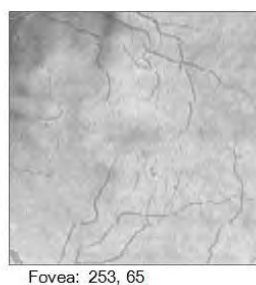
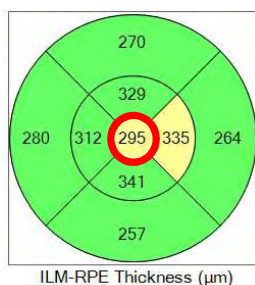
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## Grading Macular Oedema

**“Severe” vs. “clinically significant” vs. “centre-involved”**



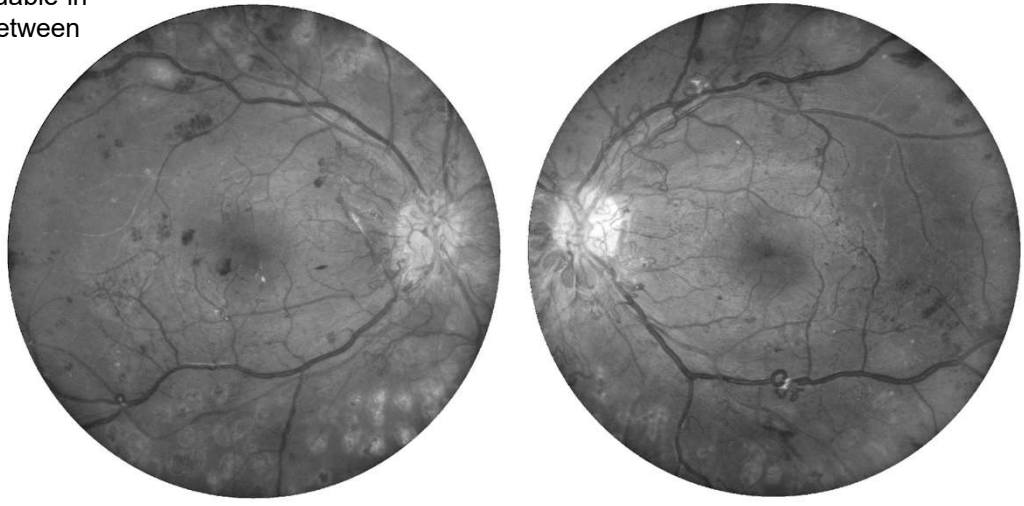
- International Council of Ophthalmology Guidelines (revised 2017) have provided an **definition for severe DME that is more easily applied to OCT results:** thickening **within the central 1000µm\*** (centre-involved)
- This is equivalent to a previous definition for CSME (thickening with 500µm of centre)



OCT in PDR  
Case 2. 38 year old male with Type I DM

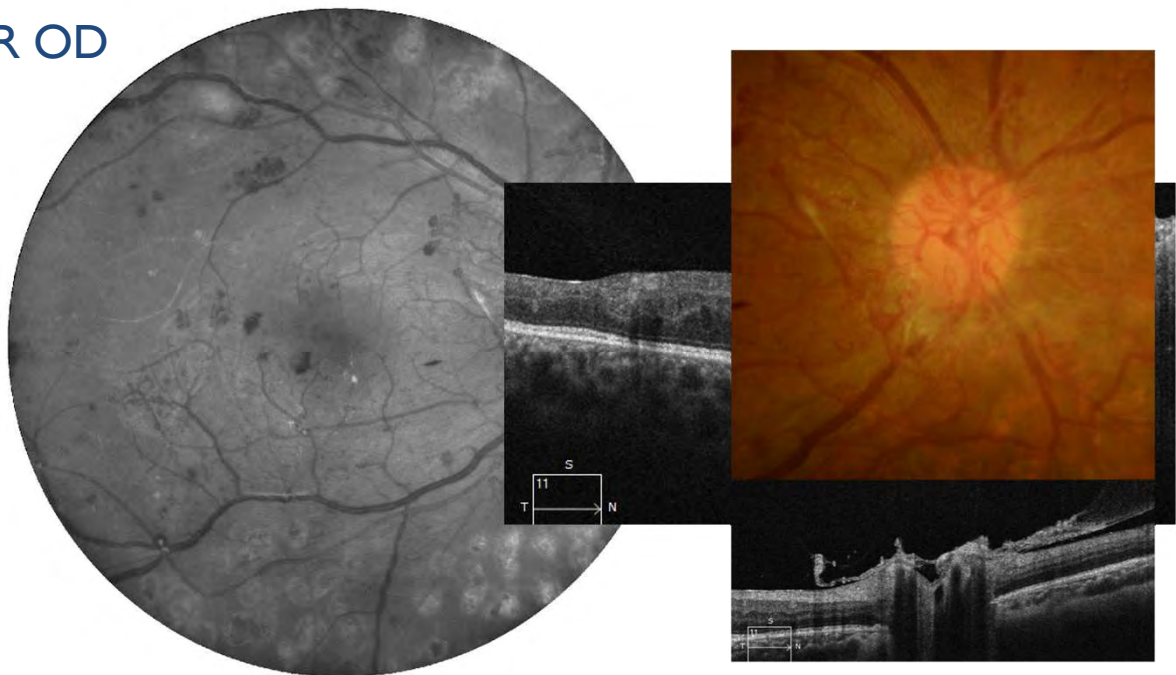


OCT can be valuable in discriminating between IRMA and NV



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PDR OD





## PDR OS

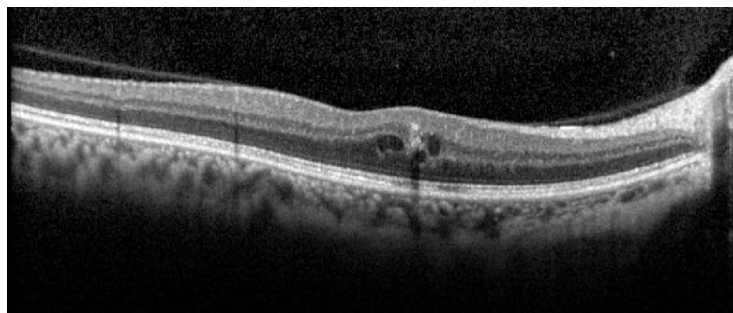


## Key learning points: OCT



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1. Enables detection of early macular oedema which may be missed with slit lamp fundoscopy or retinal photography
2. Has the potential to alter management and improve visual outcomes



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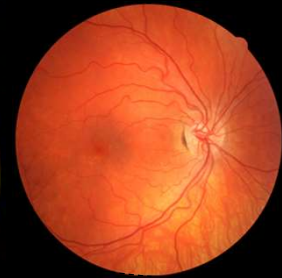
## Ultrawidefield imaging

### Benefits

- 'Global' view of retina
- Less affected by media opacity
- Red-free view highlight DR

### Limitations

- Lower resolution than retinal photography
- Loss of resolution at superior and inferior part of image
- Variable magnification across fields



45-degree digital image

## Optomap in diabetic retinopathy evaluation



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[Am J Ophthalmol](#). 2012 Sep;154(3):549-559.e2. doi: 10.1016/j.ajo.2012.03.019. Epub 2012 May 23.

**Nonmydriatic ultrawide field retinal imaging compared with dilated standard 7-field 35-mm photography and retinal specialist examination for evaluation of diabetic retinopathy.**

[Silva PS](#)<sup>1</sup>, [Cavallerano JD](#), [Sun JK](#), [Noble J](#), [Aiello LM](#), [Aiello LP](#).

**Exact agreement in 84% between**  
level of DR graded from *7-standard-field photos*  
and *Optomap 100 degree images (Resmax)*  
**91% agreement within 1 level**

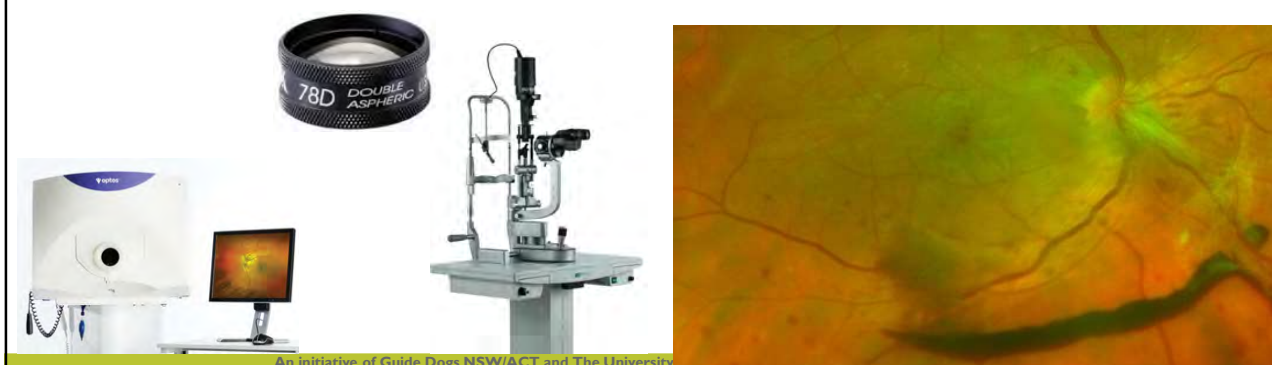
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## Why examine the retinal periphery in DM?



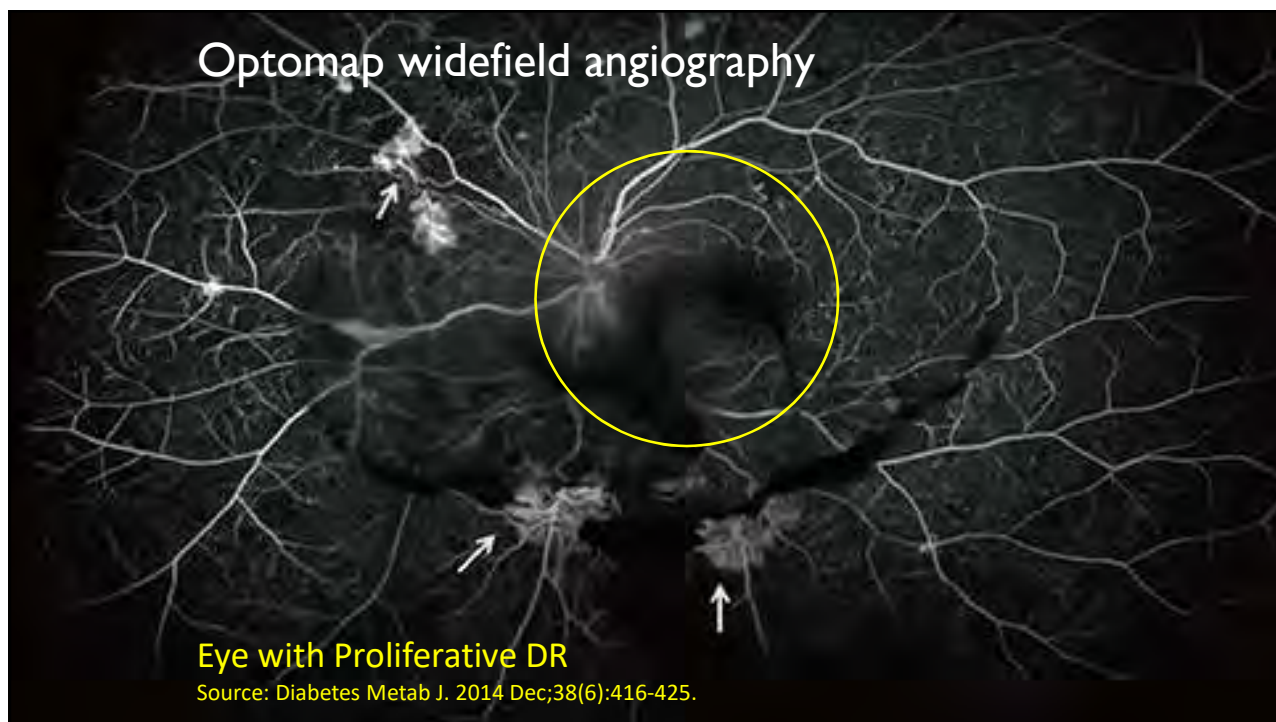
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- NV develops at the border of perfused and non-perfused retina, often in the vascular arcades
- NV may occur in midperiphery without NV in posterior pole



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## Optomap widefield angiography



**Eye with Proliferative DR**

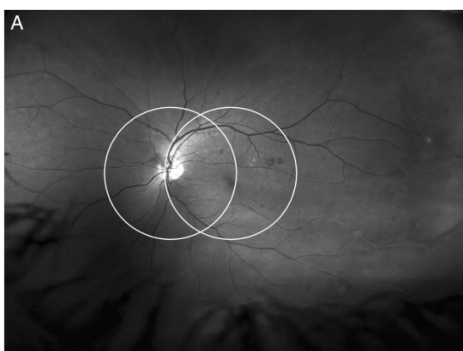
Source: Diabetes Metab J. 2014 Dec;38(6):416-425.

## Why is retinal photography alone not enough?



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Two recent widefield imaging studies have highlighted the **limitations** of assessing only the posterior pole



*Talbot SJ et al. Br J Ophthalmology, 2015*

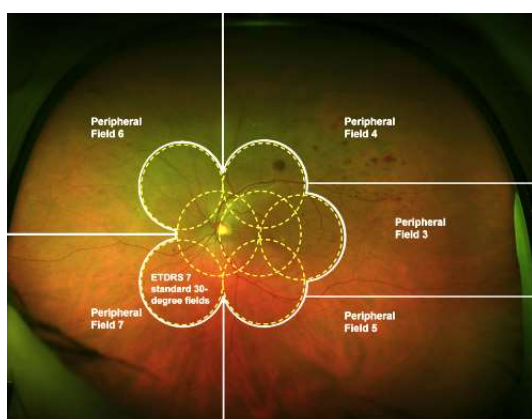
UK national DR screening service evaluated 1562 consecutive, treatment-naïve eyes (781 patients) with > mild NPDR on screening

**24% of NV was found outside the disc/macula centred 45° images**

## Why is retinal photography alone not enough?



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*2. Silva PS et al. Ophthalmology, 2013*

206 eyes of 103 diabetic patients selected to represent all levels of DR

**About 1/3**  
H/Mas, IRMA & NVE  
located outside 7-standard  
fields (central 90 degrees)



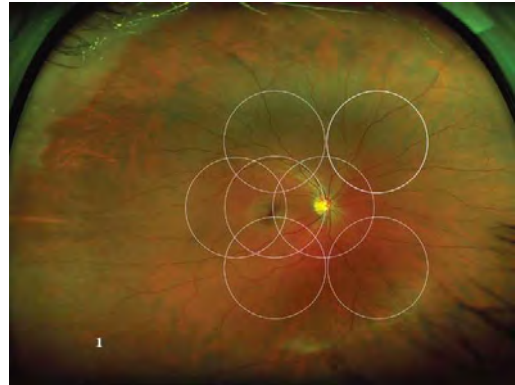
## Progression Risk



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The same researchers subsequently showed:

- Retinal lesions *outside the area of the ETDRS 7-standard fields*:  
**confer a 4.7-fold increased risk of progression to PDR over 4-years**
- The findings remained significant after controlling for gender, DM type, DM duration, HbA1c, baseline DR severity.



Silva PS et al. *Ophthalmology*, 2013

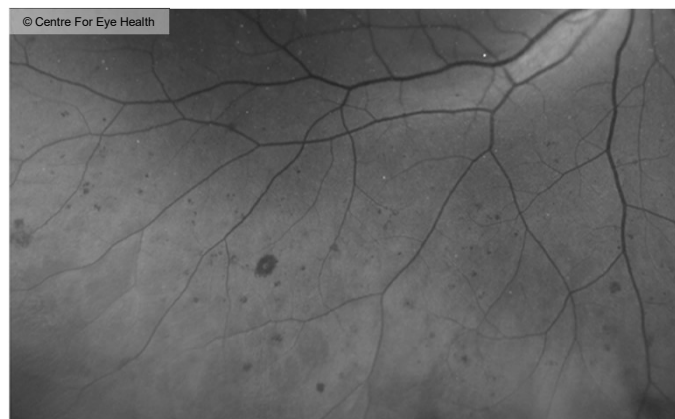
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## Progression of Risk



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- A greater number of peripheral fields with DR further increased the risk of progression
- Especially in cases with **less severe DR in posterior pole** at baseline



**Highlights need for detailed peripheral retinal evaluation with pupil dilation to completely assess the risk of DR progression**

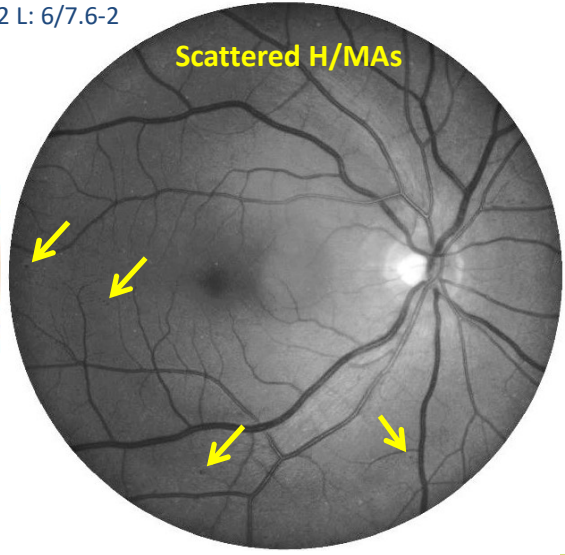
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49 year old Caucasian female  
Type I DM x 28 years with no previous DR

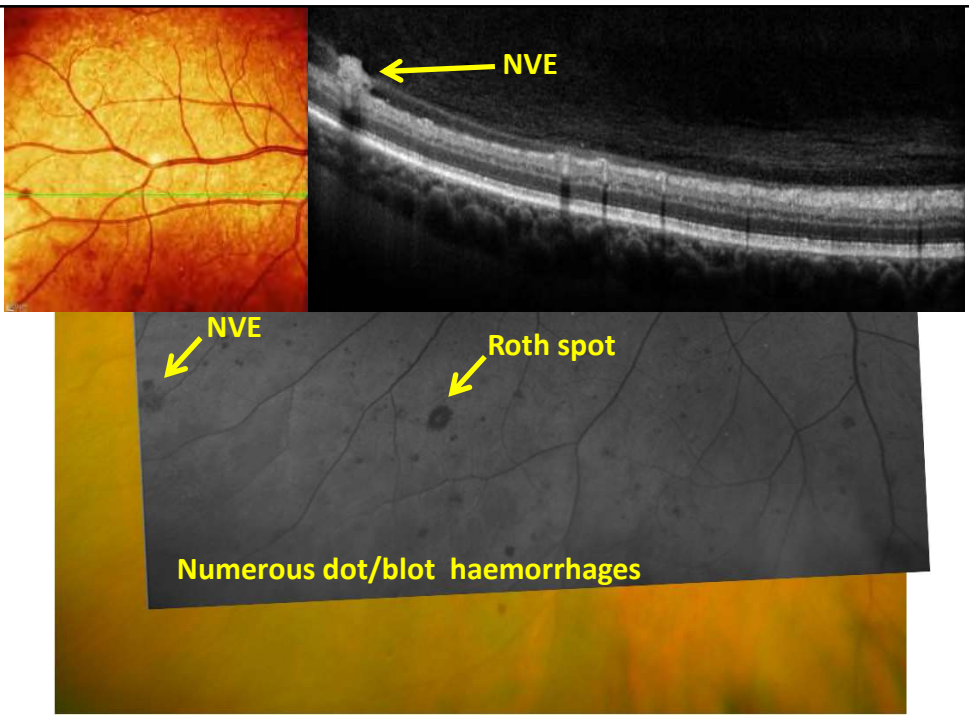


Aided VA R: 6/6-2 L: 6/7.6-2  
IOPs 15/14

OD



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OD



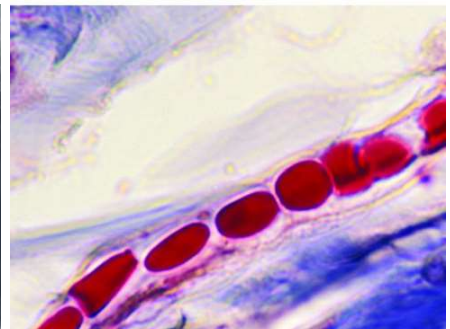
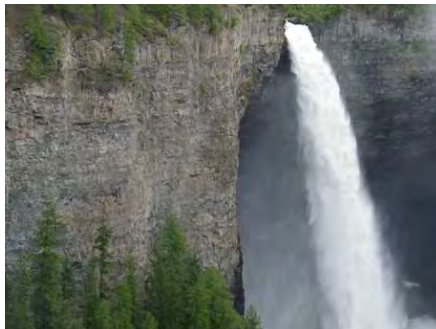
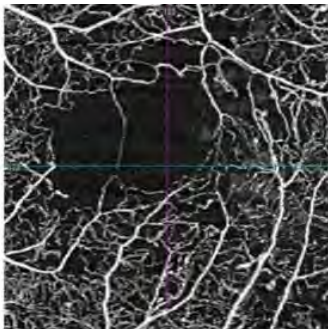
## Understanding retinal perfusion



## OCT Angiography

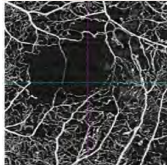


- A non-invasive, high-resolution imaging method of visualising microvasculature by detecting **motion contrast from flowing blood** (without the injection of dye)
- OCTA is a functional extension of OCT

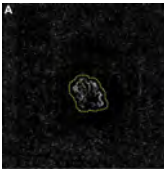


<https://biology-forums.com/index.php?action=gallery;sa=view;id=1211>

# Key indications - OCTA




**Absence or reduction of flow in normally *vascular* layers**  
e.g. BRAO, DR (ischaemia)



**Abnormal vascular patterns in normally *avascular* areas**  
e.g. CNV, PDR

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# OCTA: retina in normal eyes

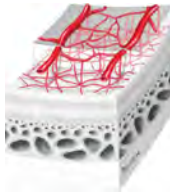
**SUPERFICIAL PLEXUS**

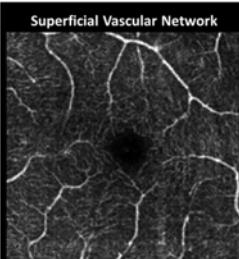
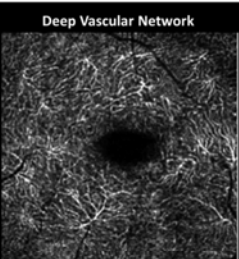

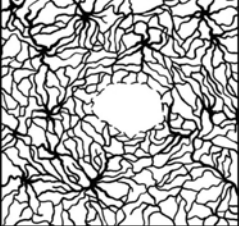
- Dark background
- Large & medium vessels in RNFL
- Arched branches around the FAZ
  - Linear, continuous
- Regular vessel course
- Homogenous
- No vascular loops



**DEEP PLEXUS**


- Homogenous
- More complex
- Radial and horizontal interconnections
- Dense vessel flow
- Small, discontinuous capillary complex at FAZ



Superficial Vascular Network	Deep Vascular Network
	
	

Savastano MC et al. In vivo characterization of retinal vascularization morphology using optical coherence tomography angiography  
Retina 0:1-8

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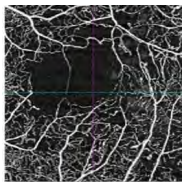
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# OCTA in DR



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## CAPILLARY PLEXUS ANOMALIES IN DIABETIC RETINOPATHY ON OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY

AUDE COUTURIER, MD, VALÉRIE MANÉ, MD, SOPHIE BONNIN, MD, ALI ERGINAY, MD, PASCALE MASSIN, MD, PhD, ALAIN GAUDRIC, MD, RAMIN TADAYONI, MD, PhD

Retrospective study 20 eyes of 14 patients with DR

	OCTA	FA
Microaneurysms	Detected only 62% of MA visualized on FA	
Capillary non-perfusion	Better detected	Some areas were not detected
IRMA	Well detected	Well detected

### Main limitations

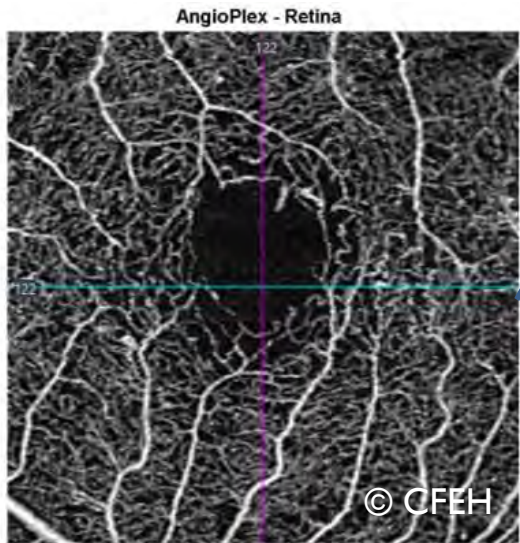
- Unlike FA, **leakage** cannot be visualised with OCTA
- Small field of view
- Affected by media opacities and eye movements

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# OCTA in diabetic macular ischaemia



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59 year old with Type 2 DM diagnosed 15 yrs  
Last HbA1c 8-9%  
Enlarged irregular FAZ, poor para-foveal perfusion, IRMA and MAs

- DMI can be present in eyes with no visible DR (*Takase, Retina 2015*)
- Vision is only affected in moderate to severe macular ischaemia

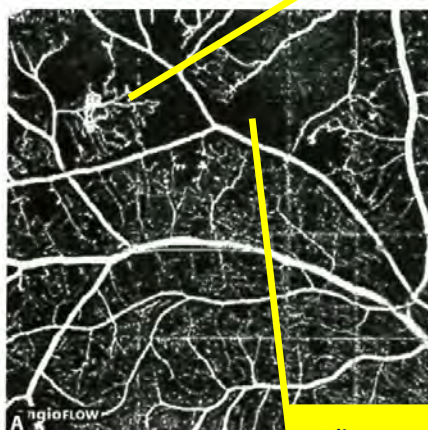
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## OCTA in NPDR



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IRMA



Severe NPDR

Adjacent capillary loss  
(retinal non perfusion)

OCTA may show

- Microaneurysms
- Looser capillary network or areas of non-perfusion areas
- Vascular loops/capillary tortuosity
- IRMA appear as dilated terminal vessels surrounded by capillary loss

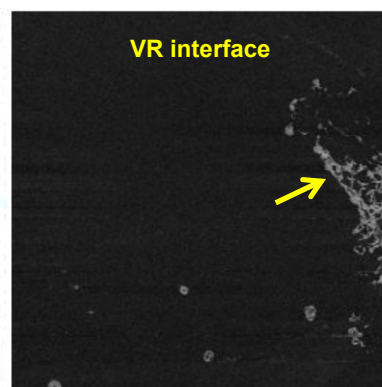
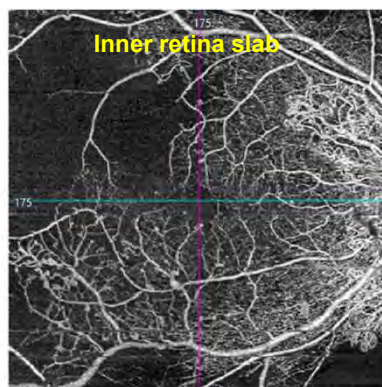
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## OCTA in proliferative DR



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- Detection of retinal NV is limited by small field of view
- Allows precise delineation of the extent and morphology of NV
- Can be performed when pupil dilation may be contraindicated e.g. during pregnancy



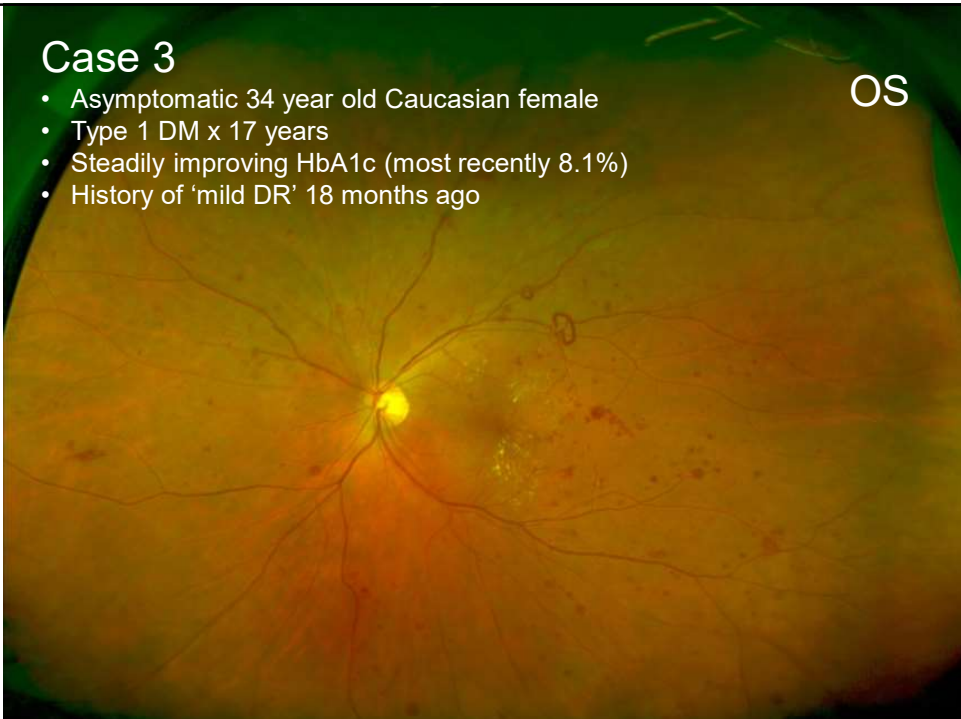
VRI

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### Case 3

- Asymptomatic 34 year old Caucasian female
- Type 1 DM x 17 years
- Steadily improving HbA1c (most recently 8.1%)
- History of 'mild DR' 18 months ago

OS

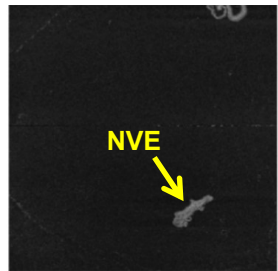




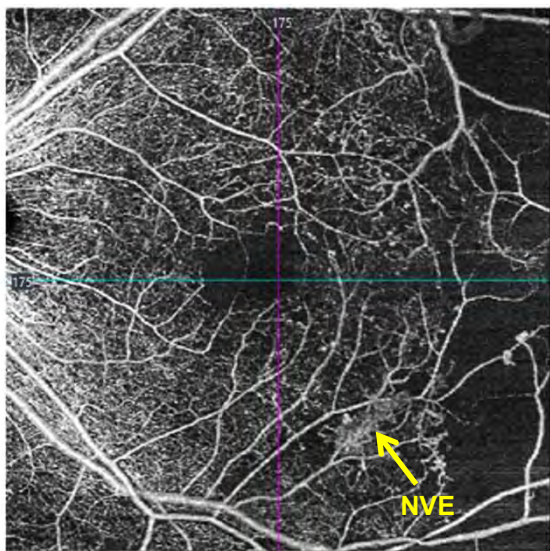
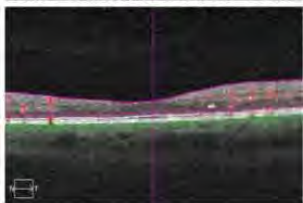
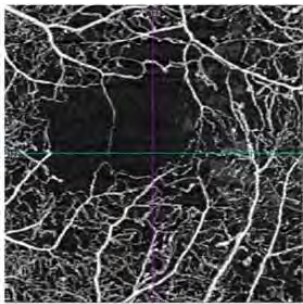
OCTA slabs: VRI, 3x3mm Retina, 8x8mm Retina



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VRI



NVE

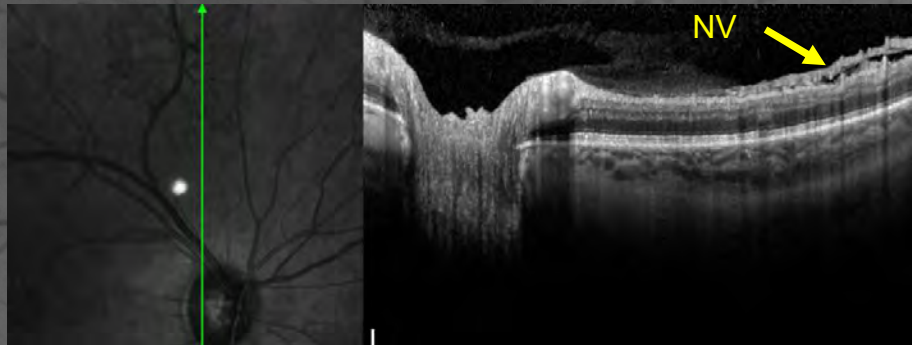
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OD



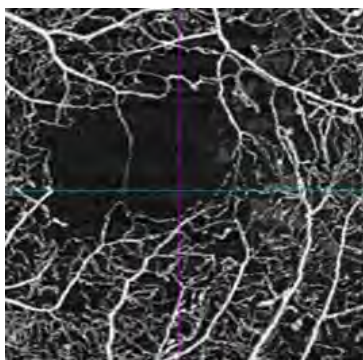
## NVE and moderate macular oedema OD



## FAZ as a predictor of progression



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- FAZ has been found enlarge with more severe levels of DR
- Looking to the future, we may use FAZ measurements as a predictor of progression

## Unexplained vision loss and OCT



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- In the first instance, OCT and OCT angiography may be useful to rule out DMO or DMI
- These techniques are also useful to help stratify necessity and urgency of referral to ophthalmologist



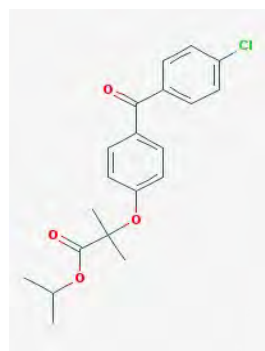
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## What is fenofibrate?



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- An oral hypolipidaemic agent that reduces both cholesterol and triglycerides in the blood (adjunct)
- Peroxisome proliferator-activated receptor  $\alpha$  agonist
- Fenofibrate upregulates the PPAR $\alpha$  receptor proteins responsible for fatty acid transport and  $\beta$ -oxidation, thus *inhibiting formation* of triglycerides and VLDLs



In 2014, Australian TGA expanded the indications of fenofibrate to include “the reduction in the progression of DR in patients with T2DM and existing DR”

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## FENOFIBRATE

### Role in diabetic retinopathy



The ACCORD and FIELD studies showed possible benefits of fenofibrate in **slowing DR progression** for high risk patients with **type 2 diabetes and mild or moderate NPDR**

Results suggests that fenofibrate may also reduce:

- The need for treatment of macular oedema and PDR
- Progression of albuminuria
- The risk of amputation



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## ACCORD and FIELD study limitations



- Primary outcome was the effect of fenofibrate on cardiovascular disease events in type 2 DM
- Diabetic retinopathy was a tertiary end point
- There was no improvement in VA outcomes

Results only apply to those:

- *At high risk of, or with, cardiovascular disease*
- *With type 2 DM*
- *Older than 45 years of age*



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## Fenofibrate side-effects



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- Generally well tolerated
- Raised serum creatinine levels reverted to normal after discontinuation – *kidney function should be monitored*
- Pancreatitis - 0.8% vs. 0.5% on placebo
- Pulmonary embolism - 1% vs. 0.7% on placebo

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## Optometry Australia Recommendation



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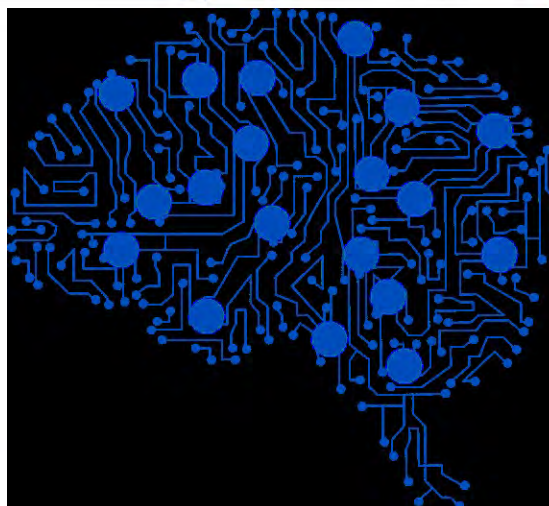
Optometrists should communicate to the GP the possible benefits of fenofibrate in slowing DR progression for high risk patients **with mild to moderate NPDR**

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## The future – artificial intelligence

- Deep learning artificial intelligence tool (IDx-DR) which detects retinopathy in retinal photographs was recently **approved by US FDA**
- Currently limited by resolution & field of view of photos
- These algorithms will inevitably be built into future retinal cameras and OCTs



## Automatic DR Detection – the future



### **Automatic detection of diabetic retinopathy features in Ultra-Wide Field retinal images**

Anastasia Levenkova<sup>\*1a</sup>, Arcot Sowmya<sup>1a</sup>, Michael Kalloniatis<sup>1b,2</sup>, Angelica Ly<sup>1b,2</sup>, Arthur Ho<sup>1b,3</sup>

<sup>1a</sup> School of Computer Science & Engineering, <sup>1b</sup> School of Optometry & Vision Science, University of New South Wales, Sydney, Australia; <sup>2</sup> Centre for Eye Health, Sydney, Australia;

<sup>3</sup> Brien Holden Vision Institute, Sydney, Australia.

Medical Imaging 2017: Computer-Aided Diagnosis, edited by Samuel G. Armato III, Nicholas A. Petrick, Proc. of SPIE Vol. 10134, 101341M · © 2017 SPIE · CCC code: 1605-7422/17/\$18 · doi: 10.1117/12.2253980

## Final take home points – connecting the dots



- Imaging is rapidly becoming standard of care in diagnosis and management of DR
  - If in doubt, OCT!
- New risk factors, detectable with advanced imaging, will change future management
- Peripheral retinopathy increases progression risk (dilate, dilate!!)
- Keep in mind the potential role of fenofibrate in mild to moderate NPDR



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**Thank you!**

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