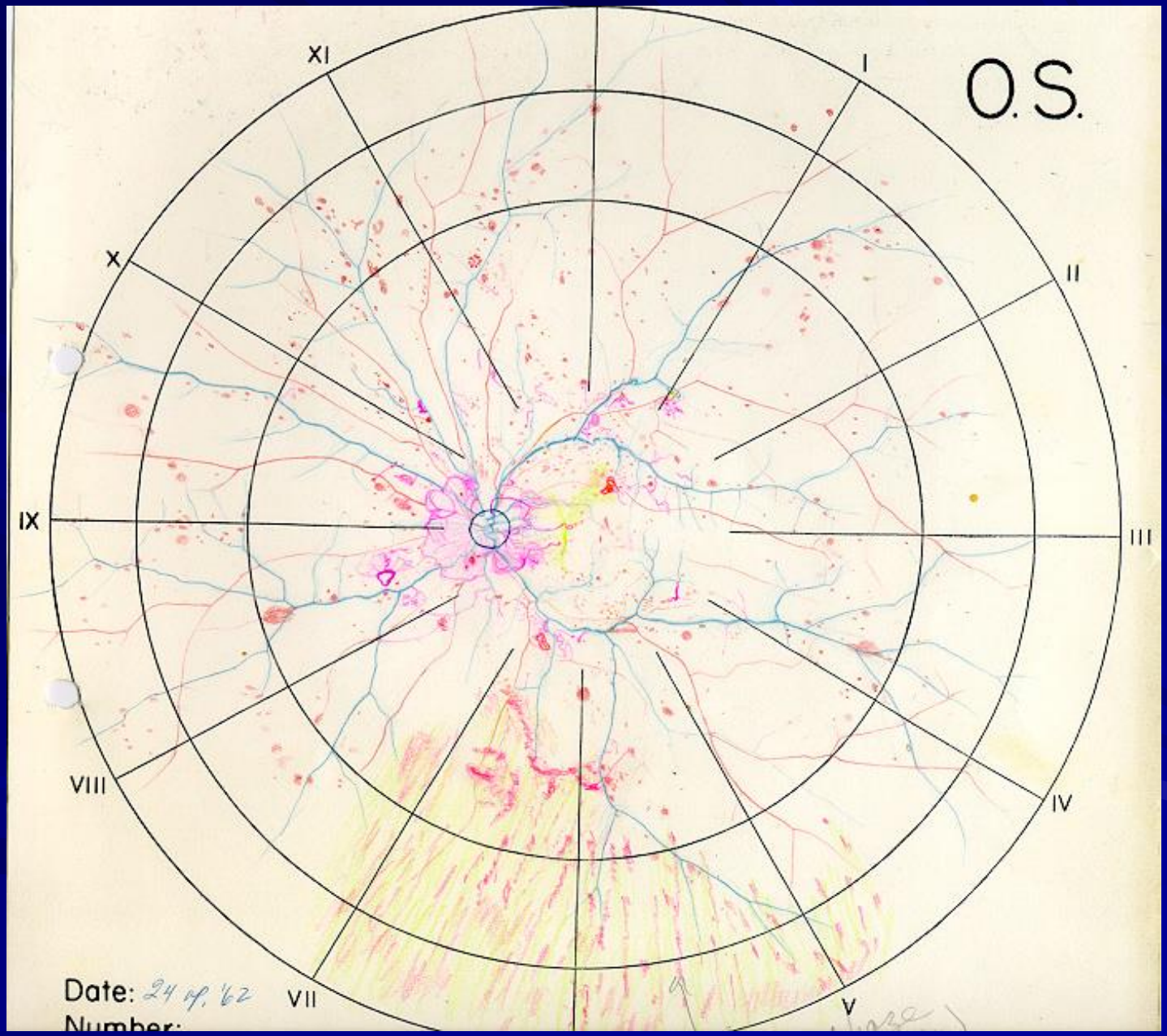
What do new imaging modalities, especially SLO, add to diabetic retinopathy screening?

Dr Tunde Peto
Head of Reading Centre
Moorfields Eye Hospital

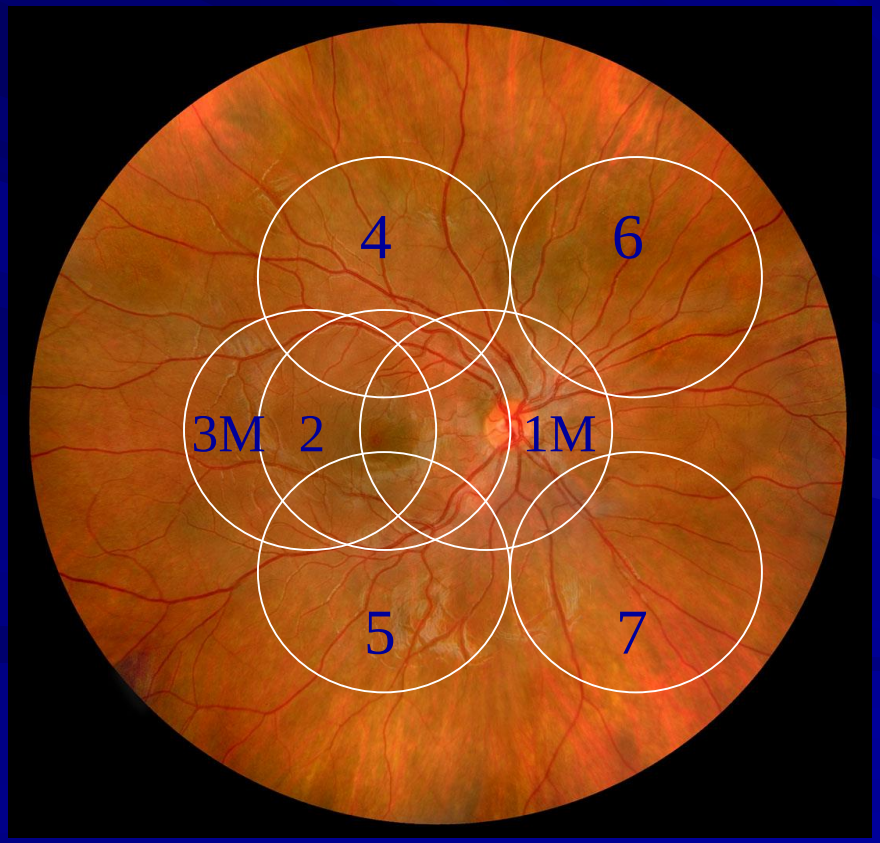
Retinal drawing circa 1962



Courtesy of Wisconsin Reading Centre

Historical Perspective

The Modified Airlie House fields are further modified to their current configuration in the early 1990s to better capture DME



What is screening?

WHO definition:

Screening is a public health service in which members of a defined population, who do not necessarily perceive they are at risk of, or are already affected by a disease or its complications, are asked a question or offered a test, to identify those individuals who are more likely to be helped than harmed by further tests or treatment to reduce the risk of a disease or its complications.

Primary aim is to diagnose, then refer and consequently treat sight threatening DR retinopathy

Diabetes is on the increase mainly due to public health achievements

DIABETES AND DIABETIC RETINOPATHY

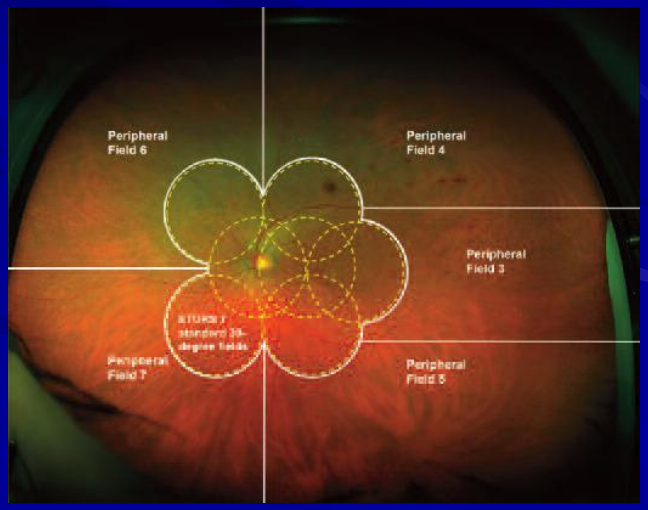
•Diabetes is expected to grow by 50% worldwide by 2025; but incidence of blindness in the UK started to fall after 10 years of organised screening

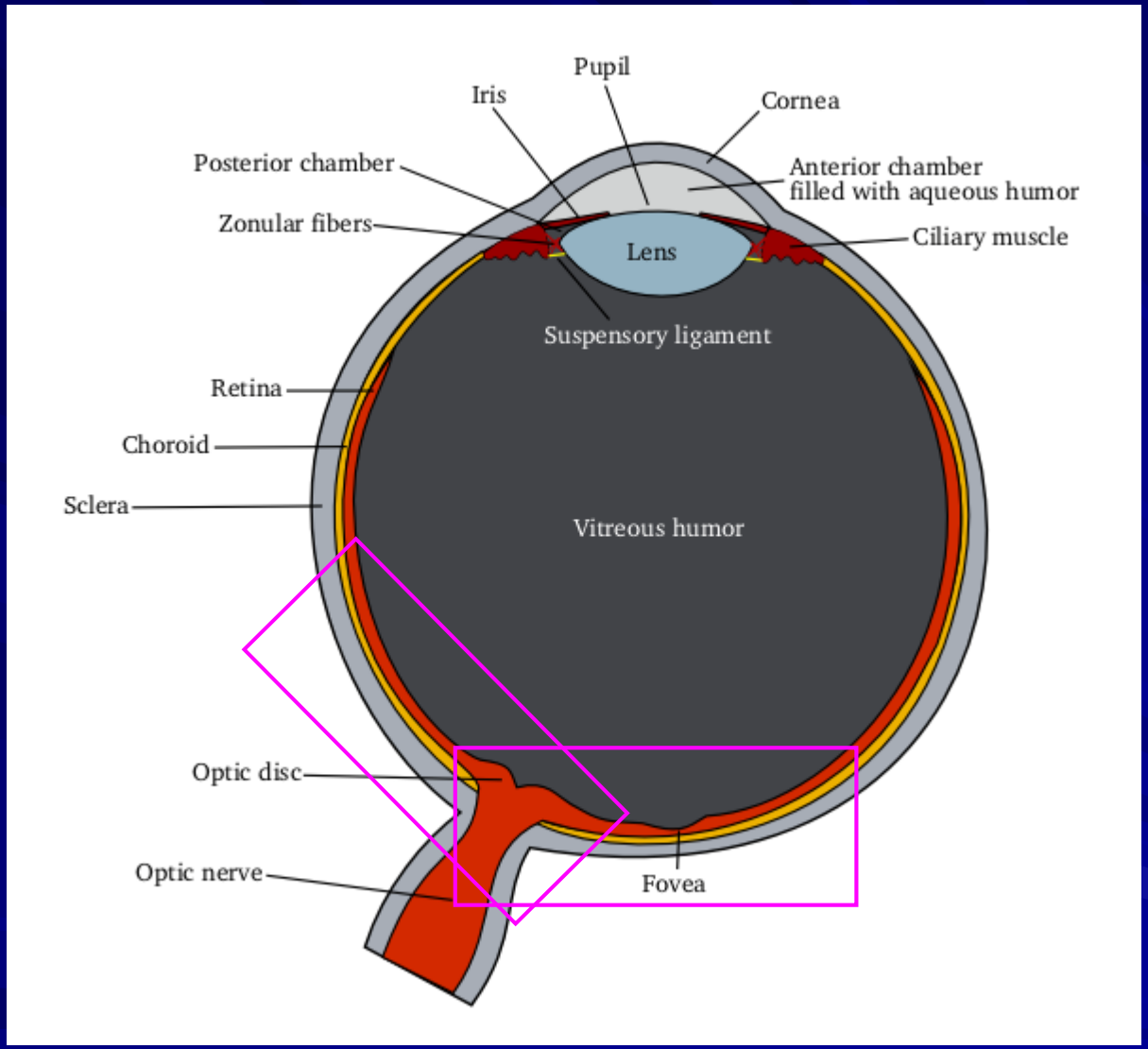
•The integration of ultra widefield imaging into clinical practice has enhanced the ability to visualize the retinal periphery.

•A recent study reported by Aiello et al. found that the presence of peripheral lesions identified outside of ETDRS are associated with a 4-fold greater risk of disease progression at a 4 year follow-up evaluation.

•Incidence of DME is 30% in patients who have had diabetes for more than 20 years. Current treatment regimes place large burden on society.

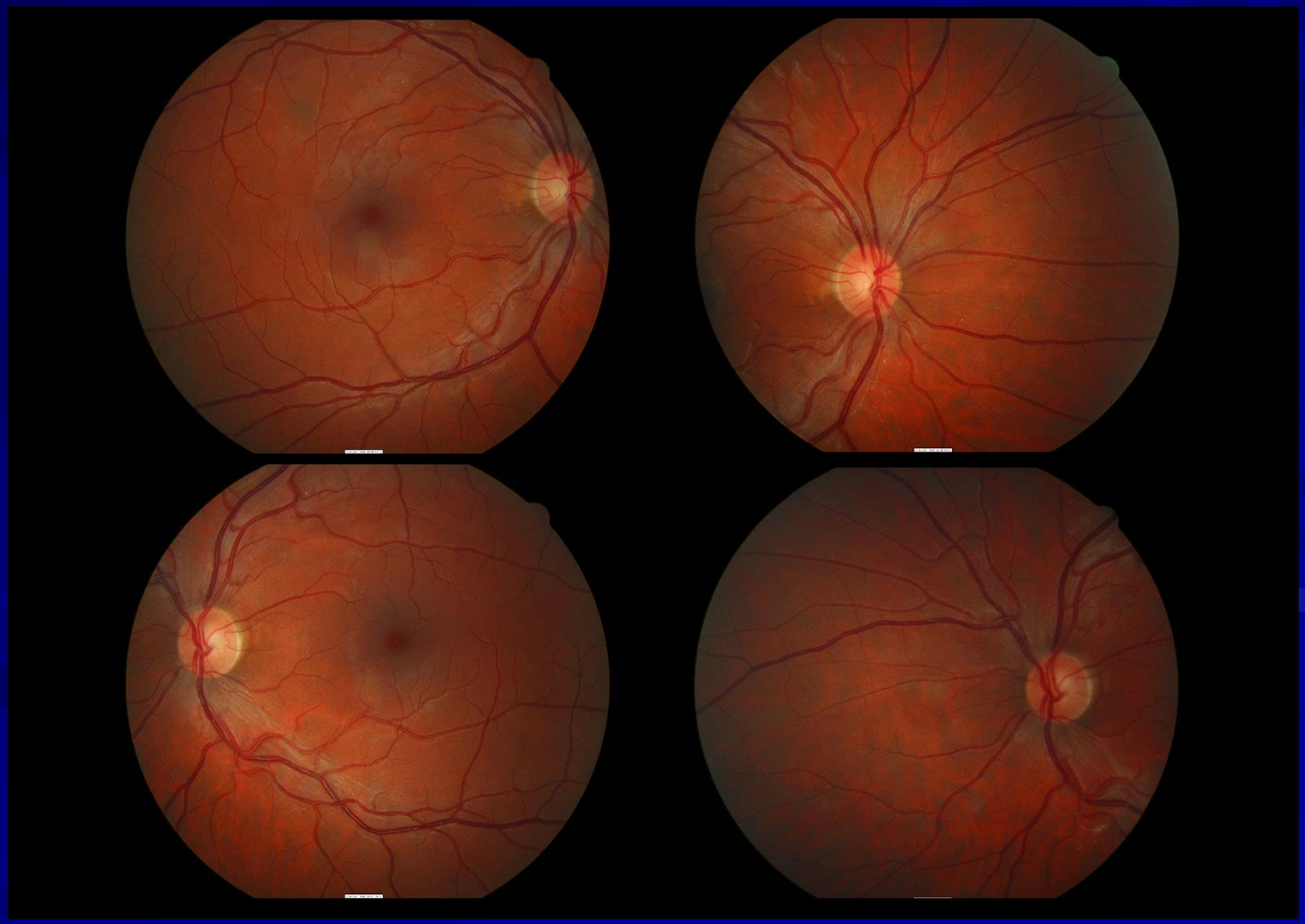
Conventional FA only allows for 45 to 60 degrees of the retina to be visualized per image.



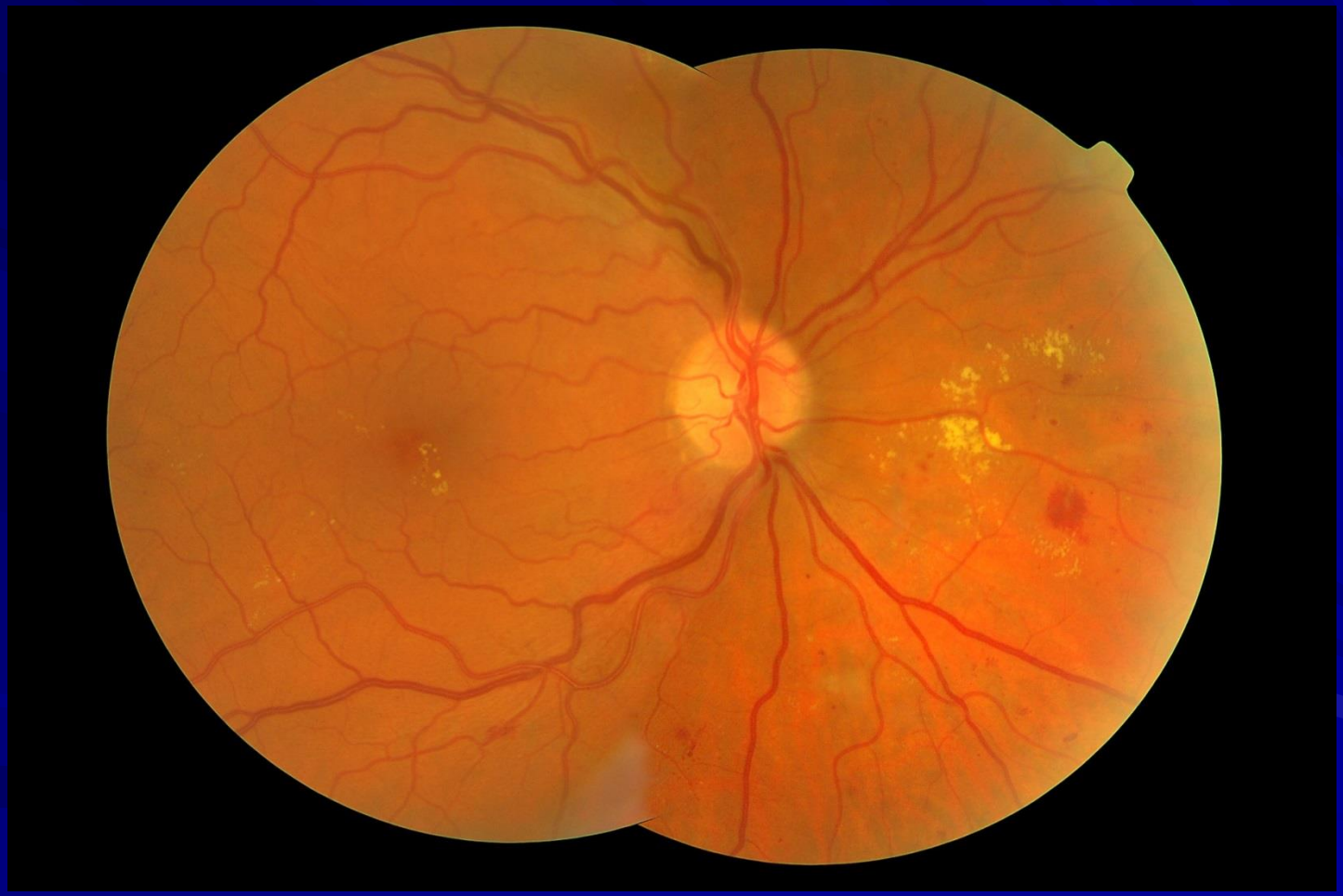


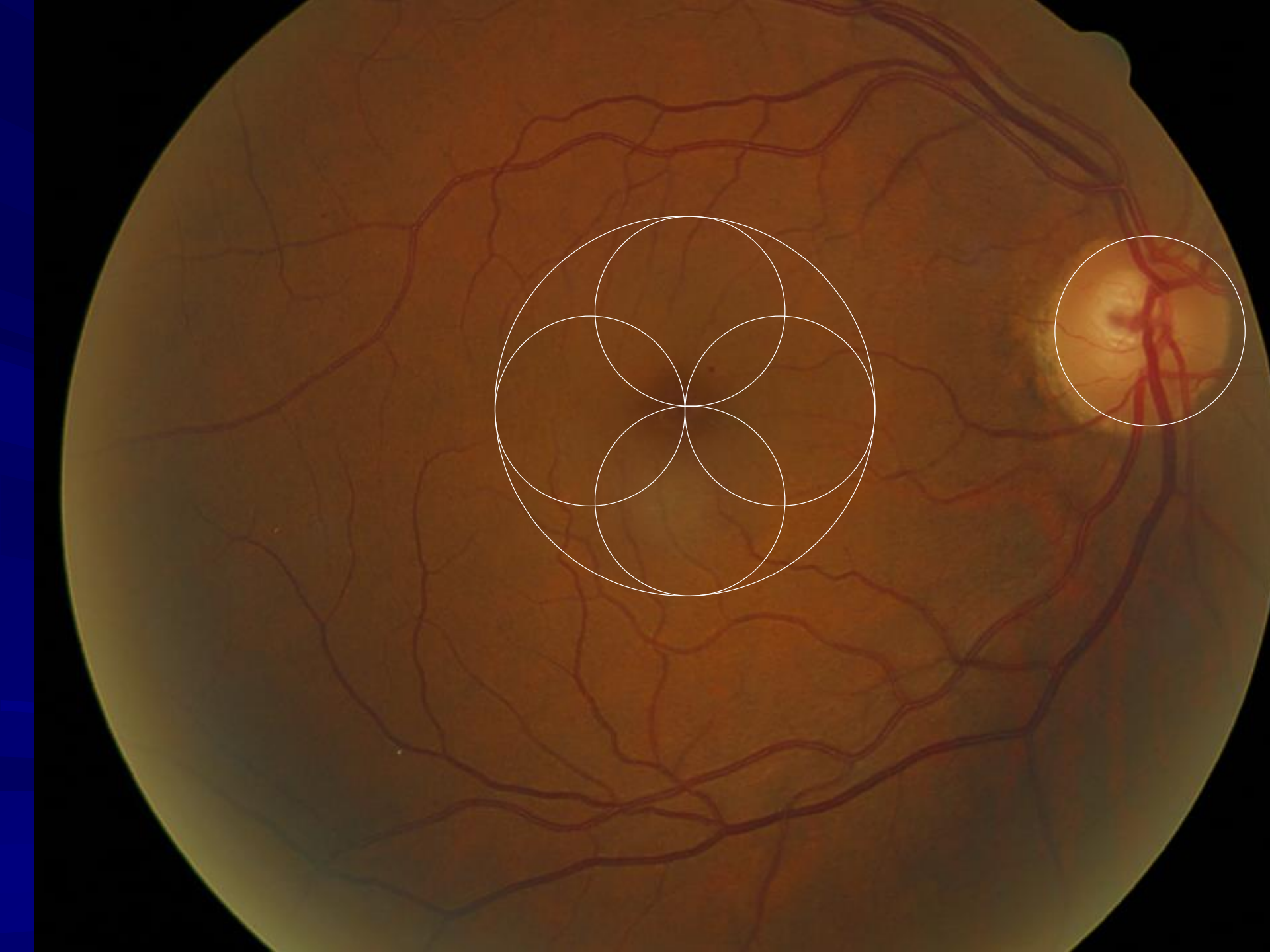
The areas of the two screening images per eye

Digital photographs of each eye, 45 degrees one centred on the macula and one centred on the optic disc

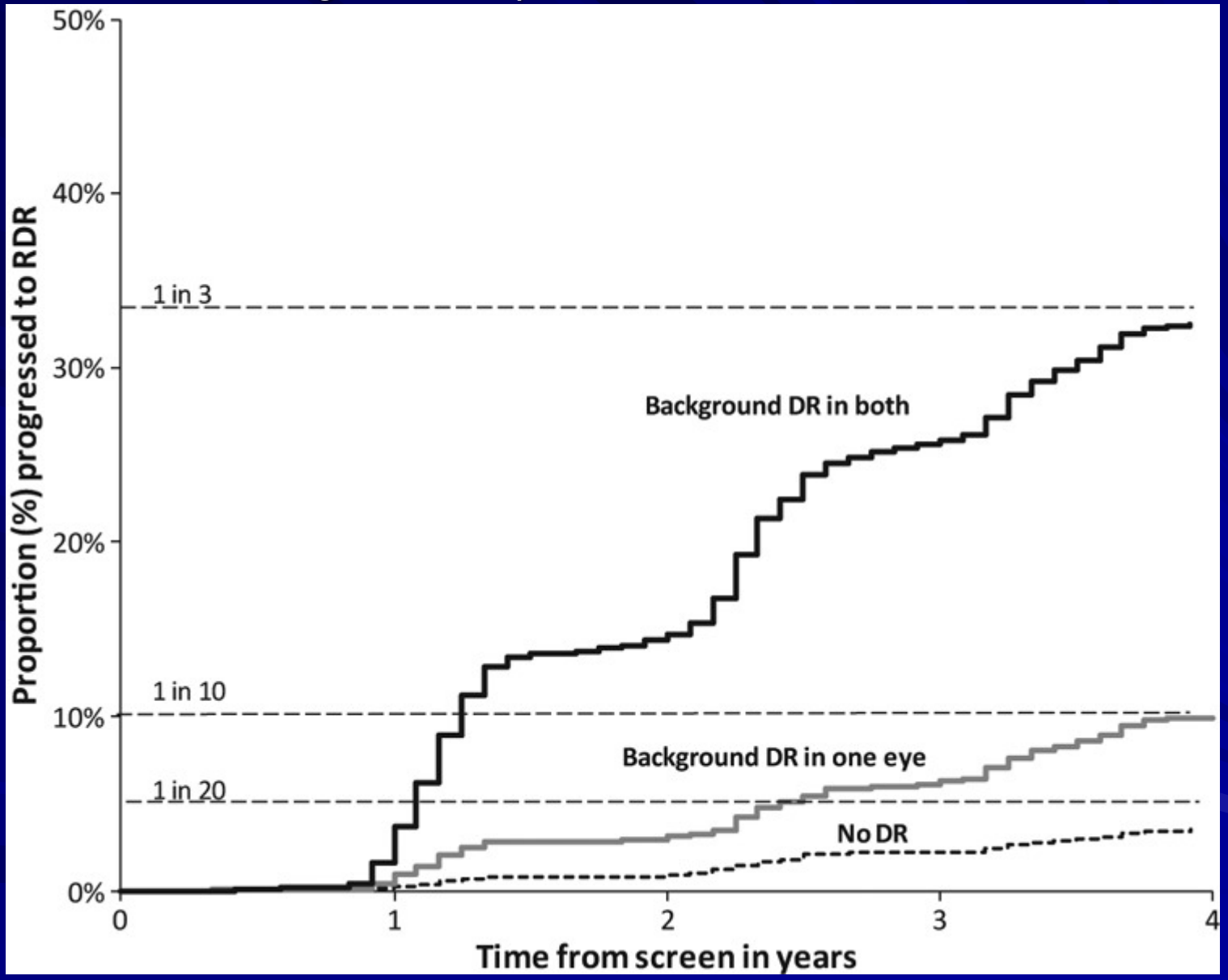


This is what the screener sees:



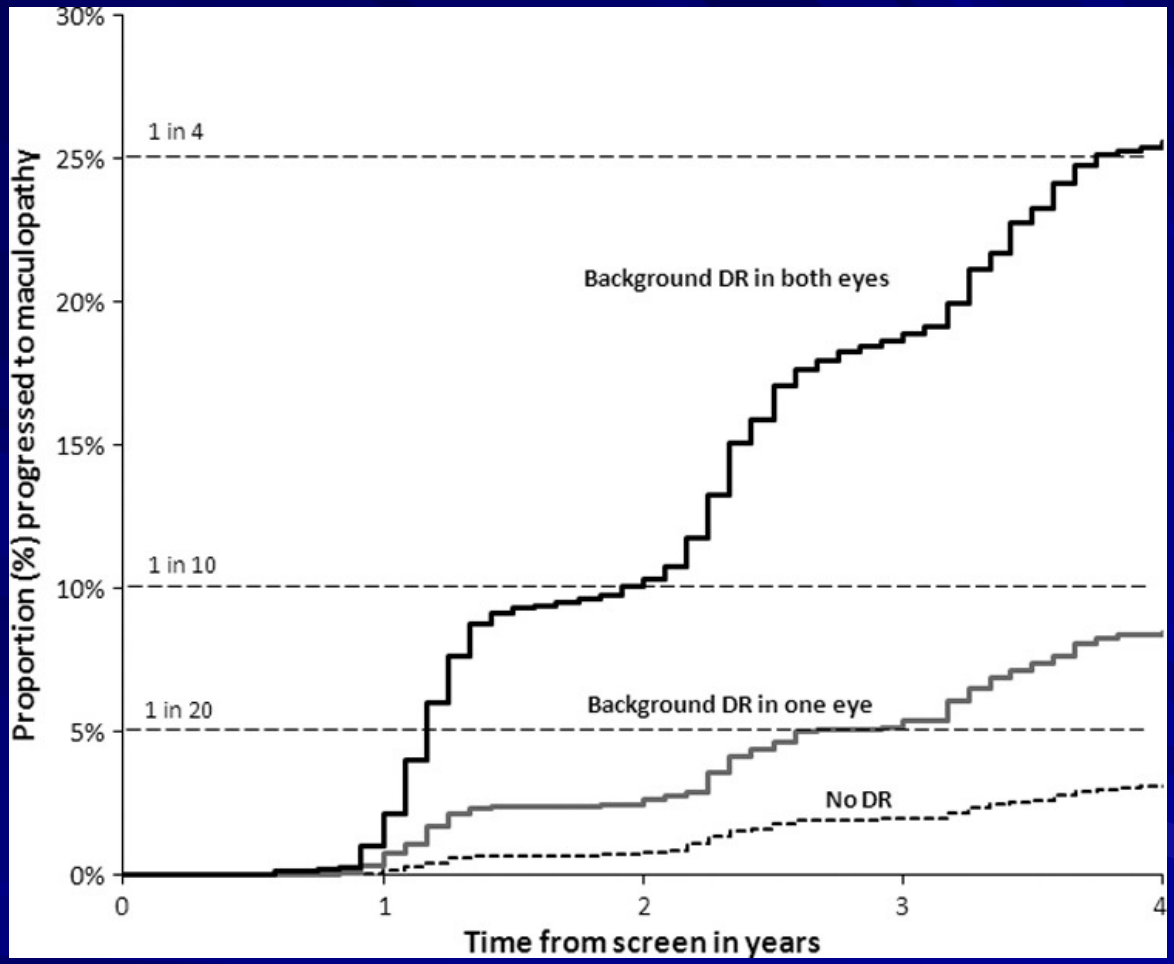


Progression to proliferative disease

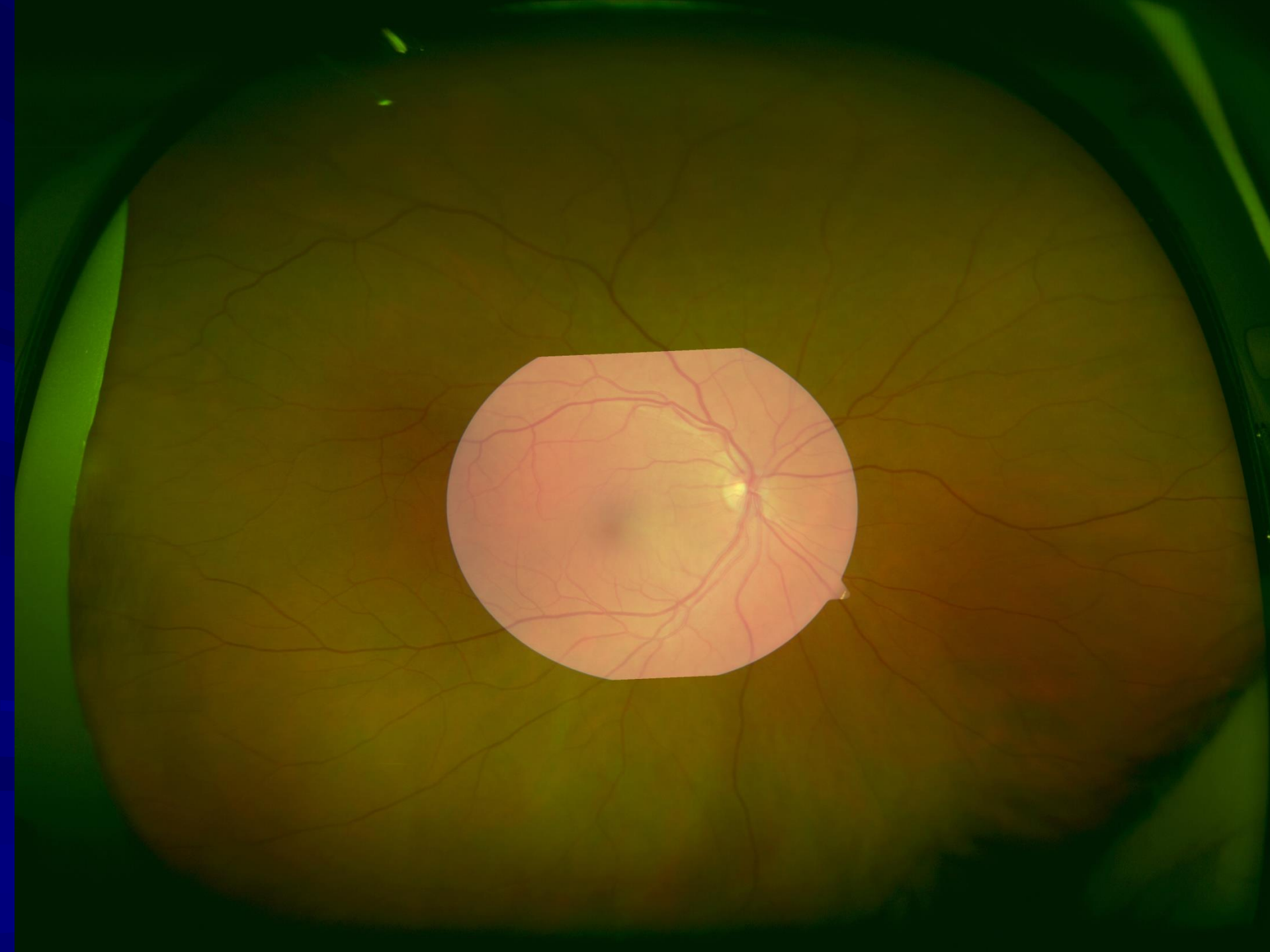


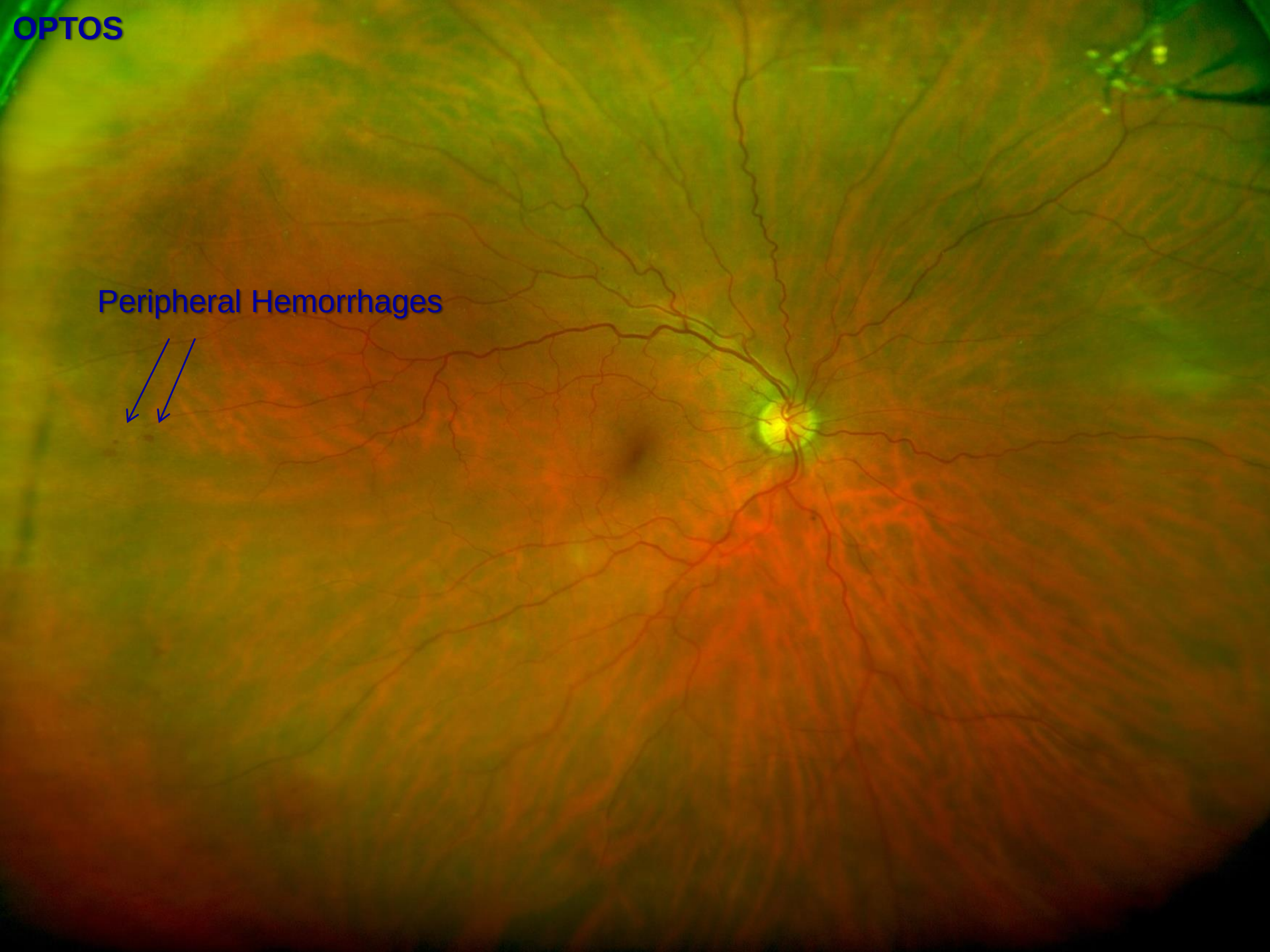
Scanlon PH, Stratton IM, Histed M, Chave SJ, Aldington SJ. Acta Ophthalmol. 2013 Aug;91(5):e335-9.

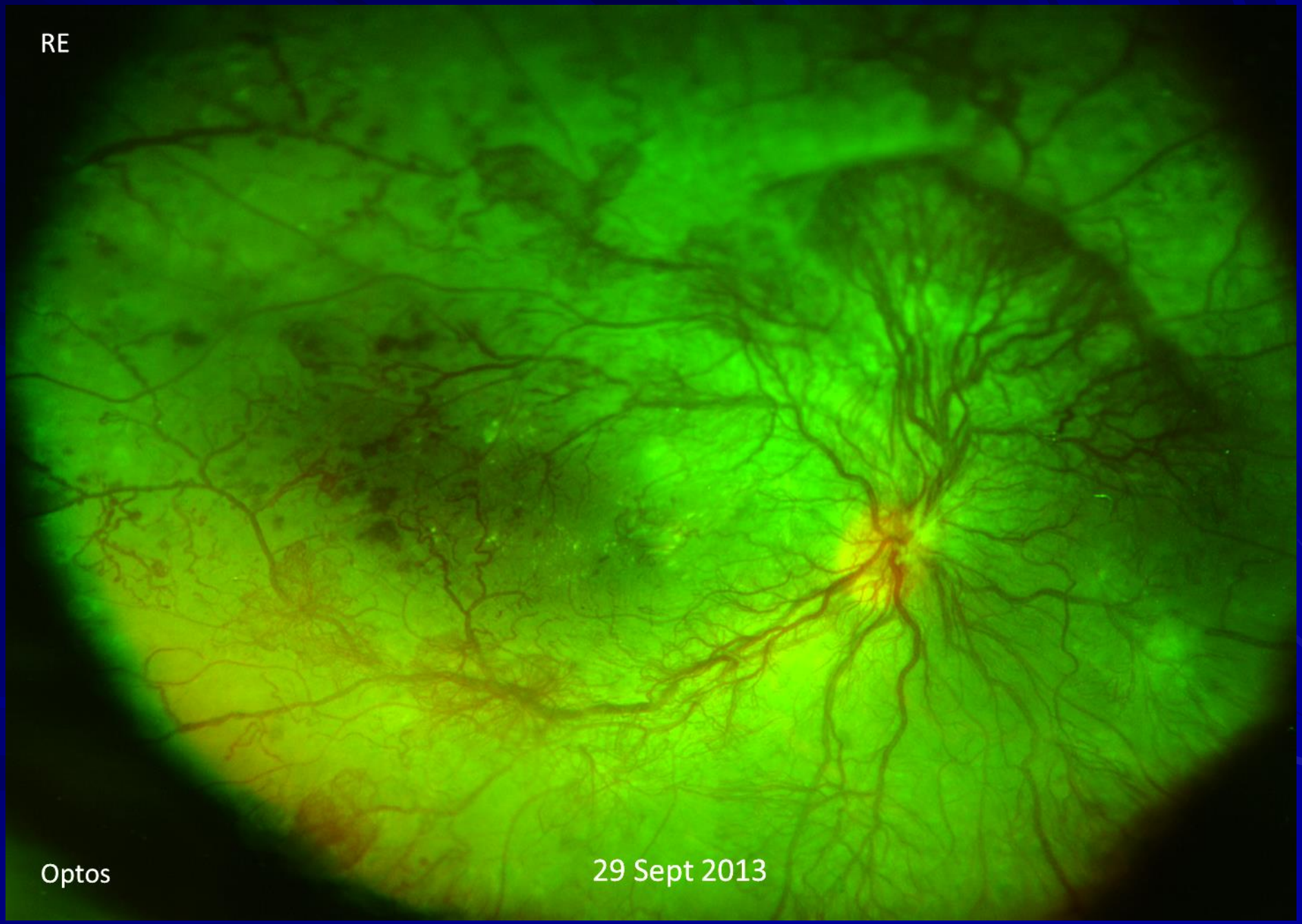
Progression to maculopathy



Scanlon PH, Stratton IM, Histed M, Chave SJ, Aldington SJ. Acta Ophthalmol. 2013 Aug;91(5):e335-9.




OPTOS
Peripheral Hemorrhages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Optos
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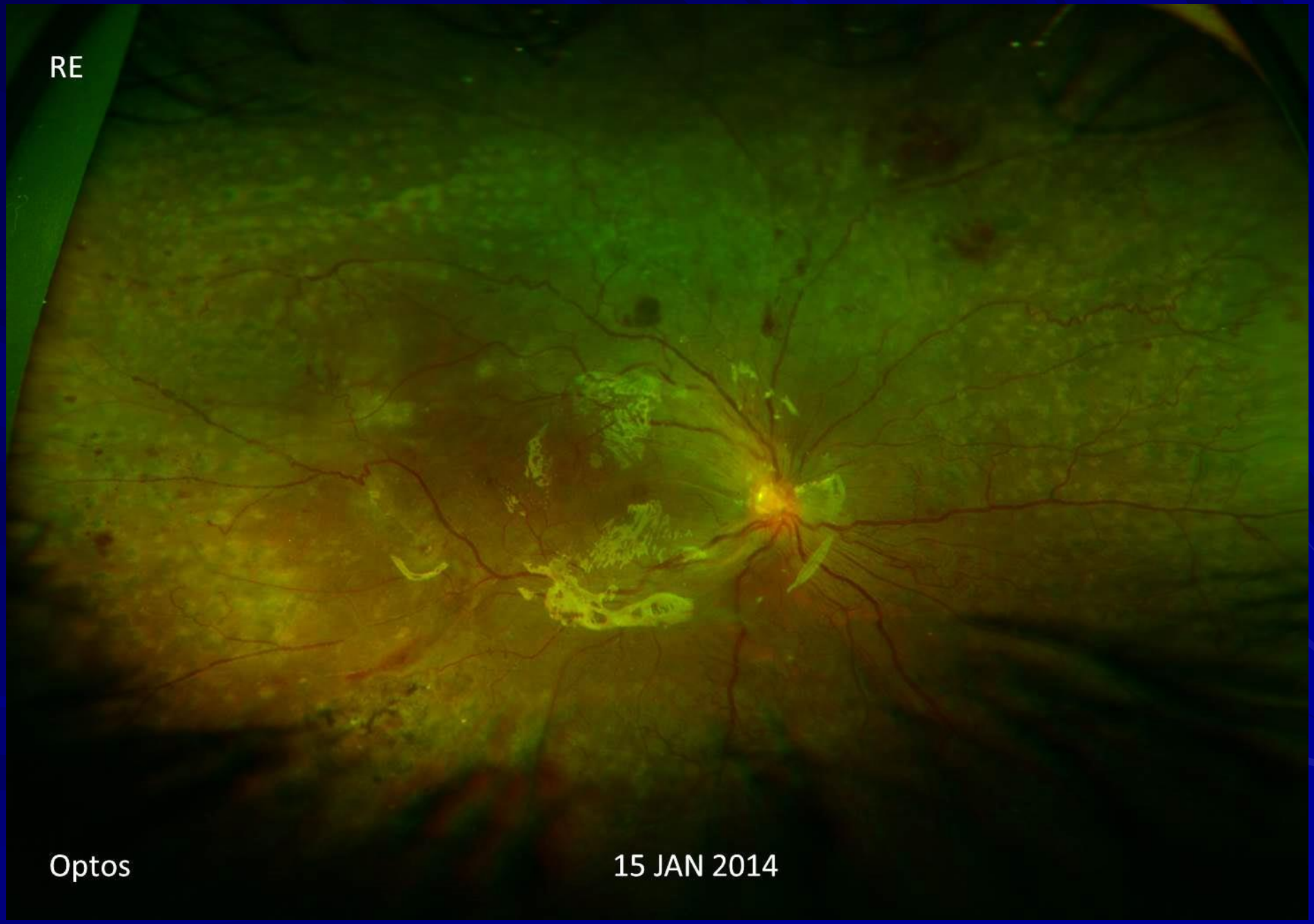
RE
Optos
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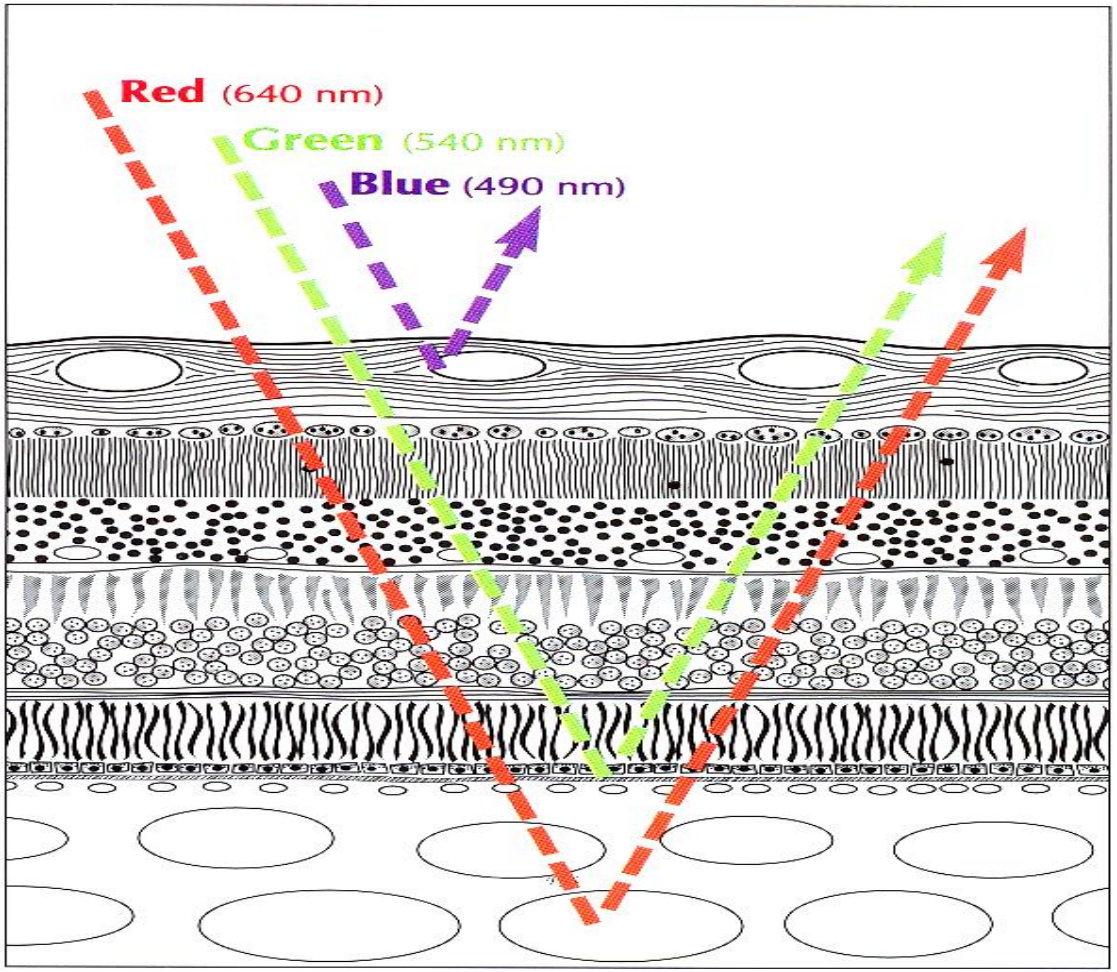
Light in all its facets

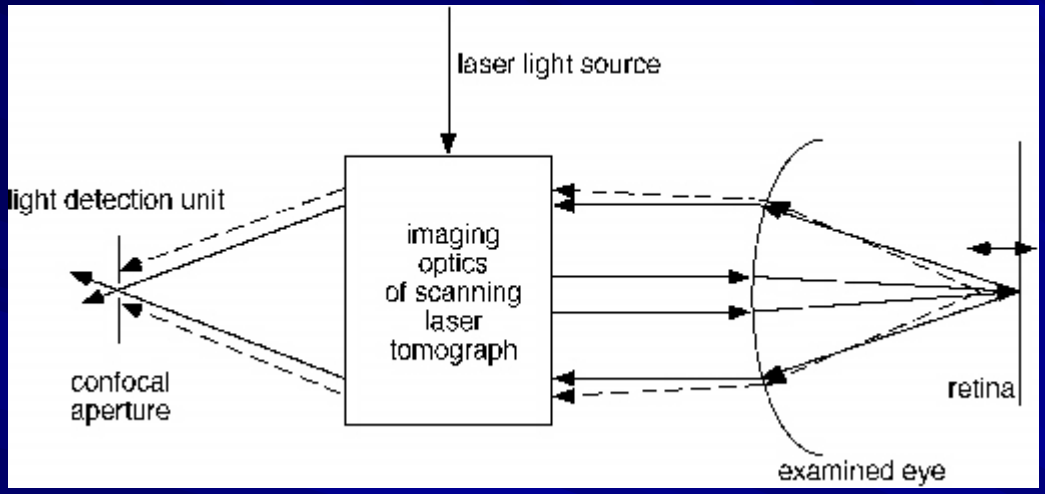
Light in technical terms

white = blue + green + red


Red (640 nm)
Green (540 nm)
Blue (490 nm)

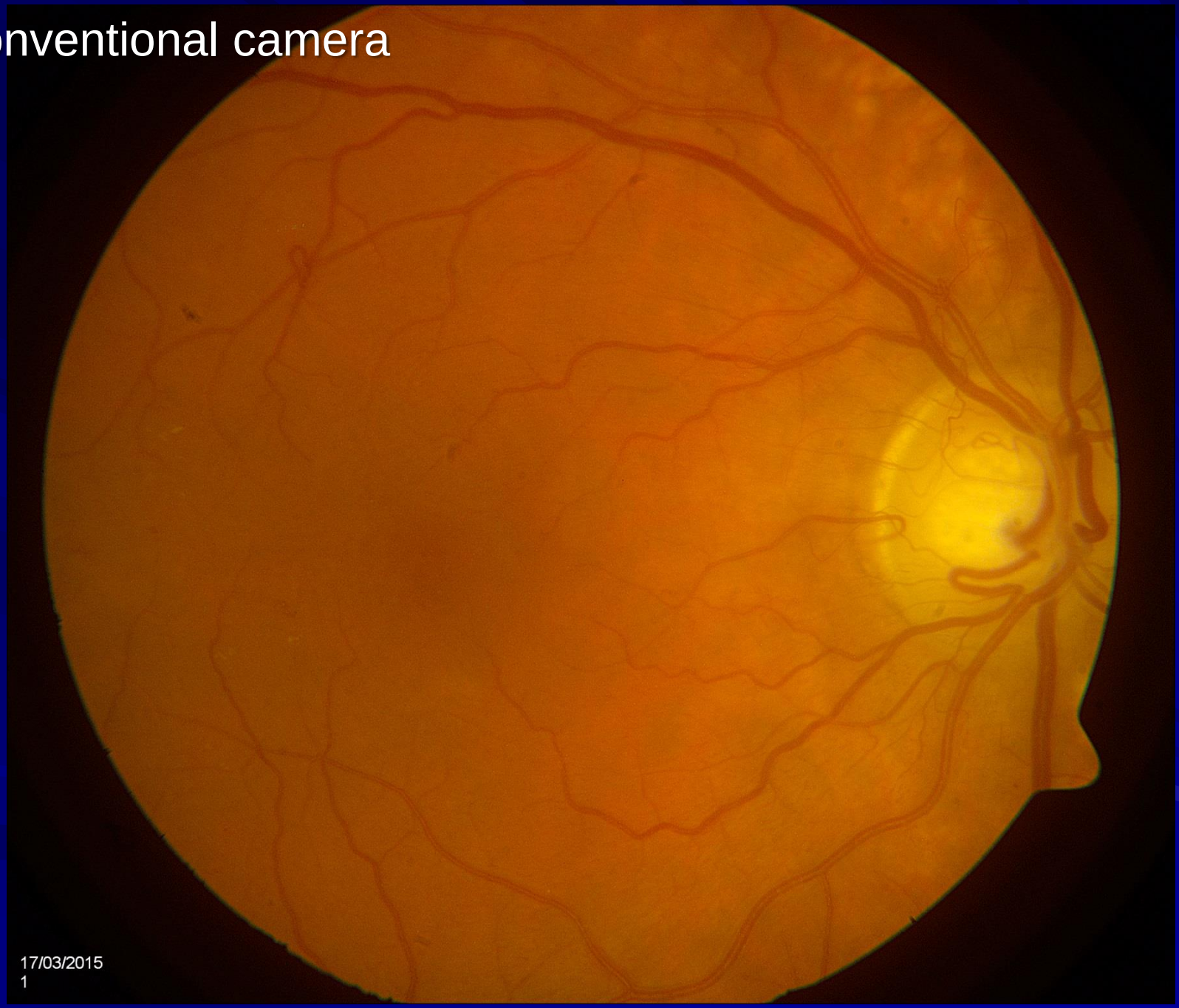
Laser light is used instead of white light

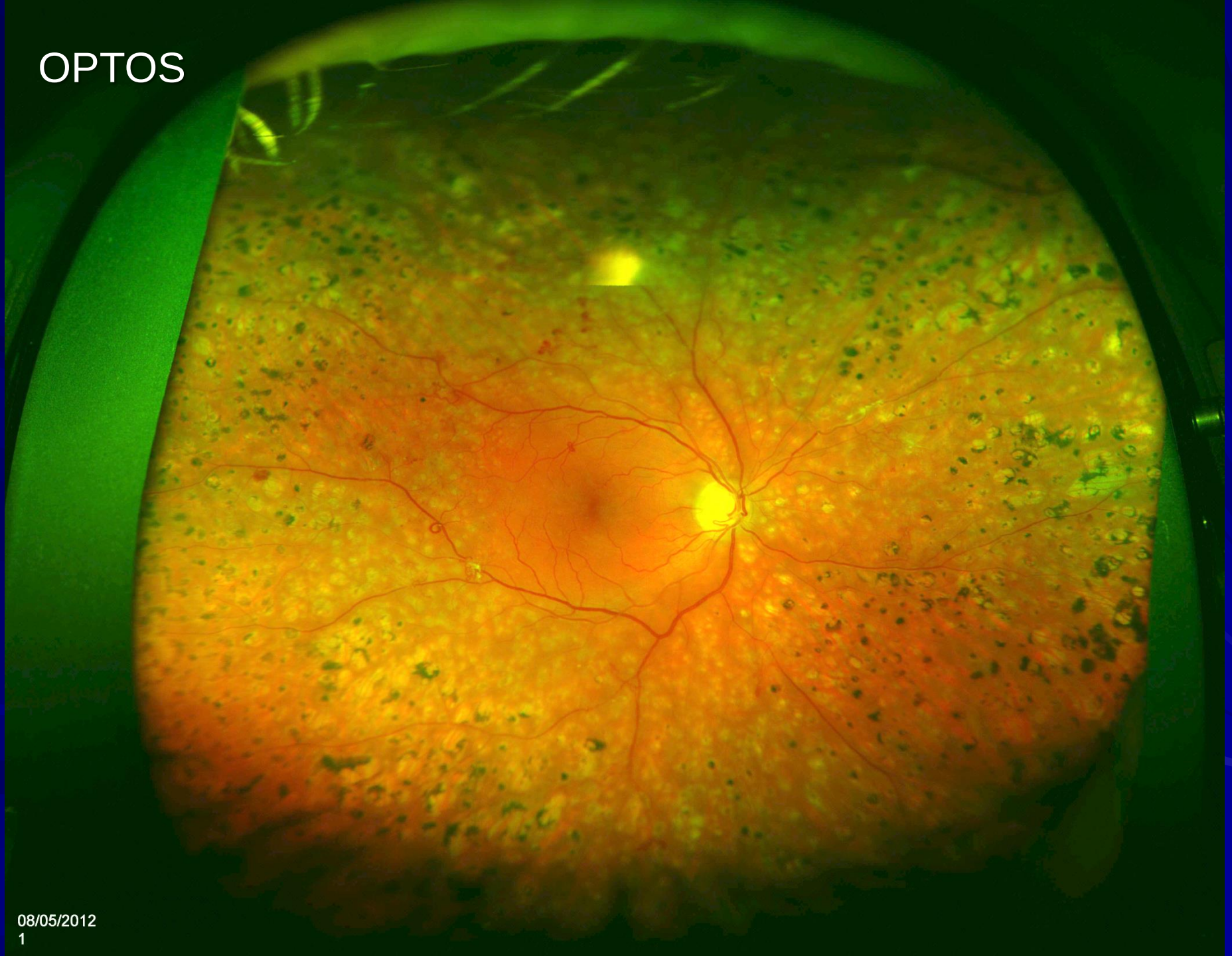
Scans the eye point by point and then captures the reflected light through a small aperture

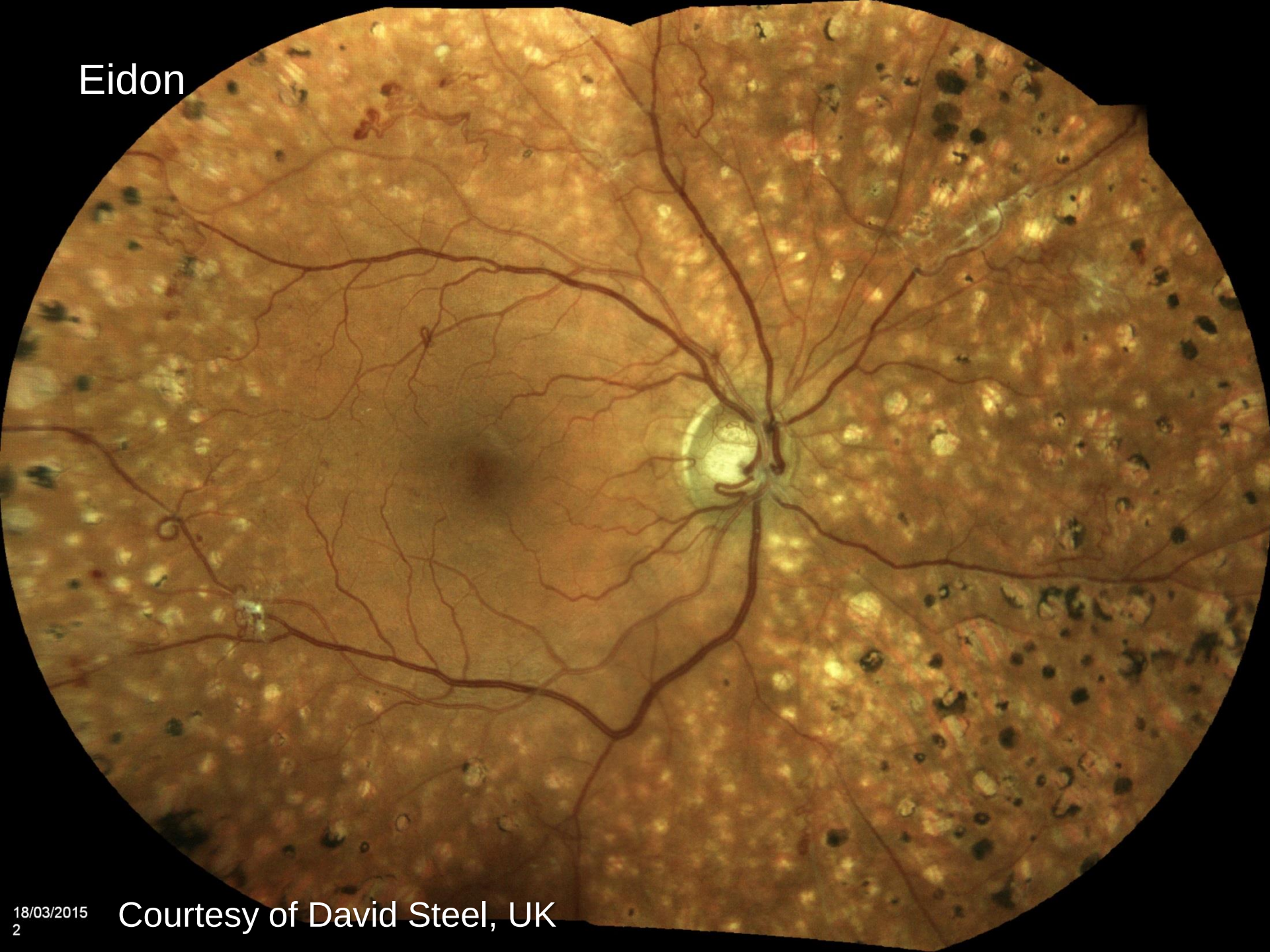


Advantages include improved image quality, small depth of focus, suppression of scattered light, patient comfort through less bright light, 3D imaging capability, video capability, and effective imaging of patients who do not dilate well. Since patients with diabetes typically do not dilate well and account for a large number of patients with vision problems, cSLO imaging is a valuable tool for most eye care providers. (Heidelberg)

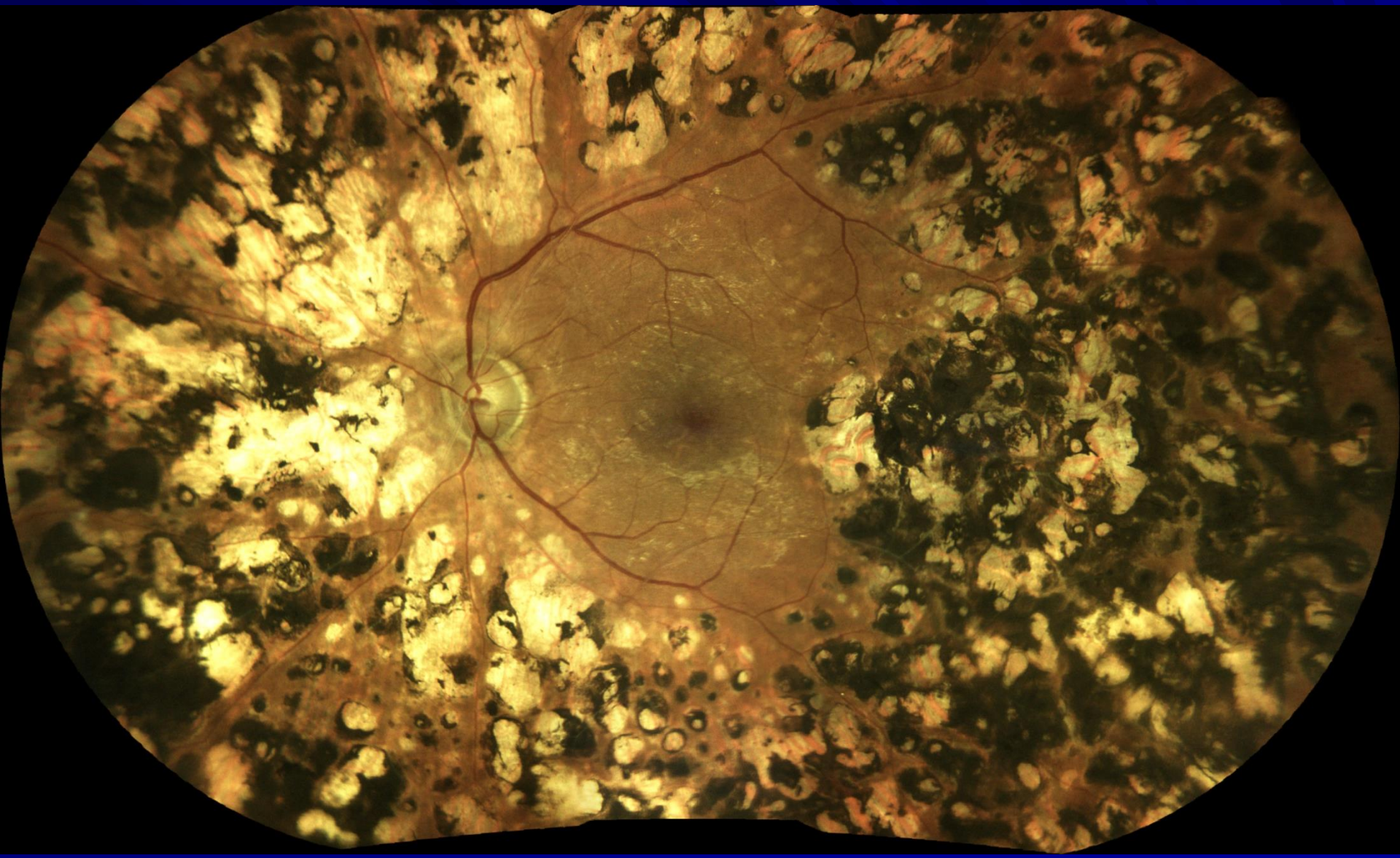
Conventional camera



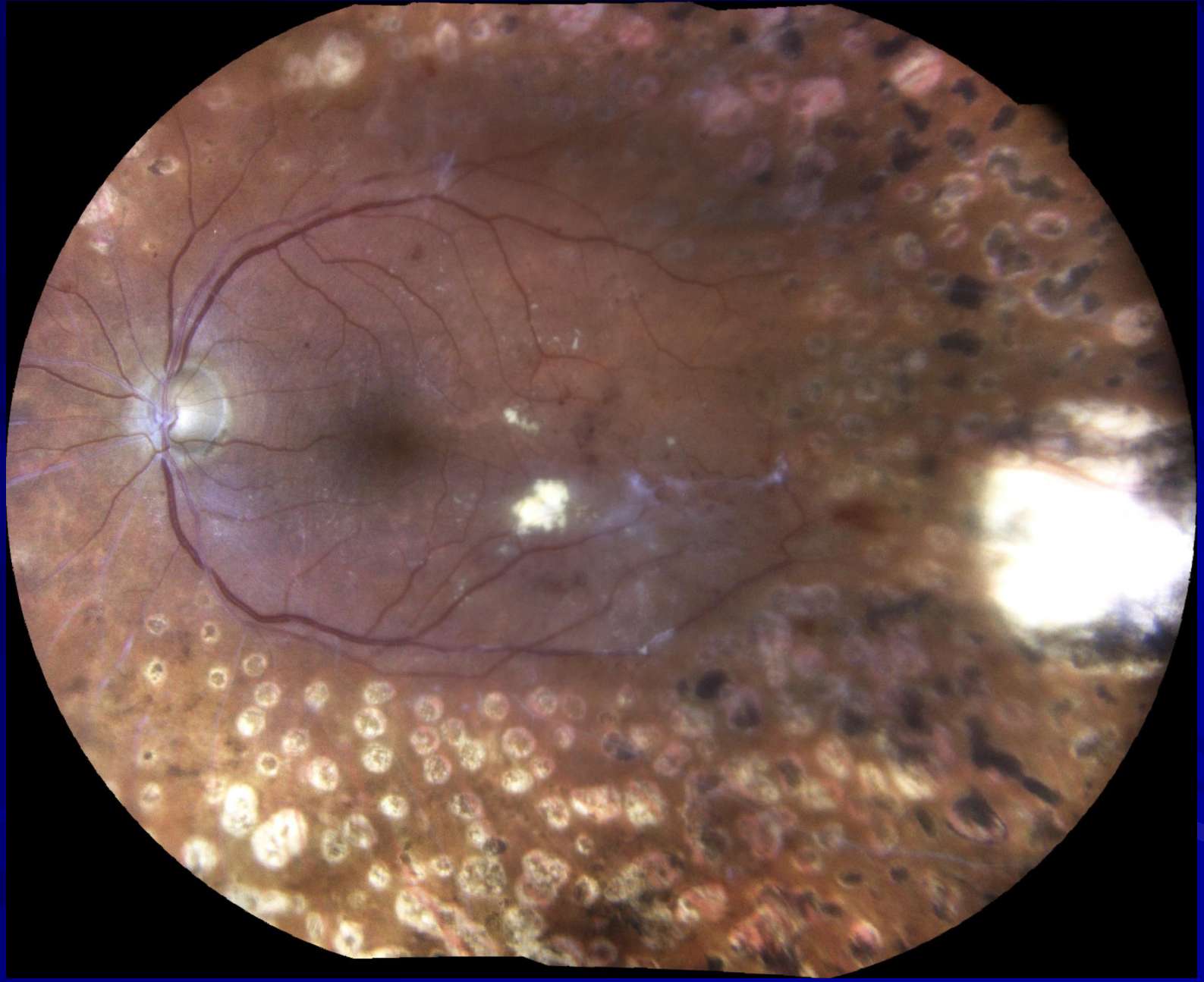

OPTOS



Courtesy of David Steel, UK

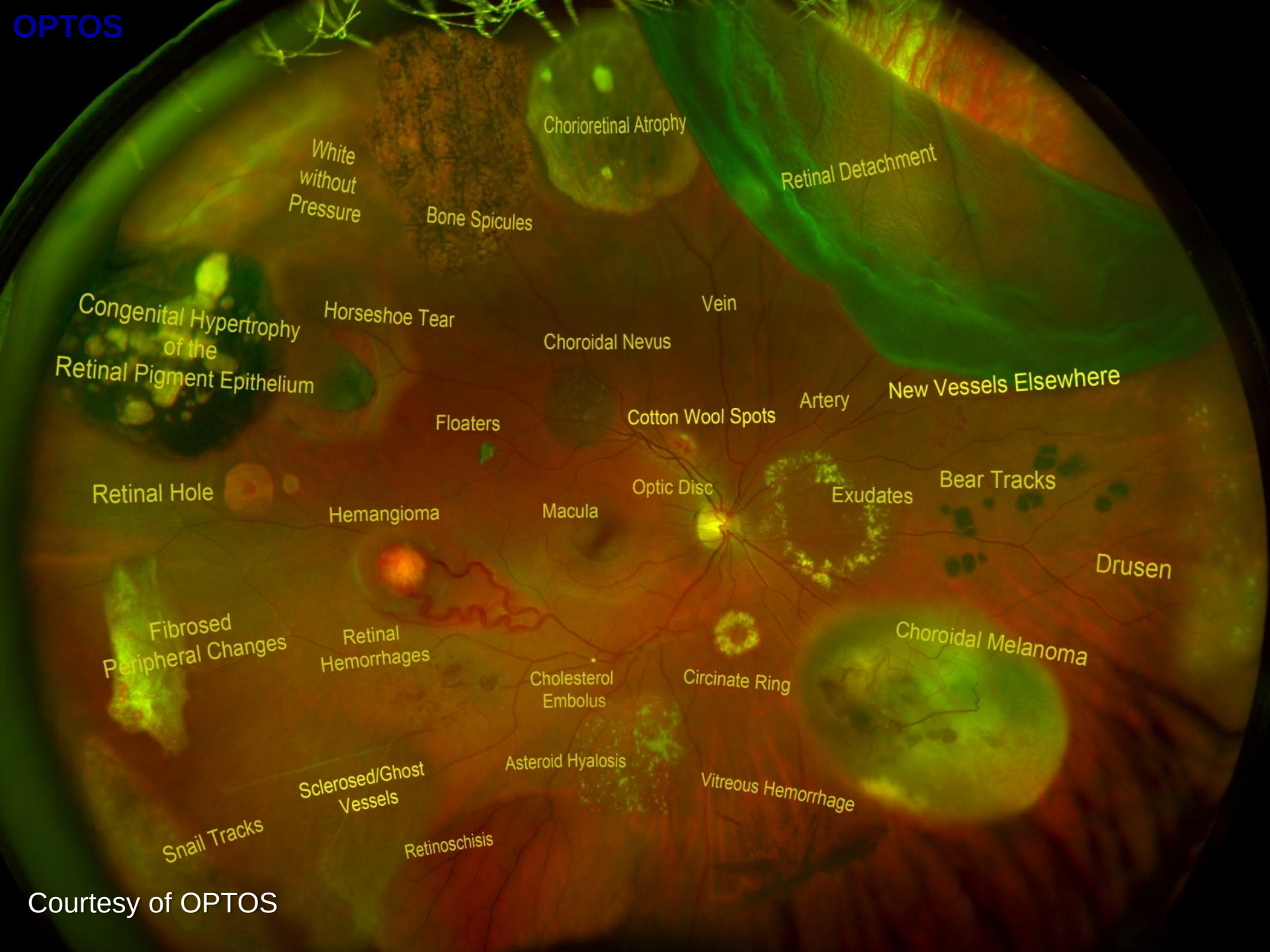


Courtesy of MEH clinic



This patient had ungradable image due to cataract, but gradable on SLO

Daytona – DR with PRP



Courtesy of OPTOS

Non-mydriatic Optos images have excellent agreement with dilated ETDRS photos and dilated fundus examination in determining severity of DR and DME.

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Nonmydriatic Ultrawide Field Retinal Imaging Compared with Dilated Standard 7-Field 35-mm Photography and Retinal Specialist Examination for Evaluation of Diabetic Retinopathy

PAOLO S. SILVA, JERRY D. CAVALLERANO, JENNIFER K. SUN, JASON NOBLE, LLOYD M. AIELLO, AND LLOYD PAUL AIELLO

• PURPOSE: To compare nonmydriatic stereoscopic Optomap ultrawide field images with dilated stereoscopic Early Treatment Diabetic Retinopathy Study 7-standard field 35-mm color 30-degree fundus photographs (ETDRS photography) and clinical examination for determining diabetic retinopathy (DR) and diabetic macular edema (DME) severity.

• DESIGN: Single-site, prospective, comparative, instrument validation study.

• METHODS: One hundred three diabetic patients (206 eyes) representing the full spectrum of DR severity underwent nonmydriatic ultrawide field 100-degree and 200-degree imaging, dilated ETDRS photography, and dilated fundus examination by a retina specialist. Two independent readers graded images to determine DR and DME severity. A third masked retina specialist adjudicated discrepancies.

• RESULTS: Based on ETDRS photography (n = 200), the results were as follows: no DR (n = 25 eyes [12.5%]), mild nonproliferative DR (NPDR; 47 [23.5%]), moderate NPDR (61 [30.5%]), severe NPDR (11 [5.5%]), very severe NPDR (3 [1.5%]), and proliferative DR (52 [2.5%]). One (0.5%) eye was ungradable and 6 eyes did not complete ETDRS photography. No DME was found in 114 eyes (57.0%), DME was found in 28 eyes (14.0%), and clinically significant DME was found in 47 eyes (23.5%), and 11 (5.5%) eyes were ungradable. Exact DR severity agreement between ultrawide field 100-degree imaging and ETDRS photography occurred in 84%, with agreement within 1 level in 91% ($K_W = 0.85$; $K = 0.79$). Nonmydriatic ultrawide field images exactly matched clinical examination results for DR in 70% and were within 1 level in 93% ($K_W = 0.71$; $K = 0.61$). Nonmydriatic ultrawide field imaging acquisition time was less than half that of dilated ETDRS photography ($P < .0001$).

• CONCLUSIONS: Nonmydriatic ultrawide field images compare favorably with dilated ETDRS photography and dilated fundus examination in determining DR and DME severity; however, they are acquired more rapidly. If confirmed in broader diabetic populations, nonmydriatic ultrawide field imaging may prove to be beneficial in DR evaluation in research and clinical settings. (Am J Ophthalmol 2012;xx:xxx. © 2012 by Elsevier Inc. All rights reserved.)

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Jason Noble is now at the Department of Ophthalmology and Vision Sciences, University of Toronto, Ontario, Canada.

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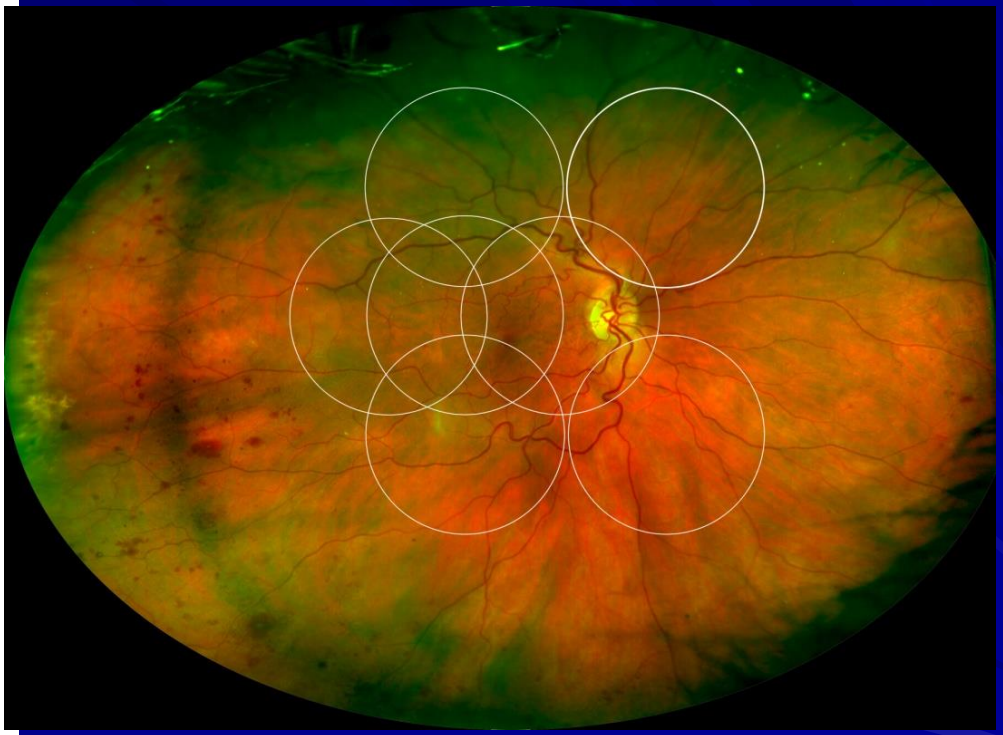
0002-9394/$36.00
http://dx.doi.org/10.1016/j.ajo.2012.03.019

CURRENT EVIDENCE-BASED DIABETES EYE CARE IS highly effective in preserving vision and preventing vision loss from diabetic retinopathy (DR).[1–6] Because DR frequently is asymptomatic when most amenable to treatment, regular eye examination is recommended for all persons with diabetes mellitus to identify the presence and degree of DR and to initiate sight-preserving treatments as indicated. Only an estimated 60% of the diabetic population in the United States receives the recommended annual eye examination.[7] Retinal evaluation and photography are important components of clinical care for DR and an integral element of clinical trials and telemedicine programs. Early Treatment Diabetic Retinopathy Study (ETDRS) 7-standard field 35-mm color 30-degree stereoscopic color fundus photographs (ETDRS photography) evaluated using the modified Airlie House classification of diabetic retinopathy are an accepted standard for determining severity of DR.[8,9]

Given the rapidly increasing number of patients at risk, retinal imaging of all patients is a daunting task that requires ever more rapid, readily obtained images for evaluation. Although ETDRS photography and grading protocols provide an established and documented standard for detecting and assessing severity of DR, ETDRS photography requires skilled photographers, pharmacologic pupil dilation, and traditionally, the use of 35-mm slide film. These requirements impact efficiency, convenience, and cost of the procedure. Examiners and researchers have evaluated numerous alternatives to ETDRS photography for retinal imaging and assessment of DR severity. These studies have included the use of nonmydriatic retinal cameras,[10–14] digital video imaging,[15–18] fewer nonstereoscopic retinal fields,[19–24] and multiple image montages.[25,26]



Peripheral Lesions Study

- The study identified that **33% more** lesions were in the area outside of ETDRS and that in **10%** of patients these lesions suggested a **more severe** grade of retinopathy.
- There are ongoing longitudinal studies in this cohort to determine the clinical significance of these peripheral lesions. This paper suggests "**this information might be useful in determining more accurately the specific risk of DR progression**… as previous studies have suggested that some of the earliest clinical changes in DR occur in the mid-peripheral fundus… **more peripheral lesions might be associated with a greater risk of retinopathy progression and complications even though the patient may have the same ETDRS severity level**."

ARTICLE IN PRESS

Peripheral Lesions Identified by Mydriatic Ultrawide Field Imaging: Distribution and Potential Impact on Diabetic Retinopathy Severity

Paolo S. Silva, MD,[1,2] Jerry D. Cavallerano, OD, PhD,[1,2] Jennifer K. Sun, MD, MPH,[1,2] Ahmed Z. Soliman, MD,[1,2] Lloyd M. Aiello, MD,[1,2] Lloyd Paul Aiello, MD, PhD[1,2]

Objective: To assess diabetic retinopathy (DR) as determined by lesions identified using mydriatic ultrawide field imaging (DSLO200; Optos plc, Scotland, UK) compared with Early Treatment Diabetic Retinopathy Study (ETDRS) 7-standard field film photography.

Design: Prospective comparative study of DSLO200, ETDRS 7-standard field film photographs, and dilated fundus examination (DFE).

Participants: A total of 206 eyes of 103 diabetic patients selected to represent all levels of DR.

Methods: Subjects had DSLO200, ETDRS 7-standard field film photographs, and DFE. Images were graded for severity and distribution of DR lesions. Discrepancies were adjudicated, and images were compared side by side.

Main Outcome Measures: Distribution of hemorrhage and/or microaneurysm (H/Ma), venous beading (VB), intraretinal microvascular abnormality (IRMA), and new vessels elsewhere (NVE). Kappa (κ) and weighted κ statistics for agreement.

Results: The distribution of DR severity by ETDRS 7-standard field film photographs was no DR 12.5%; nonproliferative DR mild 22.5%, moderate 30%, and severe/very severe 8%; and proliferative DR 27%. Diabetic retinopathy severity between DSLO200 and ETDRS film photographs matched in 80% of eyes (weighted $\kappa = 0.74$,$\kappa = 0.84$) and was within 1 level in 94.5% of eyes. DSLO200 and DFE matched in 58.8% of eyes (weighted $\kappa = 0.69$,$\kappa = 0.47$) and were within 1 level in 91.2% of eyes. Forty eyes (20%) had DR severity discrepancies between DSLO200 and ETDRS film photographs. The retinal lesions causing discrepancies were H/Ma 52%, IRMA 26%, NVE 17%, and VB 4%. Approximately one-third of H/Ma, IRMA, and NVE were predominantly outside ETDRS fields. Lesions identified on DSLO200 but not ETDRS film photographs suggested a more severe DR level in 10% of eyes. Distribution in the temporal, superotemporal, inferotemporal, superonasal, and inferonasal fields was 77%, 72%, 61%, 65%, and 59% for H/Ma, respectively ($P < 0.0001$); 22%, 24%, 21%, 28%, and 22% for VB, respectively ($P = 0.009$); 52%, 40%, 29%, 47%, and 36% for IRMA, respectively ($P < 0.0001$), and 8%, 4%, 4%, 8%, and 5% for NVE, respectively ($P = 0.03$). All lesions were more frequent in the temporal fields compared with the nasal fields ($P < 0.0001$).

Conclusions: DSLO200 images had substantial agreement with ETDRS film photographs and DFE in determining DR severity. On the basis of DSLO200 images, significant nonuniform distribution of DR lesions was evident across the retina. The additional peripheral lesions identified by DSLO200 in this cohort suggested a more severe assessment of DR in 10% of eyes than was suggested by the lesions within the ETDRS fields. However, the implications of peripheral lesions on DR progression within a specific ETDRS severity level over time are unknown and need to be evaluated prospectively.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references. *Ophthalmology 2013;■:1–9 © 2013 by the American Academy of Ophthalmology.*

Management of diabetic eye disease is guided by landmark clinical trials conducted during the past 40 years.[1–10] These clinical trials established treatment modalities and eluci-

mydriatic stereoscopic 30-degree 35-mm retinal photography obtained using a defined protocol of 7-standard retinal fields in what is referred to as "Early Treatment Diabetic

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Nonmydriatic Ultra-Wide-Field Scanning Laser Ophthalmoscopy (Optomap) versus Two-Field Fundus Photography in Diabetic Retinopathy

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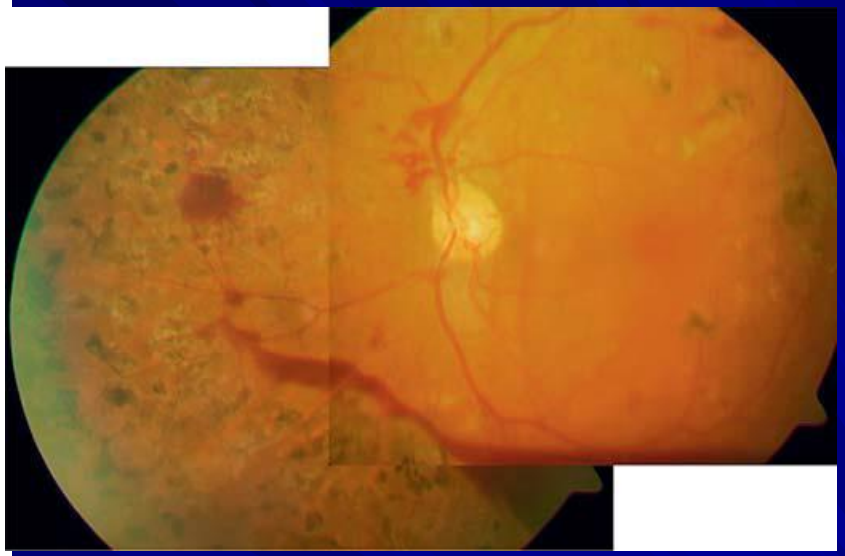
Abstract

The purpose of this study was to investigate the diagnostic properties of a 2-laser wavelength nonmydriatic 200° ultra-wide-field scanning laser ophthalmoscope (SLO) versus

Introduction

Diabetic retinopathy (DR) and particularly diabetic macular edema (DME), microvascular complications of



The Optos SLO offers a wider field of view and can better differentiate lesions by applying the 2 laser wavelengths

KARGER

E-Mail karger@karger.com
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0030–3755/13/0000–0000$38.00/0

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Peripheral retinal ischaemia, as evaluated by ultra-widefield fluorescein angiography, is associated with diabetic macular oedema

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Accepted 12 November 2011

ABSTRACT

Purpose To determine the relationship between retinal ischaemia and the presence of macular oedema (DMO) in patients with diabetic retinopathy (DR) using ultra-widefield fluorescein angiography (UWFA) imaging.

Methods A retrospective review of 122 eyes of 70 treatment-naïve diabetic patients who underwent diagnostic UWFA using the Optos 200Tx imaging system. Two independent, masked graders quantified the area of retinal ischaemia. Based on clinical examination and optical coherence tomography (OCT), each patient was given a binary classification as either having DMO or no DMO. McNemar's test (with Yates' correction as indicated) and a two-sample test of proportions were used to determine the relationship between DMO and ischaemia for binary and proportional data, respectively. Linear and logistic models were constructed using generalised estimating equations to test relationships between independent variables, covariates and outcomes while controlling for inter-eye correlation, age, gender, haemoglobin A1c, mean arterial pressure and dependence on insulin.

Results Seventy-six eyes (62%) exhibited areas of retinal ischaemia. There was a significant direct correlation between DMO and peripheral retinal ischaemia as seen on UWFA ($p<0.001$). In addition, patients with retinal ischaemia had 3.75 times increased odds of having DMO compared with those without retinal ischaemia (CI 1.26 to 11.13, $p<0.02$).

Conclusion Retinal ischaemia is significantly correlated with DMO in treatment-naïve patients with DR. UWFA is a useful tool for detecting peripheral retinal ischaemia, which may have direct implications in the diagnosis, follow-up and treatment such as targeted peripheral photocoagulation.

INTRODUCTION

Diabetic retinopathy (DR) is one of the leading causes of blindness among adults, accounting for approximately 5% of global blindness. In parts of the Americas, Europe and the Western Pacific, DR is responsible for as much as 17% of the total blindness caused by eye disease.[1] The risk of developing significant visual loss due to DR can be significantly diminished with proper control of systemic disease and prompt treatment of eye pathology.[1]

Diabetic macular oedema (DMO), in particular, is a major contributor to vision loss among patients with DR.[2] More than 25 years ago, the Early Treatment of Diabetic Retinopathy Study (ETDRS) established guidelines for identifying clinically significant macular oedema (DMO) and proved that treatment with focal laser photocoagulation decreased risk of moderate visual loss, increased the chance of moderate visual gain and reduced retinal thickening.[3] While ETDRS remains the seminal study on DMO, additional awareness of diabetic pathology, the advent of new pharmacology and improvements in retinal imaging technology have allowed us to expand upon our understanding and treatment of DMO.

Ischaemic changes and microvascular pathologies have long been hypothesised to play a role in the development of DMO. In DR, ischaemia stimulates the production of vascular endothelial growth factor (VEGF),[4] which can lead to the breakdown of blood-retinal barriers, and may cause DMO through an increase in retinal vessel permeability.[5] Anti-VEGF drugs have proven efficacious in the treatment of DMO, even in cases not responding to laser photocoagulation.[6] The success of anti-VEGF therapy lends support to the thinking that retinal ischaemia and DMO are associated, but traditional retinal imaging of ischaemia makes it difficult to study this association.

Retinal ischaemia is best characterised with fluorescein angiography (FA). Traditional FA employs retinal photography that is able to view approximately 30° of the retina at one time. The ETDRS developed the seven-standard fields (7SF) protocol in which seven photographed areas of the retina were combined to give nearly 75° of visualisation. With the advent of ultra-widefield fluorescein angiography (UWFA), as with the Optos 200Tx imaging system (Optos PLC, Dunfermline, Scotland), it is now possible to view up to 200° of retina in a single photograph. Initial small-scale studies have shown that UWFA is more useful in detecting capillary non-perfusion in patients with DMO than other methods with a more limited degree of retinal imaging.[7]

The principle aim of this study was to better characterise the relationship between the area of retinal ischaemia as measured with UWFA and the presence of DMO in patients with DR. We hypothesise that peripheral vascular changes can influence the posterior retina and that patients with retinal ischaemia are at an increased odds of having DMO. Given the extent of retinal thickening in patients with DMO can be determined with cross-sectional retinal visualisation in optical coherence tomography (OCT),[8] this study also evaluated whether the area of retinal

Wessel and associates showed that peripheral retinal ischemia is significantly correlated with DME in treatment-naive patients with DR using Optos 200Tx UWF imaging.

Even the treatment algorithms might be changed?

Acta Ophthalmologica

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Optos-guided pattern scan laser (Pascal)-targeted retinal photocoagulation in proliferative diabetic retinopathy

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[1]Manchester Royal Eye Hospital, Manchester, UK
[2]University of Manchester, Manchester, UK
[3]OptiMedica Corporation, Santa Clara, California, USA

ABSTRACT.

Purpose: To investigate the clinical effects and safety of targeted pattern scan laser (Pascal) retinal photocoagulation (TRP) in proliferative diabetic retinopathy (PDR).

Methods: Prospective and non-randomized study of 28 eyes with treatment-naive proliferative diabetic retinopathy (PDR). Single-session 20-ms-Pascal TRP strategy applied 1500 burns to zones of retinal capillary non-perfusion and intermediate retinal ischaemia guided by wide-field fluorescein angiography (Optos). Main outcome measures at 12 and 24 weeks included; PDR grade (assessed by two masked retina specialists); central retinal thickness (CRT); mean deviation (MD) using 24-2 Swedish interactive threshold algorithm (SITA)-standard visual fields (VF); and ETDRS visual acuity (VA).

Results: Following primary TRP, there was PDR regression in 76% of patients at 12 weeks ($\kappa = 0.70$; $p < 0.001$). No laser re-treatment was required at 4 weeks, and 10 eyes underwent repeat TRP at 12 weeks. Wide-field Optos angiography at 24 weeks showed complete disease regression in 37% and partial regression in 33%. Additional panretinal laser photocoagulation (PRP) was planned for active PDR in 30%. There were significant reductions in CRT over time (10.4 μm at 12-weeks, $p = 0.007$; 12.1 μm at 24-weeks, $p = 0.0003$). The MD on VFs improved after 12 weeks (+1.25 dB; $p = 0.015$) and 24 weeks (+1.26 dB, $p = 0.01$). The VA increased by +3 letters at 24 weeks (95% CI, 1.74–5.01; $p < 0.0001$).

Conclusions: This pilot study reports that Optos-guided Pascal 20-ms TRP using 1500 burns for treatment-naive PDR is a promising procedure with favourable safety profile.

Key words: diabetic retinopathy – optos angiography – Pascal laser – targeted retinal laser

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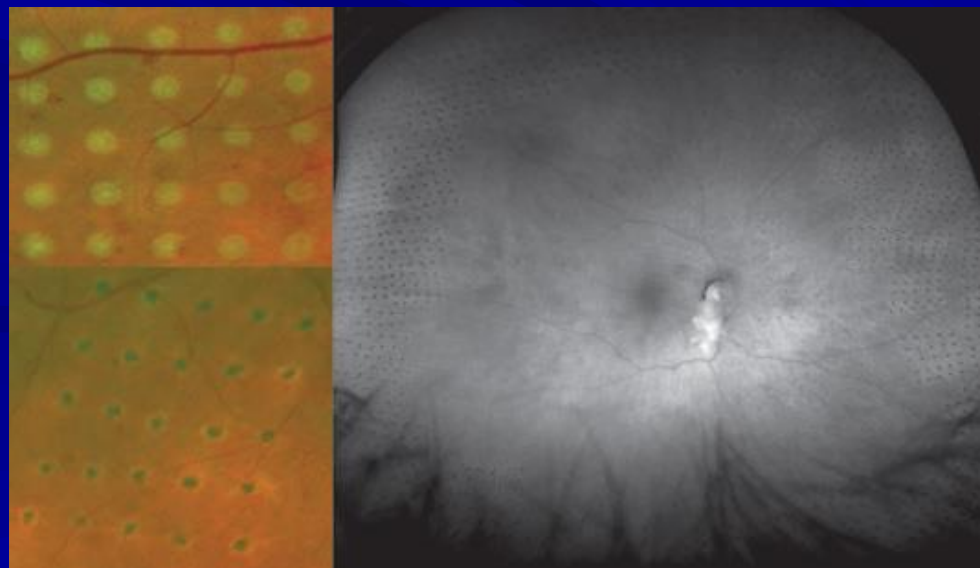
Introduction

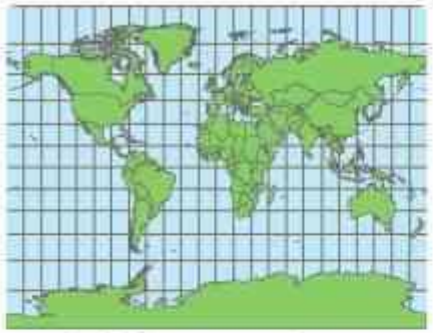
The diabetic retinopathy study (DRS) established panretinal laser photocoagulation (PRP) as the gold standard for first-line therapy in proliferative diabetic retinopathy (PDR) (Diabetic Retinopathy Study Research Group 1981). Current PRP laser practice for patients with PDR has remained relatively unchanged, with single- or multi-session PRP performed using different laser devices and parameters (Bailey et al. 1998; Diabetic Retinopathy Clinical Research Network et al. 2009; Muqit et al. 2010a). The NAVILAS® is an image-stabilized computer-targeted device, rather than a pattern laser, and initial studies of clinical efficacy in diabetic retinopathy are promising (Kernt et al., 2010).

Based on Ashton's early work and diabetic perfusion studies, the concept of 'penumbra' has been applied to the perfusion abnormalities that exist between non-proliferative and proliferative states in diabetic retinopathy (Ashton 1950, 1953; Bresnick et al. 1976; McLeod 2007). Shimizu and co-workers demonstrated that the mid-peripheral retina was far more prone to develop capillary non-perfusion than the posterior retina, with the highest rate of proliferative activity appears existing in the overlapping area between

The effects of TRP on PDR showed a regression in 76% of patients at 12 weeks and complete disease regression in 37% and partial regression in 33% at 24 weeks

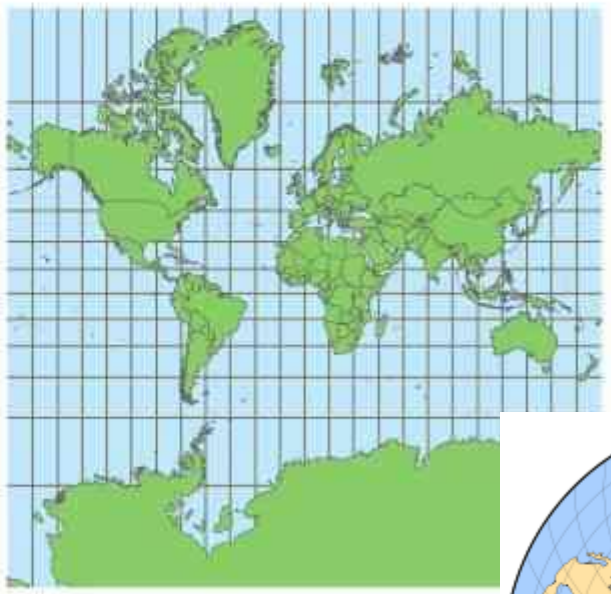


World Map Projections



Gall Sterographic

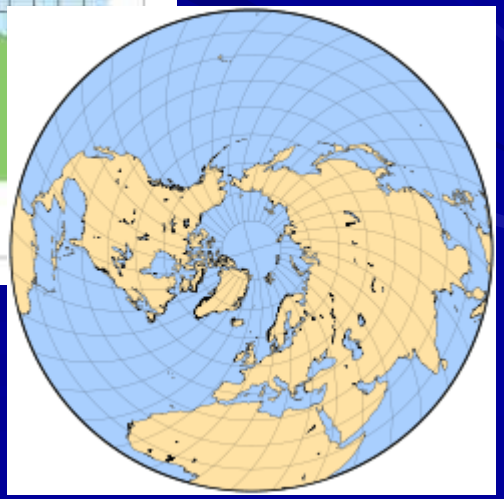
Eckert IV



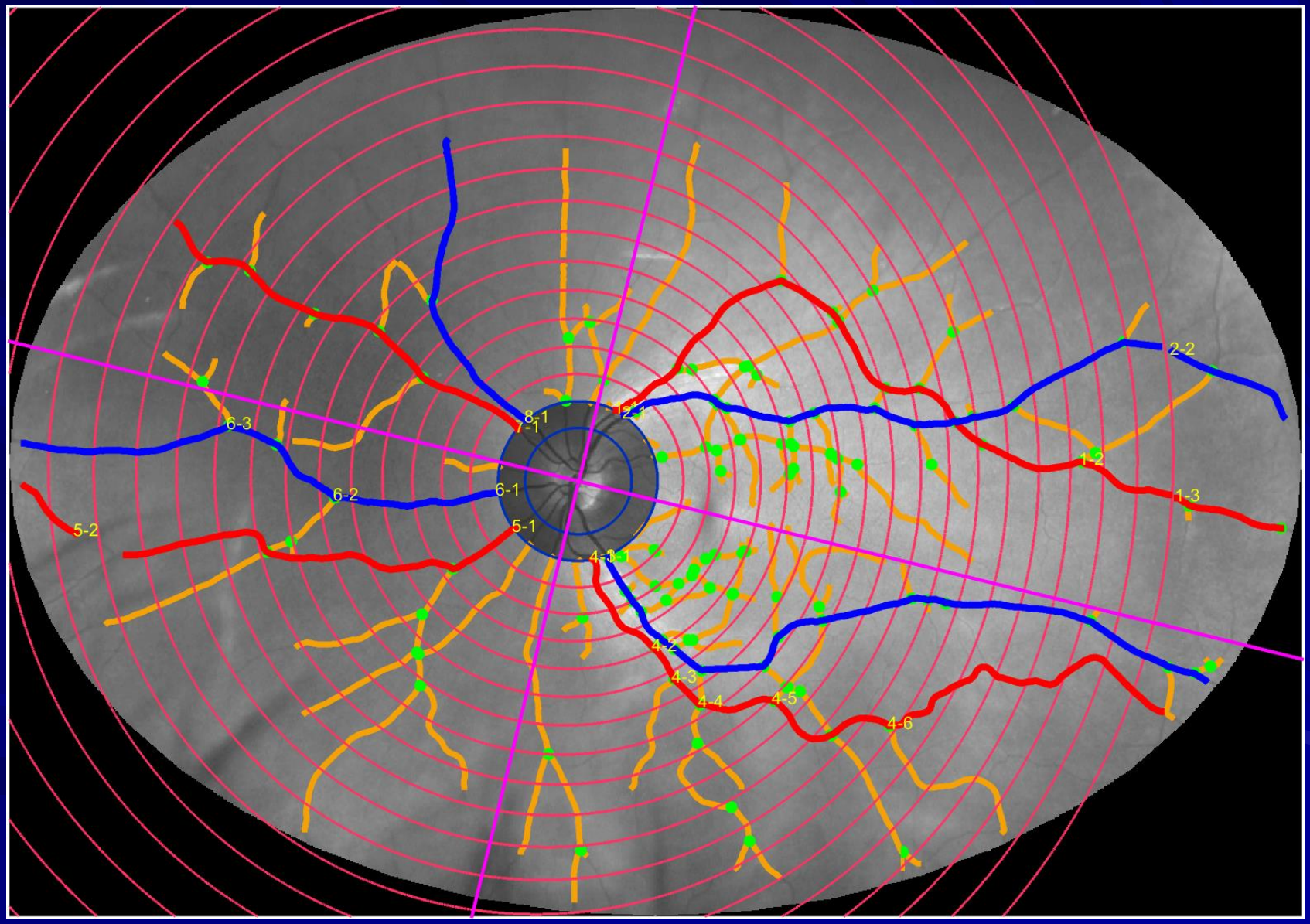
Mercator

00 20,000 Kilometers

10,000 20,000 Miles



Vascular measurements might need to be updated



Visual Electrodiagnostic Device

This device measures the 30 Hz flicker implicit time, which has a strong correlation to retinal ischemic diseases such as diabetic retinopathy.

Design Features

- Handheld
- Utilizes skin electrodes
- Mydriatic-free
- Ultra low-noise digital amplifier

Summary and conclusions

- Different new imaging modalities will give different information
- Before committing to any camera/method, it is important to understand the benefits and the limitations of the camera
- For screening, population health needs to be of the highest priority, this is likely to differ from hospital eye clinic needs!