

SOUTHERN CALIFORNIA KAISER PERMANENTE OPTOMETRY SYMPOSIUM 2019

Diabetic Retinopathy And Macular Edema

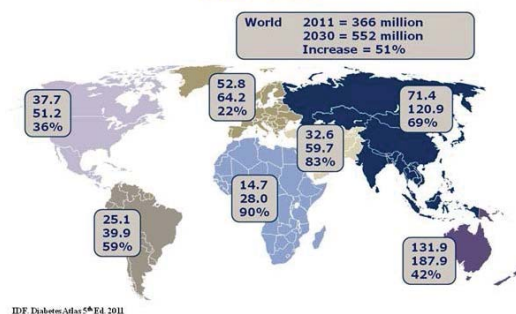
Hajir Dadgostar, MD, PhD

Diabetes: An Epidemic

- **29.1 million people in the United States (~9.3% of the population)**
 - **Leading cause of vision loss** and new-onset blindness in patients 20-74¹
 - **40%-45%** of Americans diagnosed with DM have some degree of diabetic retinopathy²
- **51% increased prevalence globally by 2030**



The Diabetes Epidemic: Global Projections, 2010–2030



1. National Diabetes Fact Sheet, 2011. <http://www.cdc.gov/diabetes/pubs/factsheet11.htm> Accessed October 27, 2014

2. National Eye Institute. Facts about diabetic retinopathy. Updated June 2012. <http://www.nei.nih.gov/health/diabetic/retinopathy.asp>. Accessed October 22, 2014.

Gaps in Diabetic Eye Care

- Many patients are not getting sufficient care to prevent visual impairment
- In a recent cross-sectional analysis of NHANES data:
 - 46.7% of patients ≥ 40 with DME reported no visits with a dietitian/diabetes nurse educator in the previous 12 months
 - 44.7% reported being informed that their eyes had been affected by DM
 - **59.7% reported receiving a dilated eye exam in the previous 12 months**
 - 28.7% had some degree of visual impairment (based on visual acuity at initial exam)

DME=diabetic macular edema; NHANES=National Health and Nutrition Examination Survey.

Bressler NM et al. *JAMA Ophthalmol.* 2014;132(2):168-173.

Diabetic Retinopathy: Screening guidelines

Adult diabetics

Initial exam: Upon diagnosis
 Follow-up: 1 to 12 (24?) months (depending on disease)

Juvenile diabetics

Initial exam: Within 5 years of diagnosis
 Follow-up: 1 to 12 (24?) months (depending on disease)

Pregnant diabetics

Initial exam: Beginning of pregnancy
 Follow-up: 1 to 3 months (depending on disease)
 until term

Eye Exams for Patients With No to Minimal NPDR



	Type 1 DM	Type 2 DM
Baseline Evaluation	DFE 3 to 5y from Dx	DFE on Dx
Follow-up	Yearly	Yearly
Proportion of Patients with DR		
At Diagnosis	NR	20 – 39%* NPDR 2 - 3% CSME
> 15 Years	78 – 97% NPDR 25% PDR	60 – 80% NPDR up to 20% PDR

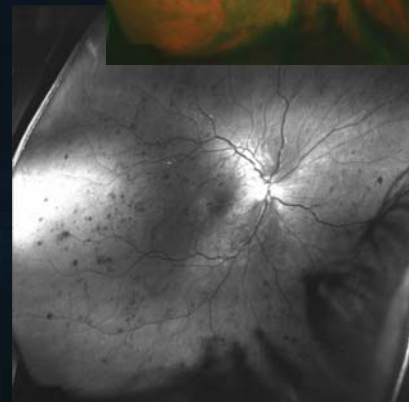
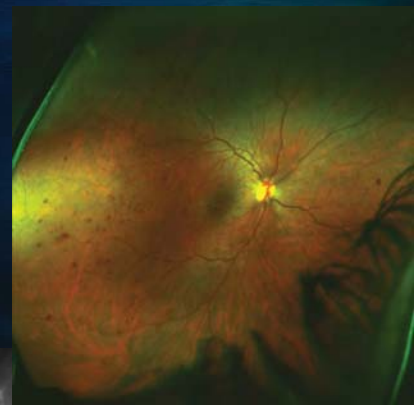
*Typical disease duration prior to diagnosis is 5-10 years

CSME=clinically significant macular edema; DFE=dilated fundus examination; NPDR=nonproliferative diabetic retinopathy. American Optometric Association Evidence-Based Optometry Guideline Development Group. *Eye Care of the Patient with Diabetes Mellitus* (Evidence-Based Clinical Practice Guideline). February 7, 2014

DR Staging



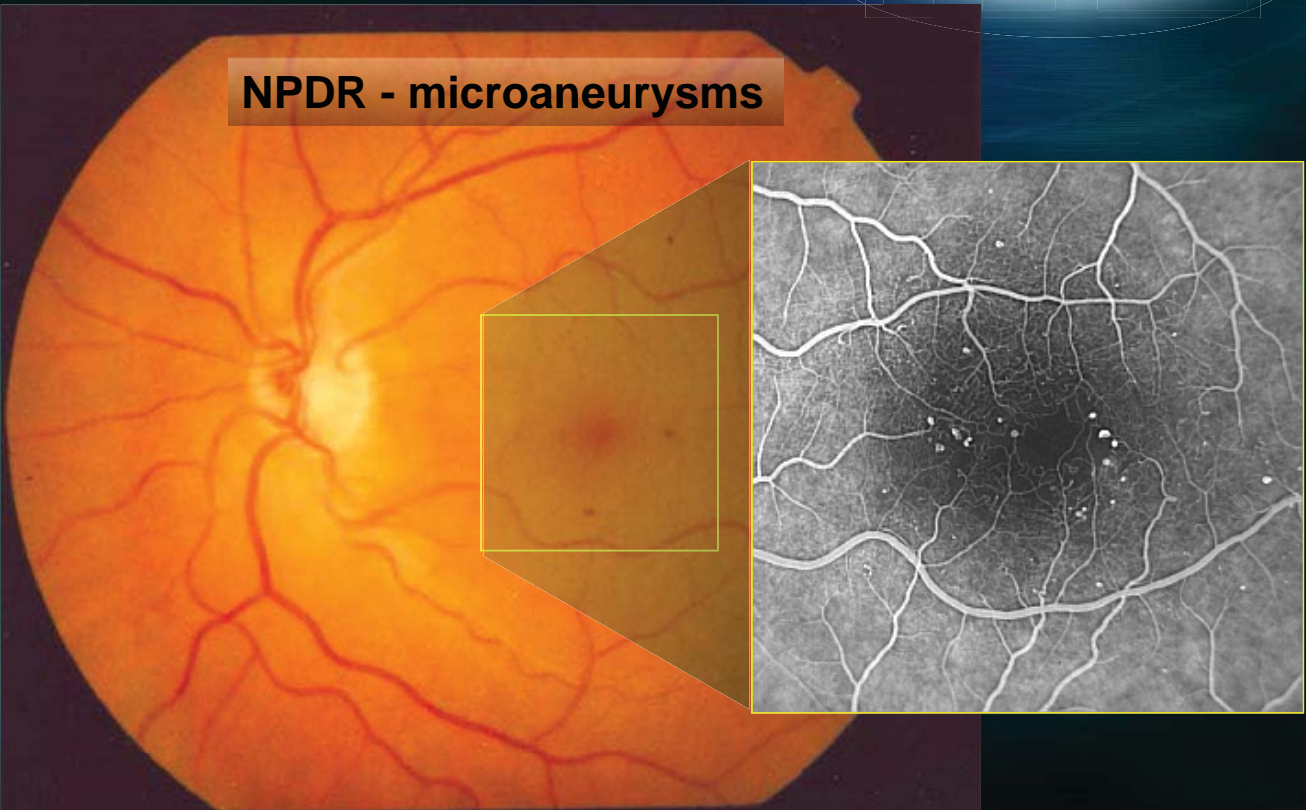
- Mild NPDR
 - At least 1 MA
- Moderate NPDR
 - Hemorrhages &/or MAs (2A), CWS, or VB (<6B) or IRMA (<8A)
- Severe NPDR
 - 4/2/1 (Hemorrhages, VB, IRMA)
 - 15% to PDR in 1 year
- Very Severe NPDR
 - 2 of severe findings
 - 45% to PDR in 1 year
- PDR
 - definite NVD or NVE and/or VH/PRH



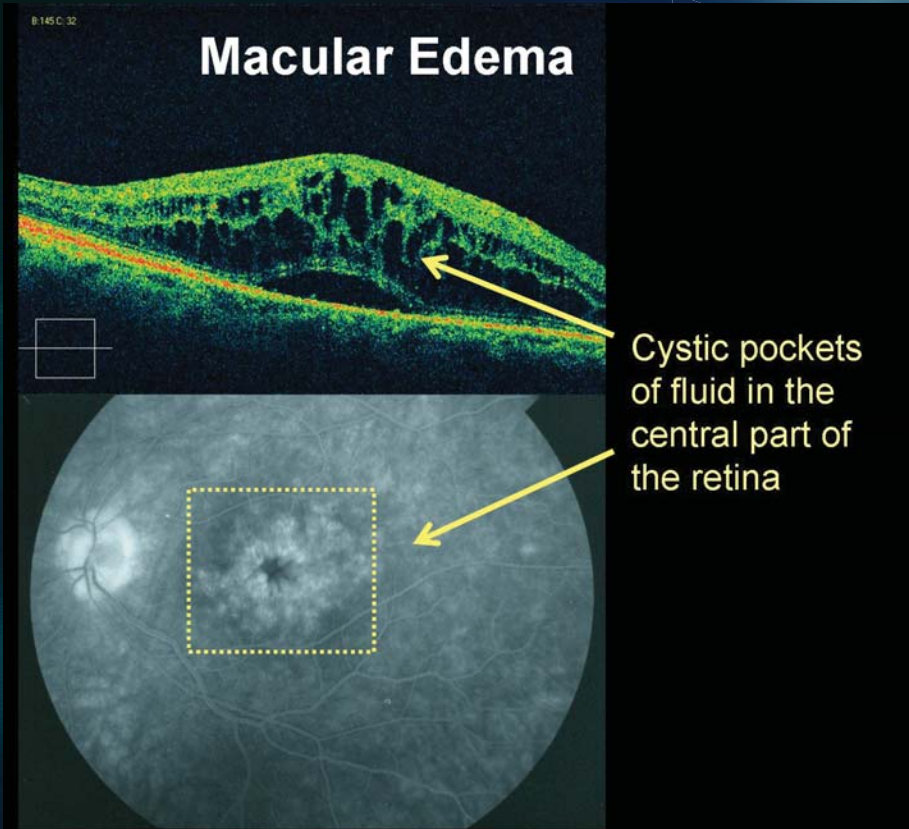
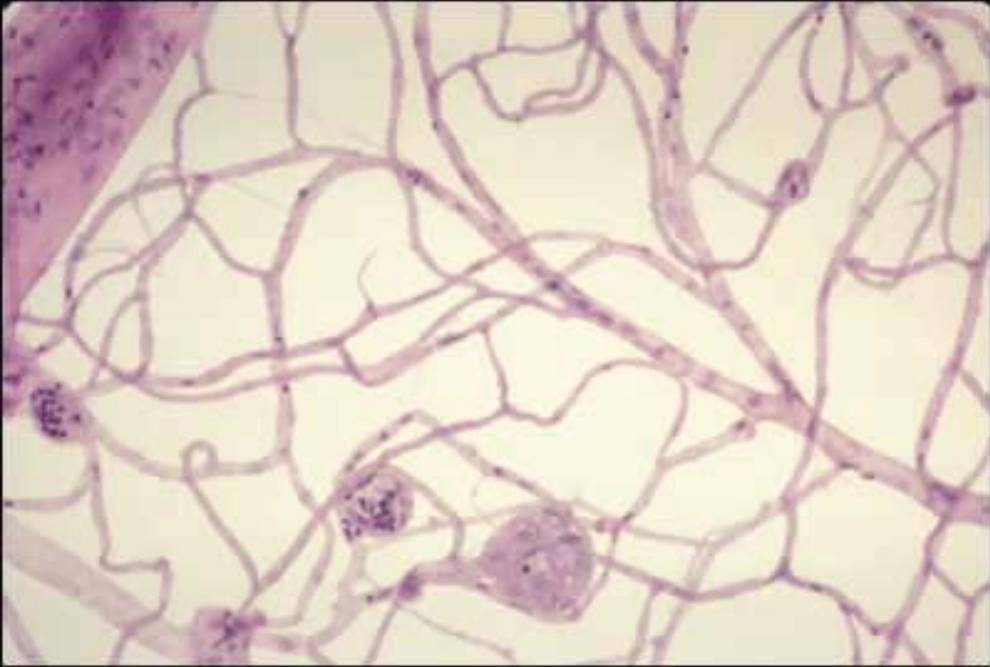
Non-proliferative Diabetic Retinopathy



NPDR - microaneurysms

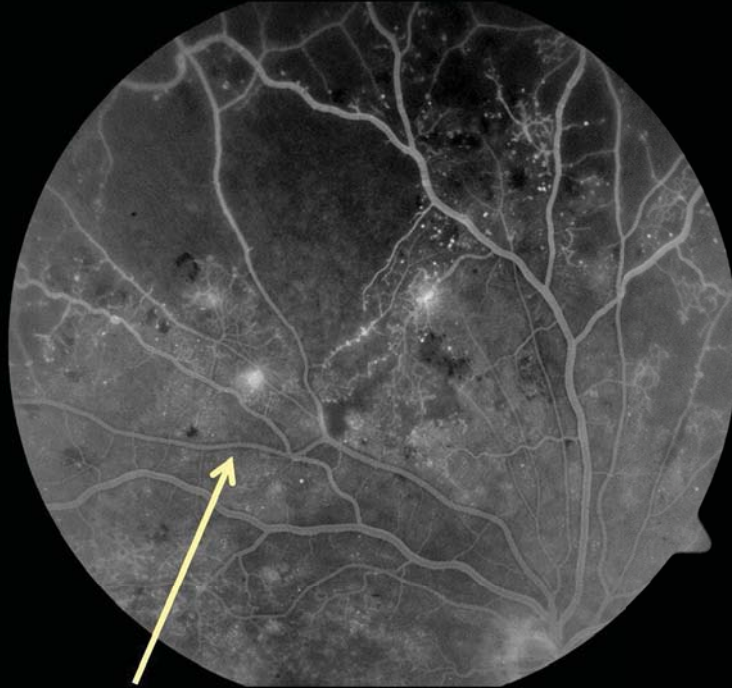


NPDR - microaneurysms



Diabetic Retinopathy

Ischemia

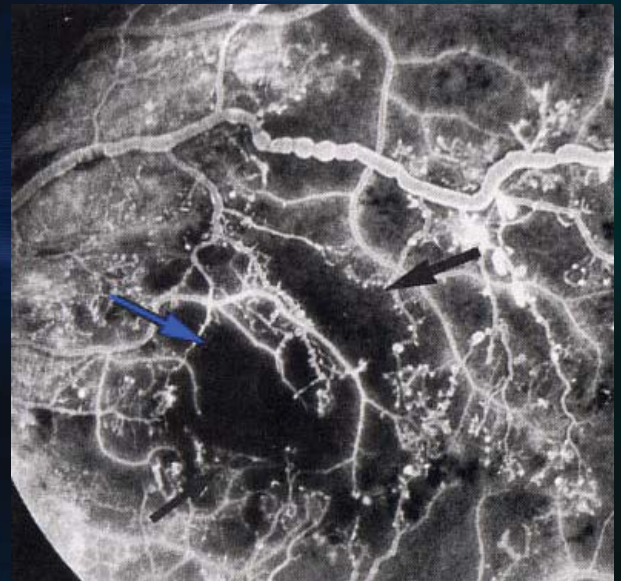


Damaged and leaky blood vessels in the retina

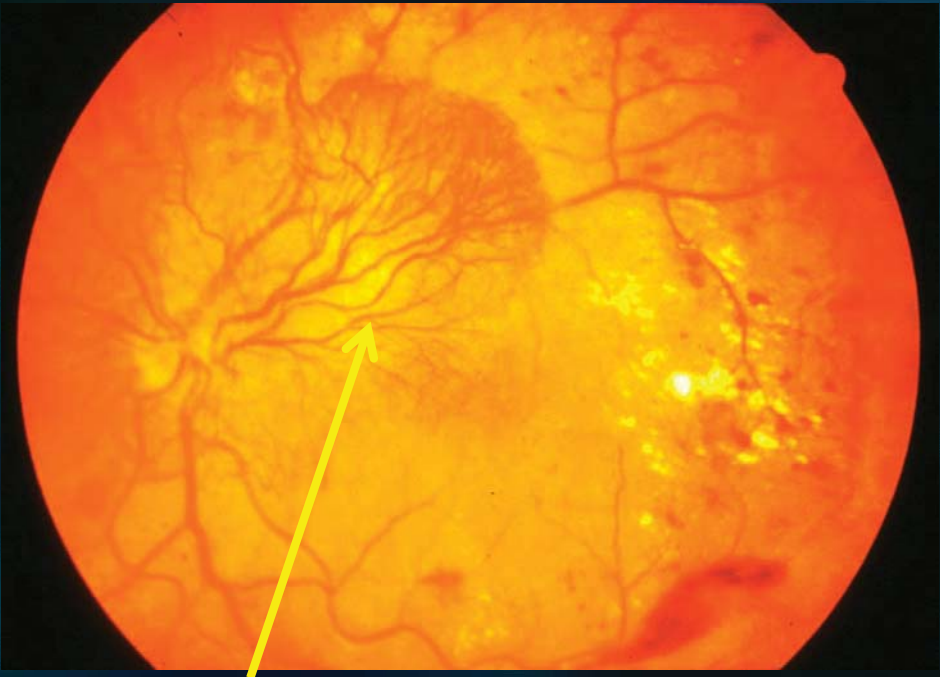
NPDR – venous beading,
capillary dropout, ischemia



NPDR – progression



Proliferative Diabetic Retinopathy

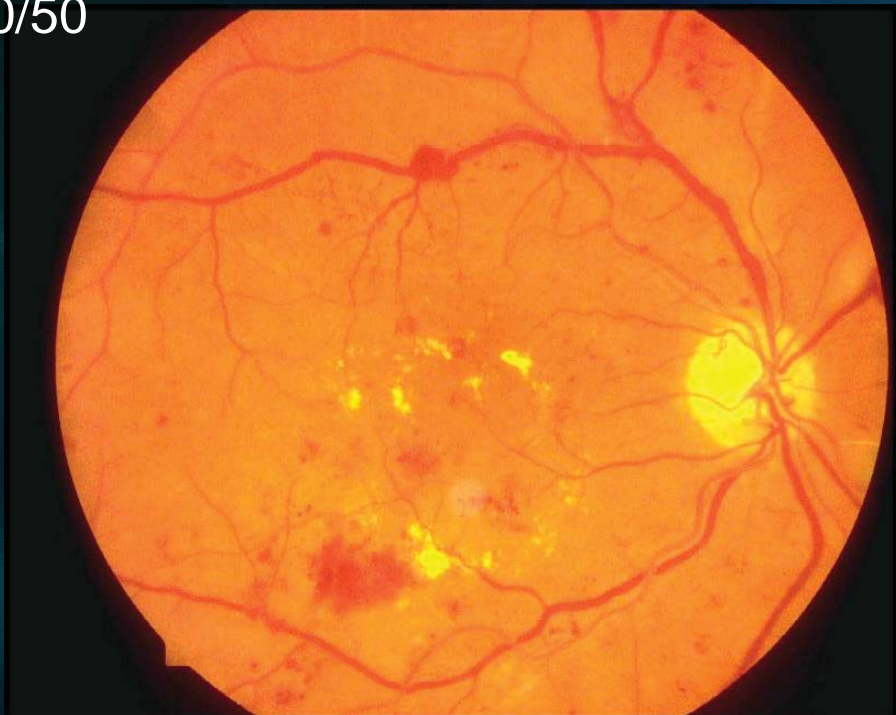


Neovascularization

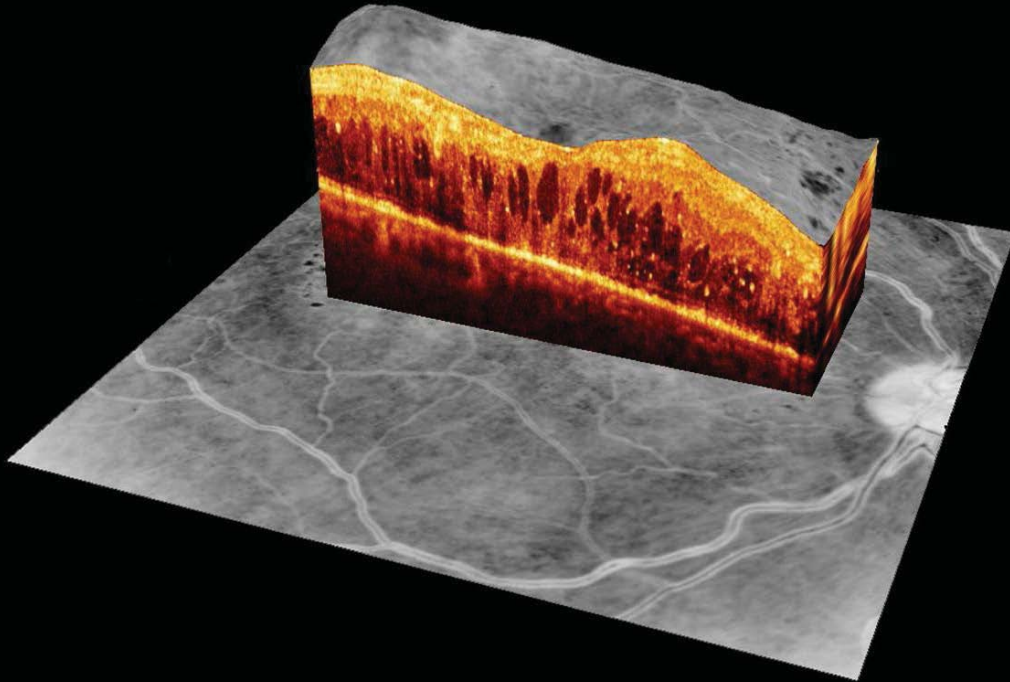
Diabetic Retinopathy: Causes of vision loss

- Macular edema
- Vitreous hemorrhage
- Tractional retinal detachment
- Ischemia

53 y/o female, DM, distorted vision OD x6 months
VA 20/50



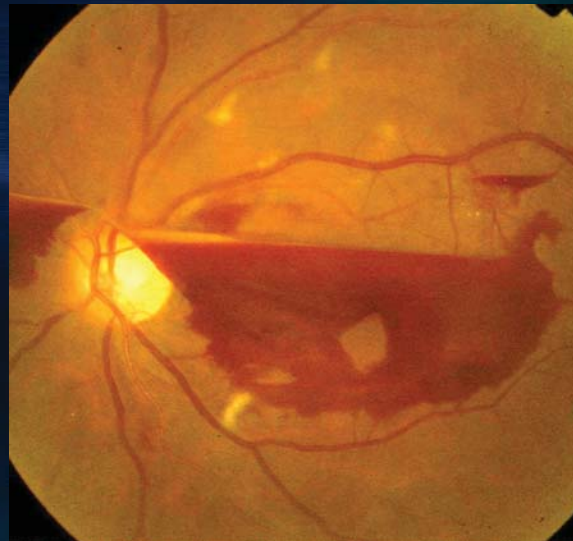
Diabetic Macular Edema



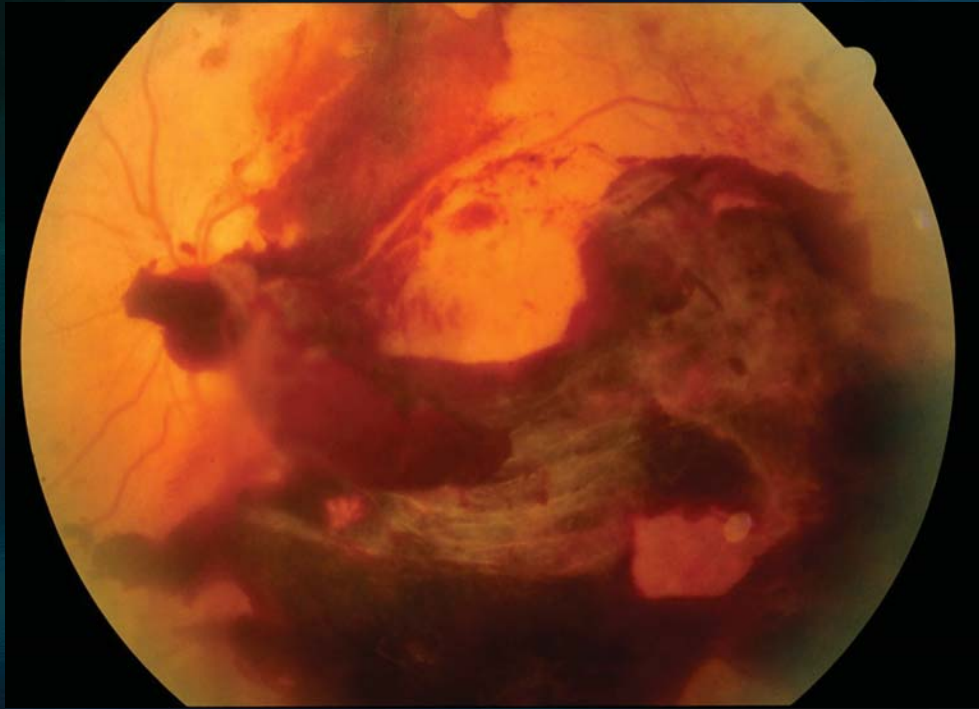
46 y/o male, DM

September 2009
VA: 20/20

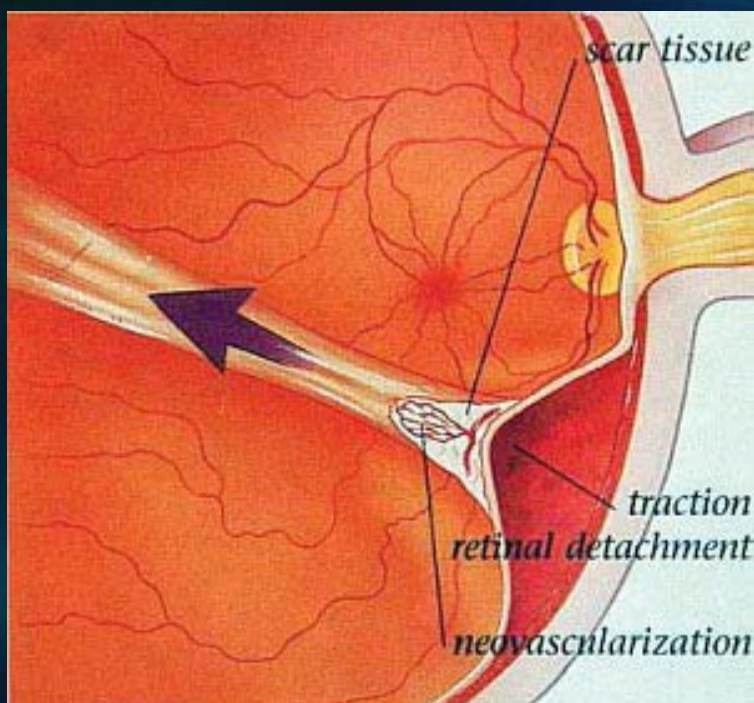
November 2010
VA: Counting Fingers



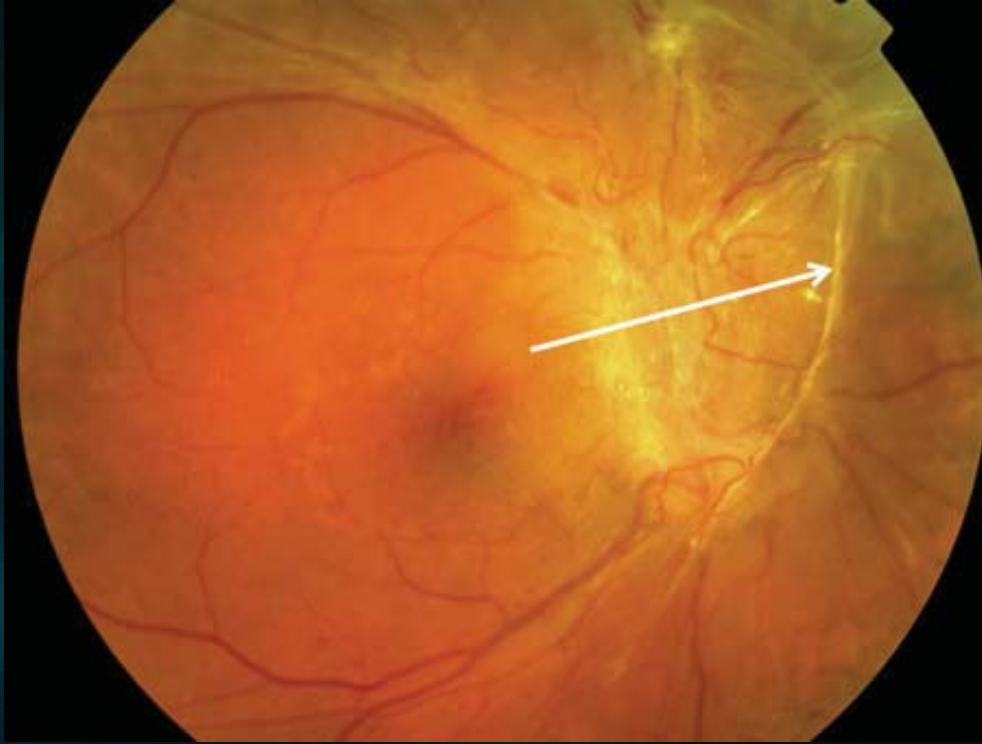
PDR – Vitreous Hemorrhage



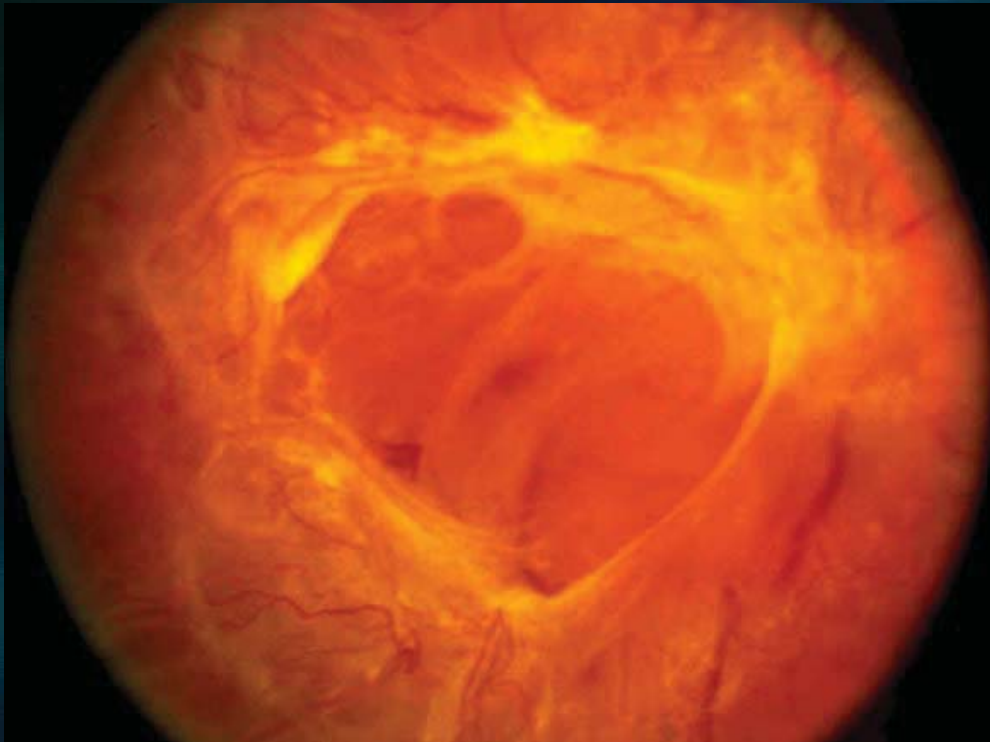
PDR – Tractional Retinal Detachment



PDR – Tractional Retinal Detachment



PDR – Tractional Retinal Detachment



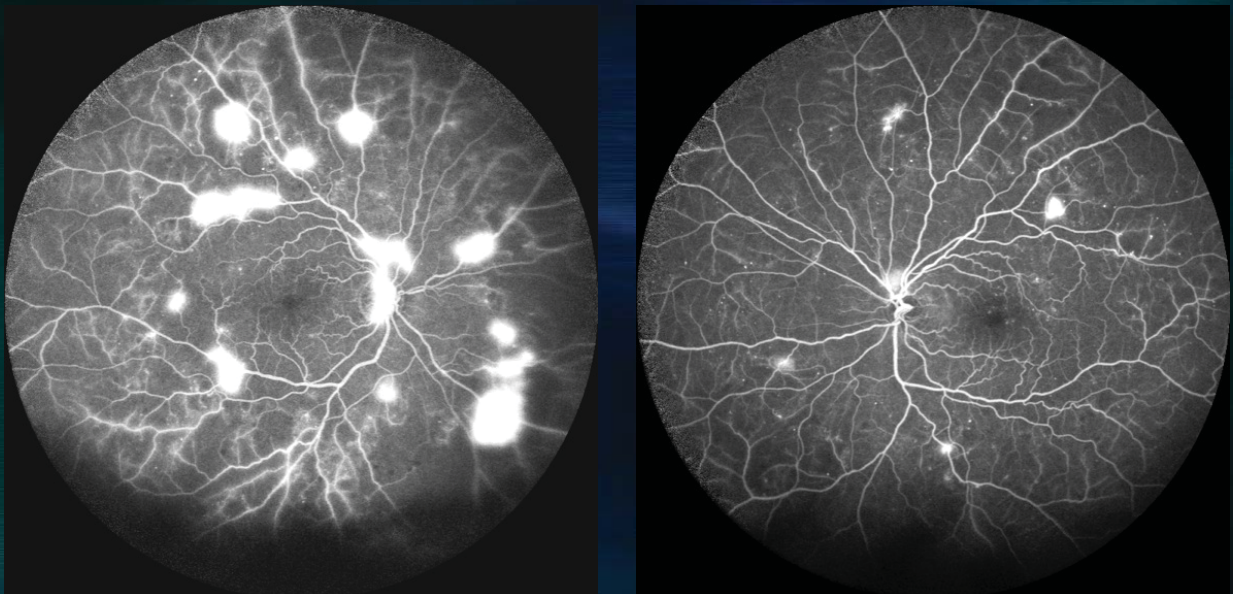
Diabetic Retinopathy: Treatments

- Blood sugar/blood pressure control
- Laser
- Pharmacotherapy
- Surgery

Panretinal Photocoagulation (DRS Study)



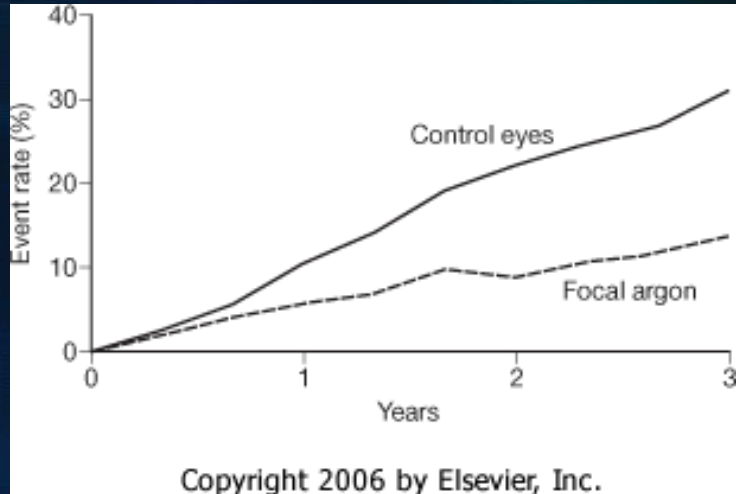
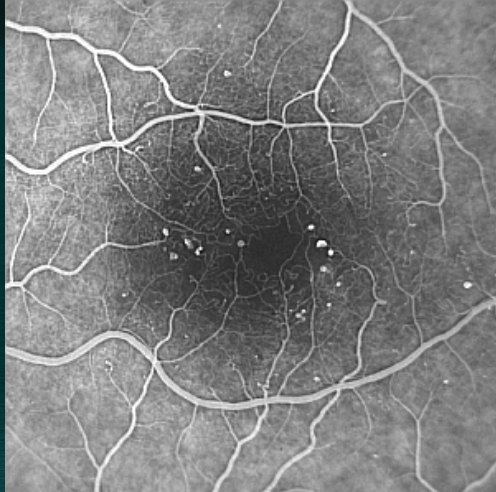
Ultra-wide Field Angiography



Earlier detection of PDR and targeted PRP

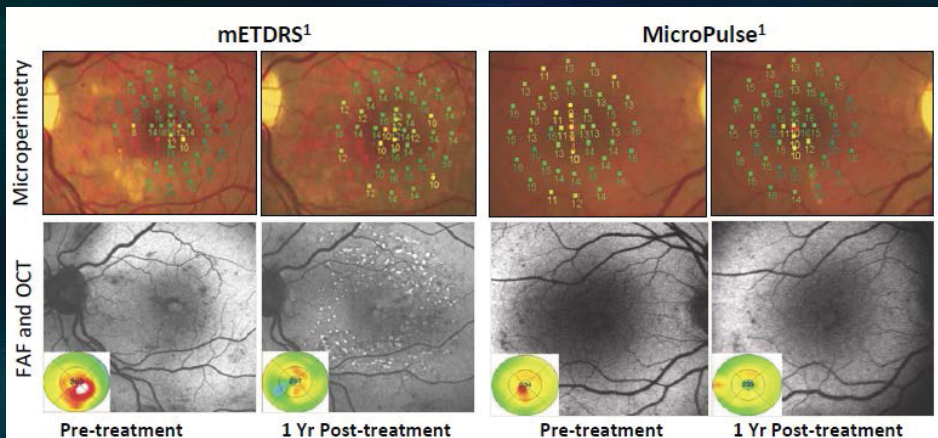
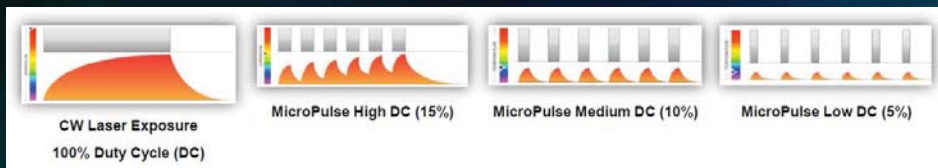
Diabetic macular edema: ETDRS Study

Focal argon laser reduces moderate vision loss



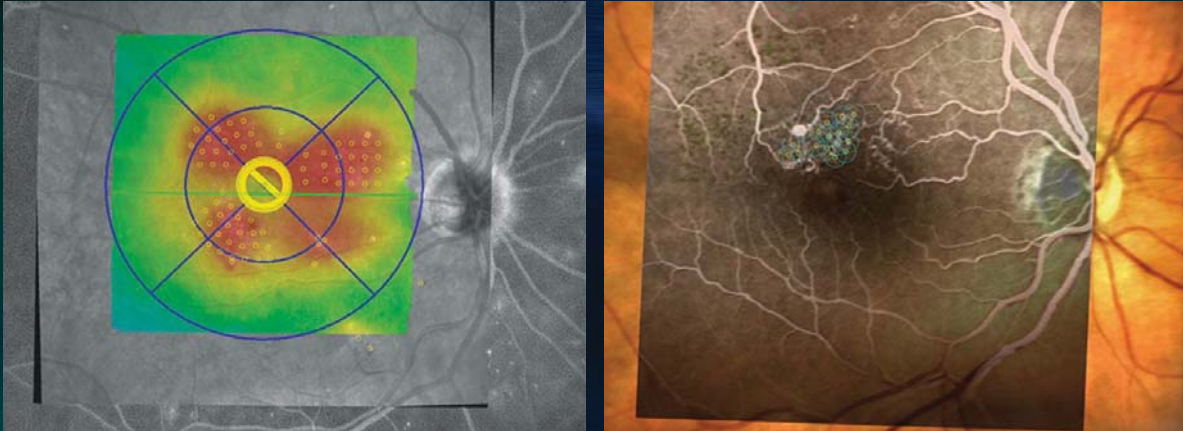
Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Arch Ophthalmol 1985; 103:1796-1806.

MicroPulse Laser for Diabetic Macular Edema

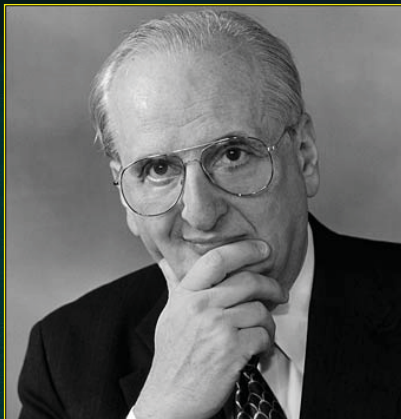


Vujosevic S, Bottega E, Casciano M, Pilotto E, Convento E, Midena E. 2010 *Retina* 30(6):908-16.

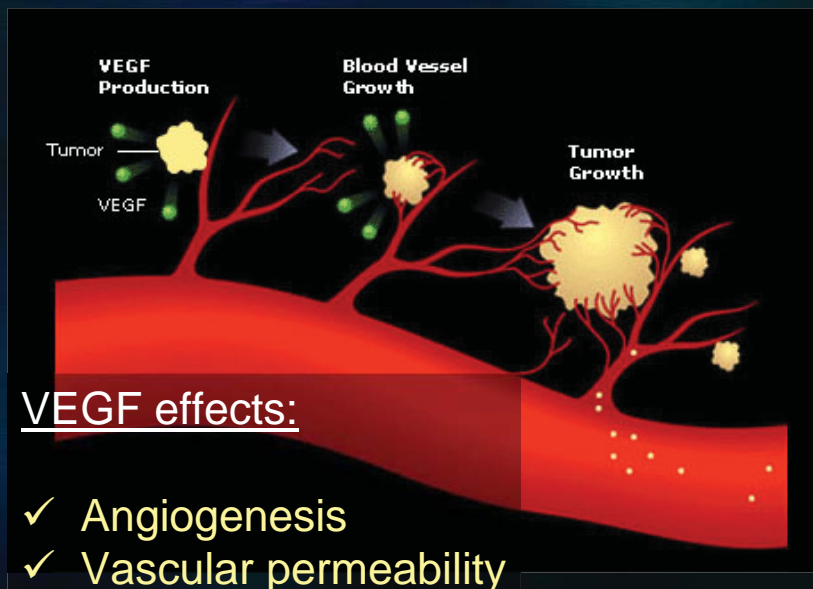
Navigated Pattern Laser: Navilas®



Vascular Endothelial Growth Factor (VEGF)



M. Judah Folkman, M.D.
(2/24/1933 – 1/14/2008)



VEGF-targeted therapy – Intravitreal injection therapy

- Anti-VEGF agents

- Aflibercept and Ranibizumab

- FDA approved for treatment of DME

- Bevacizumab

- Off-label for DME and other ophthalmic uses
 - Must be prepared through compounding process

- Pegaptanib

- Off-label for DME and investigational status is phase 2

Inflammation-targeted therapy

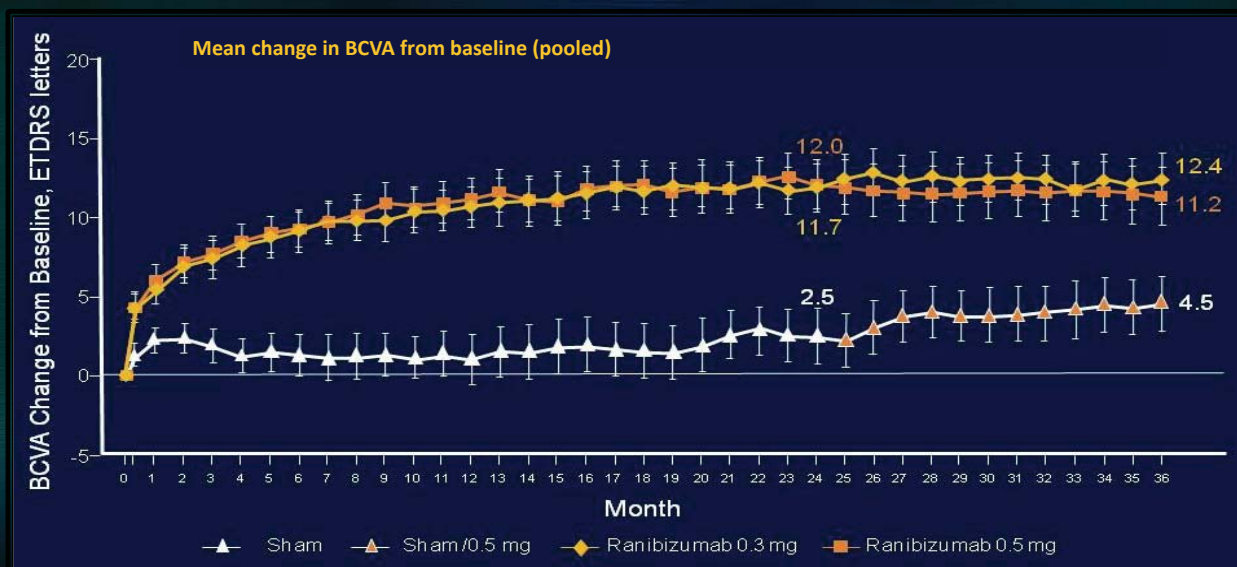
- Steroid injections

- Dexamethasone and Fluocinolone steroid implants for long term

FDA=US Food and Drug Administration; VEGF=vascular endothelial growth factor.

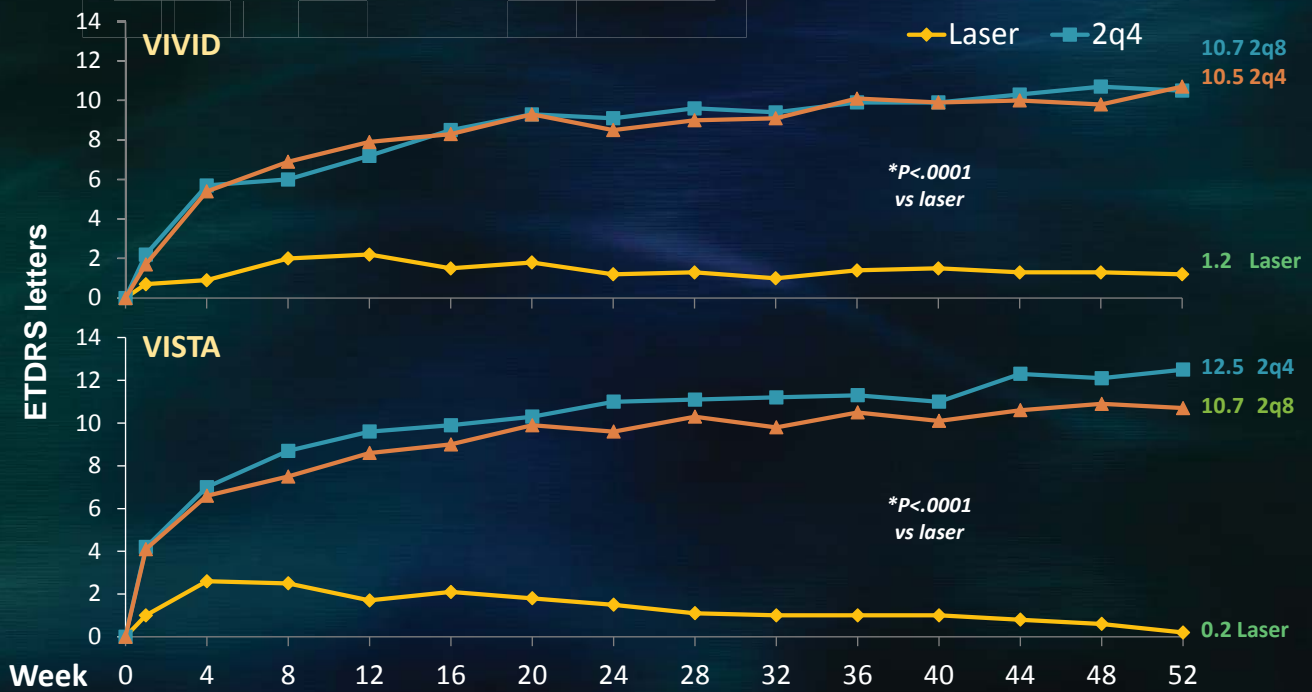
RISE and RIDE Trials: Ranibizumab for Diabetic Macular Edema

- Severe VA loss (15 letters) significantly reduced
- Rapid improvements in vision and anatomy maintained for 3 years



Brown DM et al; RISE and RIDE Research Group. *Ophthalmology*. 2013;120:2013-2022.

Anti-VEGF (Aflibercept) vs Laser

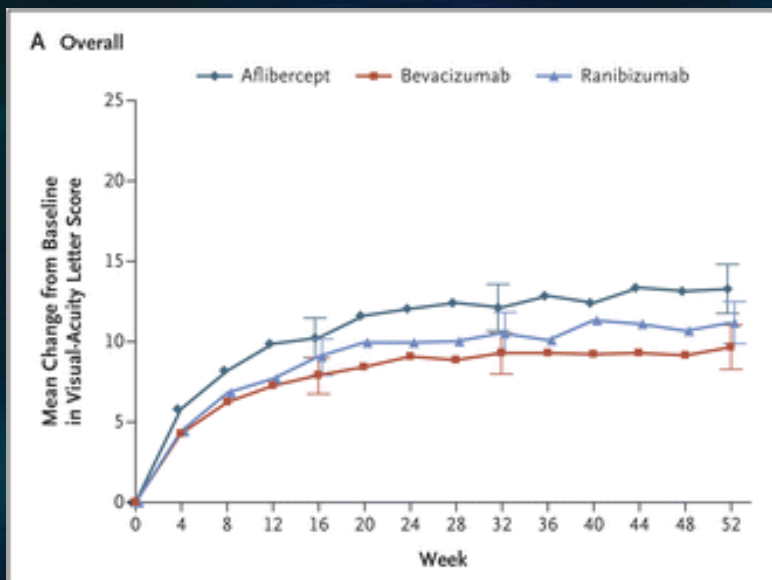


Korobelnik JF et al. *Ophthalmology*. 2014 Jul 8. [Epub ahead of print]

ETDRS: Compared to baseline; FAS; LOCF
 VISTA—Laser, n=154; 2q4, n=154; 2q8, n=151
 VIVID—Laser, n=132; 2q4, n=130; 2q8, n=135

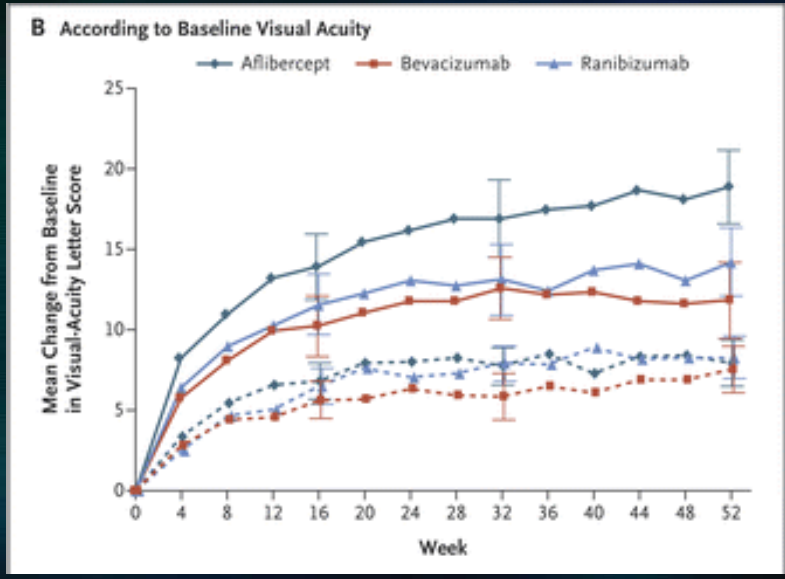
DRCR.net Protocol T

Aflibercept (Eylea) vs. bevacizumab (Avastin) vs. ranibizumab (Lucentis) for DME



DRCR.net Protocol T

- If starting VA impairment is mild, similar efficacies
- If starting VA is worse, Eylea performs better



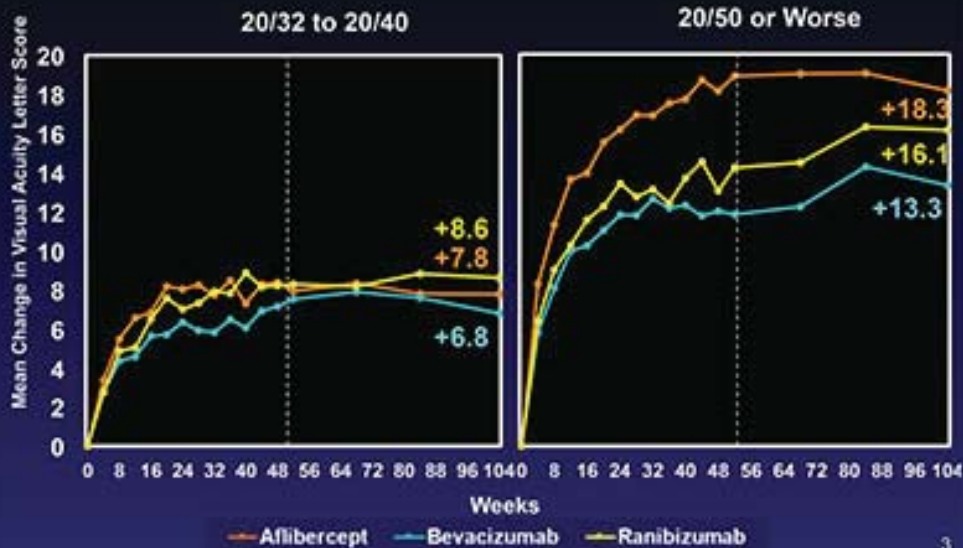
BL VA 20/50 or worse

BL VA better than 20/50

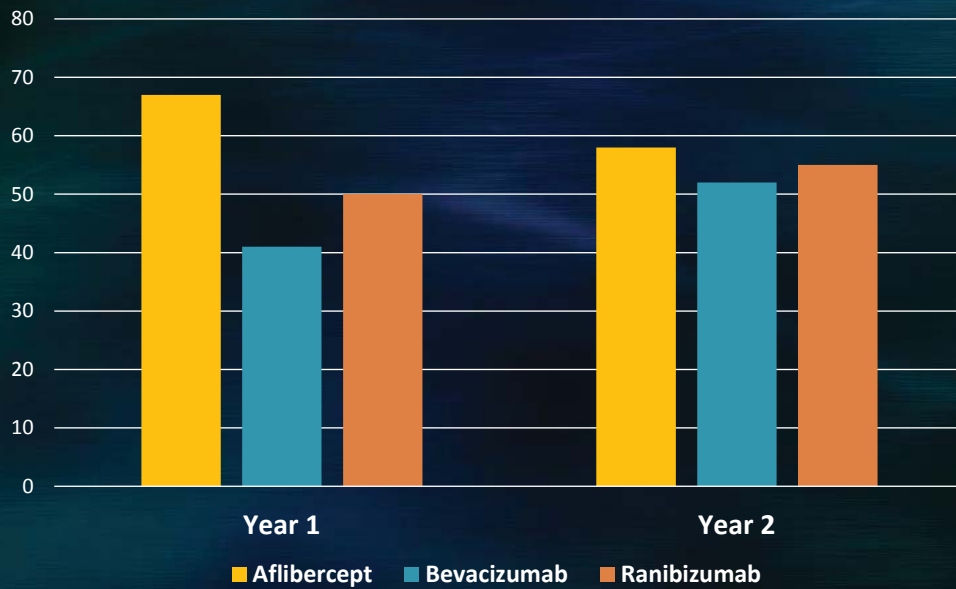
The Diabetic Retinopathy Clinical Research Network. N Engl J Med 2015; 372:1193-1203

DRCR.net Protocol T: Year 2

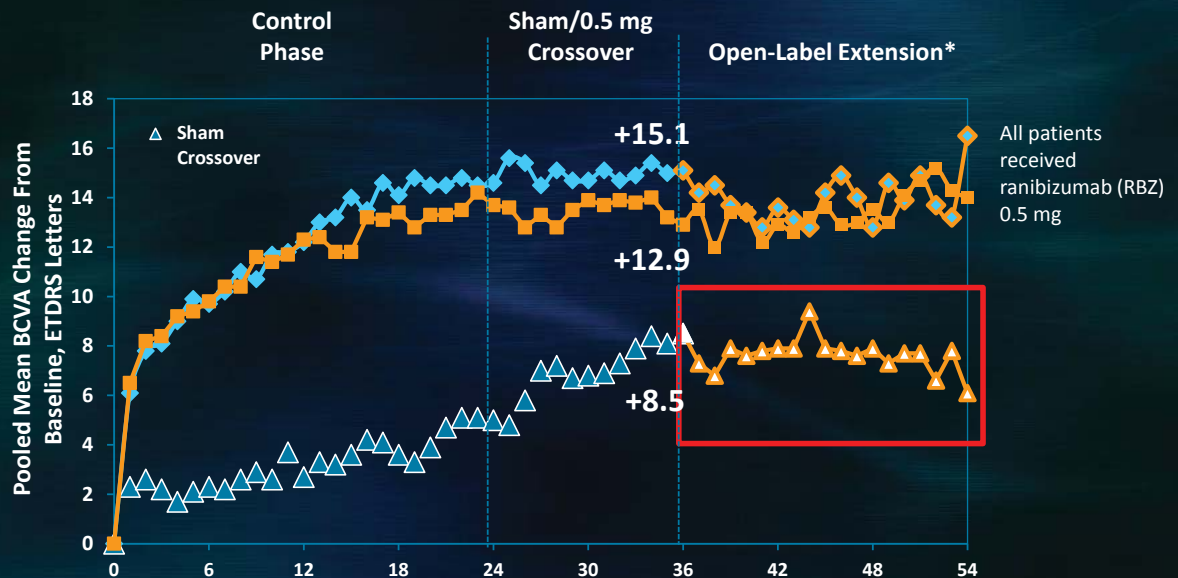
Mean Change in Visual Acuity Over 2 Years By Baseline Visual Acuity Subgroup



Protocol T: ≥ 15 Letters VA Gain



Early Treatment: Better Outcomes



Patients, n [†]	0	6	12	18	24	30	36	42	48	54
Sham crossover	158	158	155	159	152	161	115	95	47	
0.3 mg RBZ	168	168	167	170	168	172	126	101	39	
0.5 mg RBZ	163	161	162	163	163	164	124	82	35	

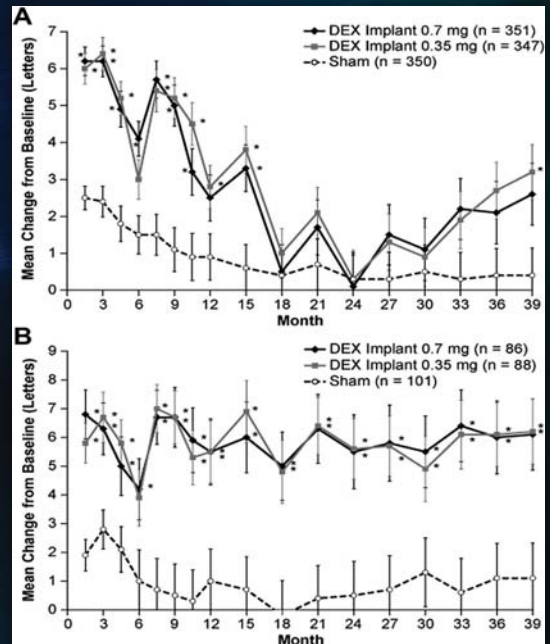
Intravitreal Steroid Implants

Slow-release implants

Dexamethasone (Ozurdex) Up to 6 months per implant

THE RETINA PARTNERS

Contains 0.7 mg dexamethasone in the NOVADUR™ solid polymer drug delivery system.

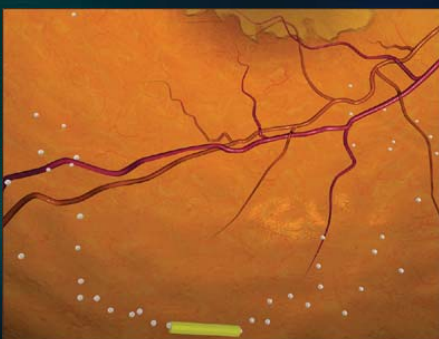
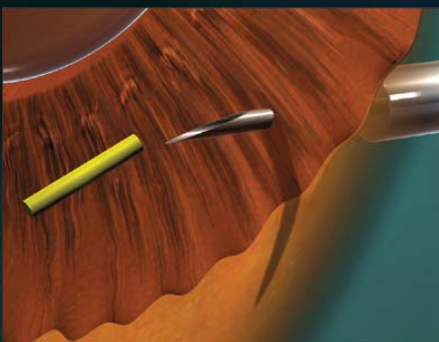


1. Ozurdex [package insert]. Irvine, CA: Allergan, Inc; 2014.
2. Ozurdex MEAD Study Group. Ophthalmology. 2014; Published online June 4, 2014.

Fluocinolone acetonide injectable implant (Iluvien)

Up to 3 years per implant

THE RETINA PARTNERS



Steroid Implant AE's

Dexamethasone (0.7mg)

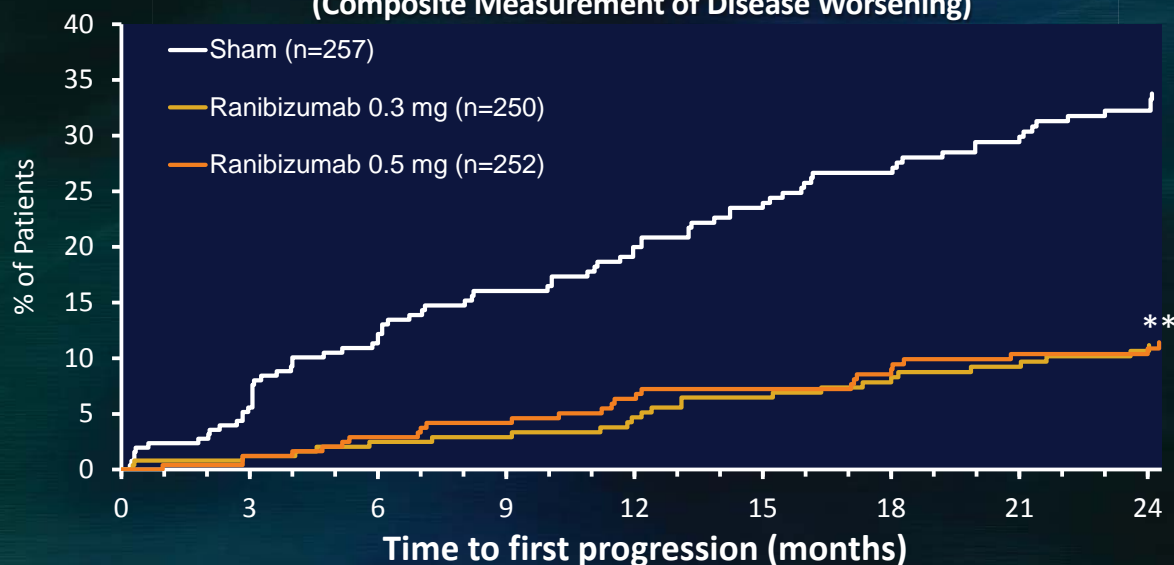
- IOP- 41.5% requiring medication
- Overall Cataract AEs- 67.9%

Fluocinolone

- IOP - 35.9% to 41.8% requiring medication
- Overall Cataract AEs– 75%-86%

Ozurdex MEAD Study Group. *Ophthalmology*. 2014; Published online June 4, 2014
 Cunha Vas J, et al. *Ophthalmology*. 2014; 121(10):1892-1903.

Reduction in Risk for Development of PDR¹ (Composite Measurement of Disease Worsening)



Cumulative probabilities calculated using the Kaplan-Meier method. Progression was defined by (1) progression from NPDR (DR severity level <60) at baseline to PDR (DR severity level ≥60) at a later time point, (2) need for PRP laser, (3) vitreous hemorrhage (AE or slit lamp grade 0 at baseline to >0 at a later time point, (4) cases identified by ophthalmoscopy, (5) vitrectomy, (6) iris neovascularization AE, or (7) retinal neovascularization AE.
 *P<.001 vs sham.

AE=adverse event.

DRCR.net Protocol S

Ranibizumab (Lucentis) vs. PRP for PDR (N=394)

Exploring injections as an alternative to laser for neovascularization

PRP: Stable vision at 2 years

Lucentis: Vision gain (2.8 vs. 0.2 Letters; $p < 0.001$)
Less DME
Less VF loss
Fewer vitrectomies

The Diabetic Retinopathy Clinical Research Network. Presented at the Annual Meeting of the American Academy of Ophthalmology. Nov 2015; Las Vegas, NV.

Anti-VEGF Therapy for DR without DME

2017:

Ranibizumab approved for treatment of all forms of diabetic retinopathy with or without macular edema.

PANORAMA:

Ongoing trial evaluating aflibercept for treatment of diabetic retinopathy without macular edema.

DME: New Treatments

PALM Study: Phase 2b (n = 151)

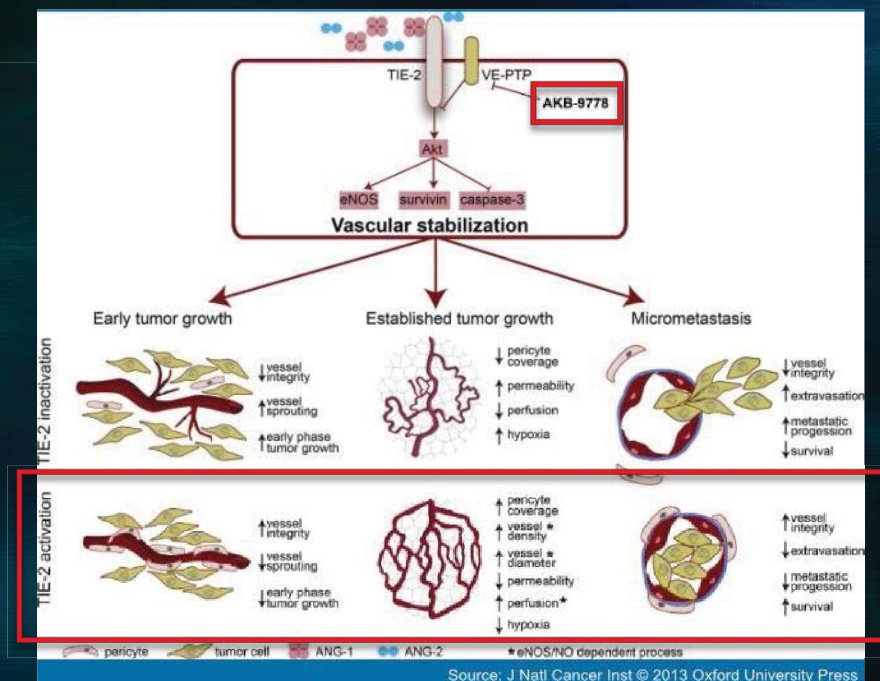
New Anti-VEGF Agent

Abicipar pegol (Allergan) injected once every 8 or 12 weeks for DME

Anatomic and functional results comparable with Ranibizumab monthly



DME: Novel Pathways?



DME: Novel Pathways?

TIME-2 Phase 2a Study (N=144)

Novel agent: AKB-9778
 VE-PTP inhibitor (subcutaneous)

Groups: Combination (AKB-9778 + Lucentis)

 Lucentis monotherapy

 AKB-9778 monotherapy

TIME-2 Phase 2a Study (N=144)

Results (AKB-9778 vs. Lucentis vs. combination)

Reduction in DME:	Combination	Lucentis
	-164.4±24.2 μm	-110.4±17.2 μm

Vision gain ≥ 15 letters:	20.8%	17.0%
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DRSS ≥ 2 step gain:	AKB-9778	Lucentis
	11.4%	4.2%

Diabetic Retinopathy and Diabetic Macular Edema

Current and Upcoming Clinical Trials

PANORAMA (Regeneron)

Aflibercept vs. Standard of care for Severe NPDR without DME

ACACIA (Allergan)

Abicipar vs. Ranibizumab for DME

BOULEVARD (Roche/Genentech)

RO6867461/RG7716 vs. Ranibizumab for DME

Other Potential Future Therapies for DME

Brolucizumab (Alcon/Novartis):

Anti-VEGF

HAWK/HARRIER Trials: Favorable results vs. Aflibercept in AMD

Conbercept (Khanghong Biotech):

Anti-VEGF

Pan-VEGF blockade: Comparable with Ranibizumab for DME

OPT-302 (Ophthea):

Anti-VEGF

Currently enrolling for AMD

Luminate (Allegro Ophthalmics):

Anti-Integrin

First in class; DEL MAR Trial: Comparable with Bevacizumab for DME

KVD001 (KaVista Pharmaceuticals):

Anti-Kallikrein

VEGF-independent mechanism of action; Phase I

CLS-TA (Clearside Biomedical):

Suprachoroidal Triamcinolone

HULK Trial: Sustained anatomic improvement 6 months after single treatment

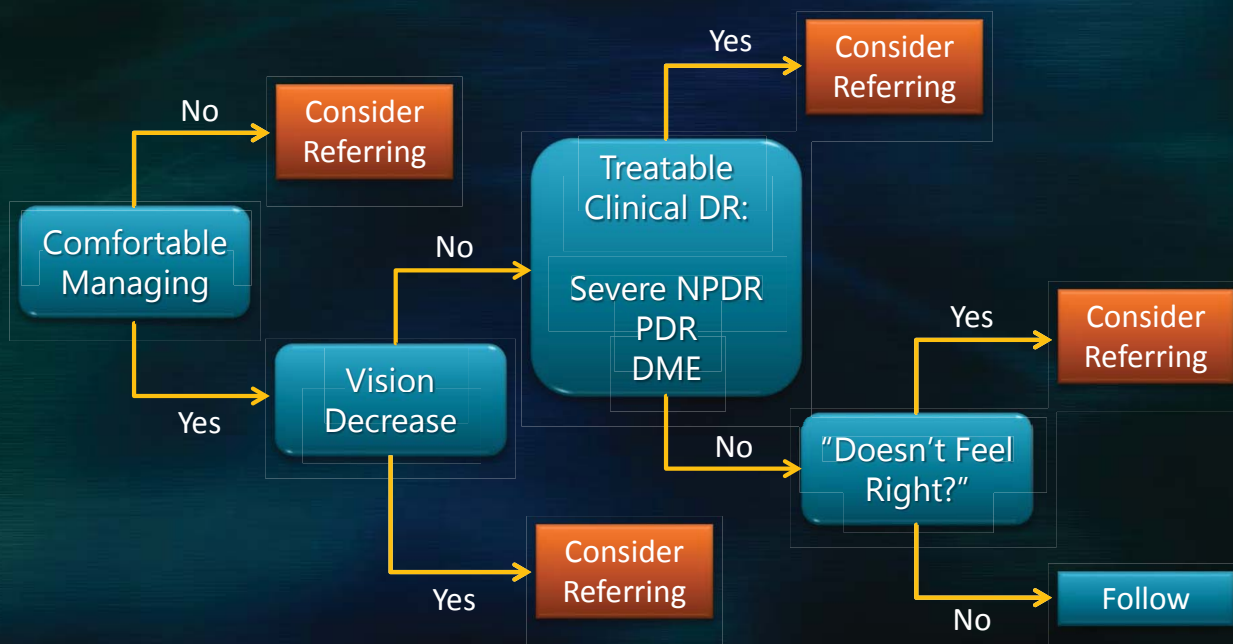
- There are approximately **1500 retina specialists** in the United States
- There are approximately **18,000 ophthalmologists** in the United States
- There are approximately **40,000 optometrists** in the United States
- **85% of all comprehensive eye exams are performed by optometrists**

United States Department of Labor. Occupational Employment Statistics. <http://www.bls.gov/oes/current/oes291041.htm>. Accessed October 22, 2014.

Smart DR. *Physician Characteristics and Distribution in the US 2011*. Chicago, IL: American Medical Association; 2010.

The State of the Optometric Profession: 2013. http://www.reviewob.com/data/sites/1/soop_070120134.pdf. Accessed October 22, 2014.

Diabetic Retinopathy: When to Seek 2nd Opinion





Diabetic Retinopathy/DME: Key Points

- Optometrists are the front line in screening for DR and DME
- More, better and safer treatment options: better outcomes
- Early intervention preserves more vision