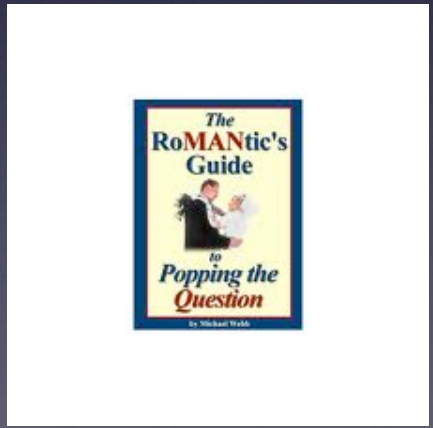
BOCA RATON REGIONAL HOSPITAL

ADVANCING THE BOUNDARIES OF MEDICINE

RETINA GROUP OF FLORIDA

ASK ????????



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RGF Communication

- www.retinagroupflorida.com
- E-mail = Lhalperin@mac.com
- Cell = 561-504-3666
- RGF Partner available 24/7/365

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Barry S. Taney, M.D.
Brown University
Mount Sinai School of Medicine
U. of Cincinnati Dept. of Ophthalmology
Retina Fellow Mayo Clinic

Lawrence S. Halperin, M.D.
Tufts University
U. of Pennsylvania School of Medicine
Washington Univ. Dept. of Ophthalmology
Retina Fellow Barnes Retina Institute

W. Scott Thompson, M.D.
Dartmouth College
Baylor College of Medicine
Bascom Palmer Eye Institute
Retina Fellow Bascom Palmer

Patrick E. Rubsamen, M.D.
Texas A&M University
U. of Texas Southwestern Medical School
Bascom Palmer Eye Institute
Retina Fellow Bascom Palmer

Scott R. Anagnoste, M.D.
Princeton University
U. of Medicine & Dentistry of New Jersey
Manhattan Eye, Ear & Throat Hospital
Retina Fellow Bascom Palmer

Krista D. Rosenberg, M.D.
University of California
Medical College of Pennsylvania
Bascom Palmer Eye Institute
Retina Fellow Bascom Palmer

Mandeep S. Dhalla, M.D.
University of Miami
U. of Miami School of Medicine
Henry Ford Hosp, Dept. of Ophthalmology
Retina Fellow Barnes Retina Institute

Kevin Kelly, M.D.
Rutgers University
UMDNJ – Rutgers Medical School
Kings County Hospital Center
Retina Fellow Baylor College of Medicine

Mario del Cid, M.D.
Florida International University
Tulane University
University of Texas Health Science Center
Retina Fellow Cincinnati Eye Center

Darin R. Goldman, M.D.
University of Florida
University of Florida
UCLA Jules Stein Ophthalmology
Retina Fellow Tufts New England Eye Center

Eduardo Uchiyama, M.D.
Universidad de San Martin de Porres - Lima, Peru
Univ Texas Southwestern
Dept of Ophthalmology
Retina Fellow Univ Texas Southwestern
Uveitis Fellow Massachusetts Eye and Ear/
Harvard Medical School

National, Multi-Centered, FDA approved, FDA monitored, CLINICAL TRIALS

Wet AMD

* CATT FS (Follow Up Study)
* Eclipse (Ophthotech)
* Investigator Sponsored Trial (Genentech)

CATT (National Eye Institute)
HARBOR (Genentech)
CABERNET (Neovista)
RACE (Alcon)
REGRESS (Ophthotech)
Anecortave for wet-AMD (Alcon)
Ozurdex for AMD (Allergan)
ANCHOR (Genentech)
MARINA (Genentech)
HORIZON (Genentech)
SAILOR (Genentech)
DENALI (Novartis)
SNET-2 (Miravant PDT)
VIO (QLT)
VIO OLD (QLT)
VIO OLS (QLT)
Macugen vs. PDT (Eyetech)
VisIT (Novartis)
Macugen EPO1010 (Eyetech)
Pfizer phase 1
SIRIUS (Allergan)
Re-view (Regeneron)
VERTACL (National Eye Institute)
EMERALD (MacuSight)
Macugen maintenance (Eyetech)
Squalamine (Genaera)
Cellgate phase 1 & 2
Visudyne + Lucentis (Novartis)
CLEAR-IT (Regeneron)
Pazopanib (GlaxoSmithKline)
VIEW-1 (Regeneron)

Dry AMD

AREDS-2
GATE (Alcon)
GAP (Alcon)
AART (Alcon)
CNTF-2 (Neurotech)
Fenretinide (Sirion)

Diabetic Retinopathy

* VISTA (Regeneron)
* DRCR- T
* Aerpio DME

READ-3 (IST - Genentech)
RIDE (Genentech)
FAME (Alimera)
IDEAL(IST)
Ozurdex (Allergan)
DRCR- A, B, H, I, J, K, O
DRCR- M
ACUITY (Acuity)
Protein Kinase C Inhibitor (Eli Lilly)
DIAMOND (MacuSight)
RACE (Cand5, Acuity)
EOP 1013 (Eyetech/Pfizer)
DA VINCI (Regeneron)

Retinal Vein Occlusion

* SCORE 2 (CRVO)

COPERNICUS (Regeneron)
Ozurdex for Vein Occlusion (Allergan)
BRAVO (Genentech)
CRUISE (Genentech)
SCORE (JAEB Center)
Macugen for CRVO (Eyetech)
HORIZON (Genentech)

Geographic Atrophy

* OLE (Genentech)
* TOGA (University of Virginia)
* Spectri (Genentech)

MAHALO (Genentech)

Other Trials

Retisert for Uveitis (Bausch and Lomb)
Silicone Oil (for RD - Kochen, Richard James)
Vitrase (for vitreous hemorrhage)
Vitrasert (for CMV retinitis)
Perfluoron (for RD - Infinitech)
CNTF-4 (Neurotech for RP)
CNTF-3 (Neurotech for RP)
Monitor for Ophthalmic Complications (Schering Plough)
Monitor for Ophthalmic Complications (Merck)
Immusol for PVR

* = Active Trial

Lawrence Halperin, MD

Education

Tufts University, BS
University of Pennsylvania, MD
Washington University Department of Ophthalmology
Ophthalmology Residency
Retina/Vitreous medical and surgical Fellowship

Affiliations

- Affiliate Associate Professor, Charles E. Schmidt College of Medicine, Florida Atlantic University
- Assistant Professor of Ophthalmology at the Miller School of Medicine at the University of Miami

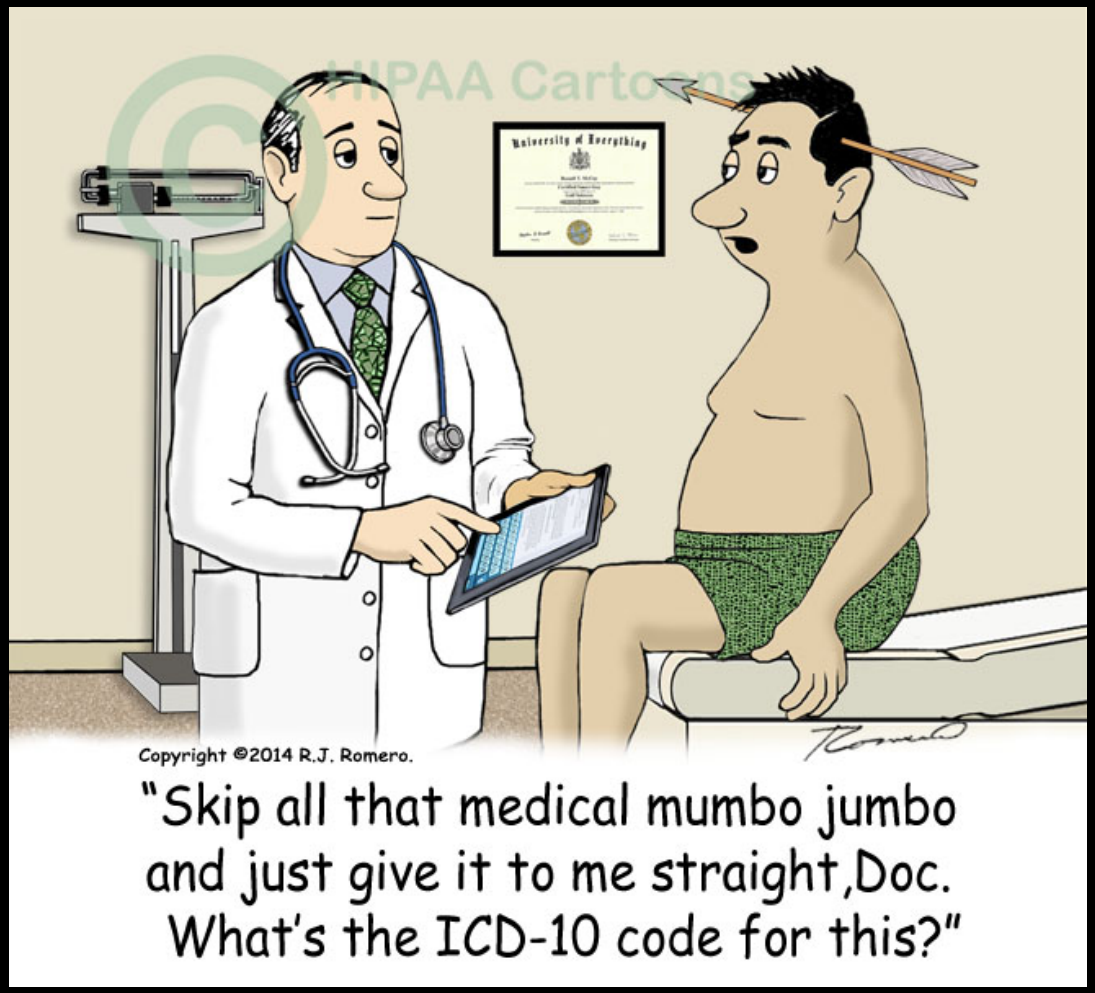
Financial Disclosures

- Covalent stock holder
- Regeneron Consultant
- Research support

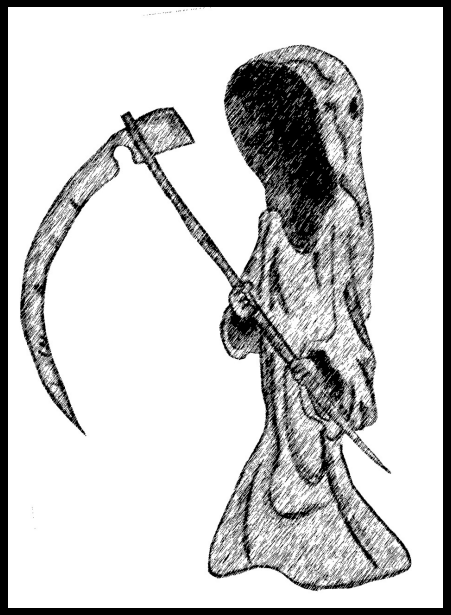
Armageddon Has Come

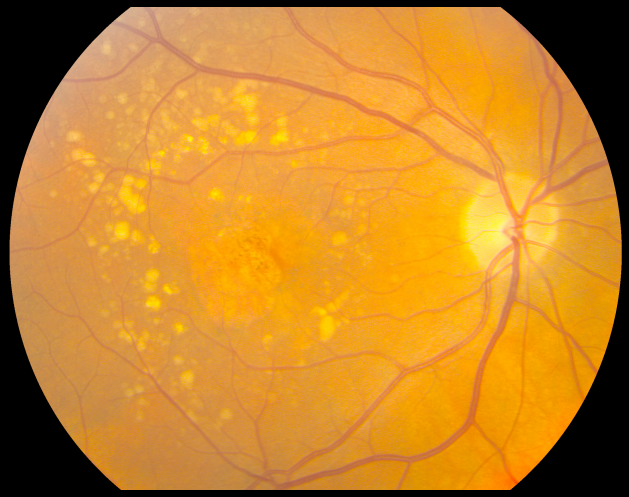
RIP Retina Group of Florida

X72.XXXA (by gun, initial)
X81.1XXA (by jumping or lying in front of a moving train, initial)
X81.1XXD (by jumping or lying in front of a moving train, subsequent)


HIPAA Cartoons
University of Everything
Copyright ©2014 R.J. Romero.
"Skip all that medical mumbo jumbo and just give it to me straight,Doc. What's the ICD-10 code for this?"

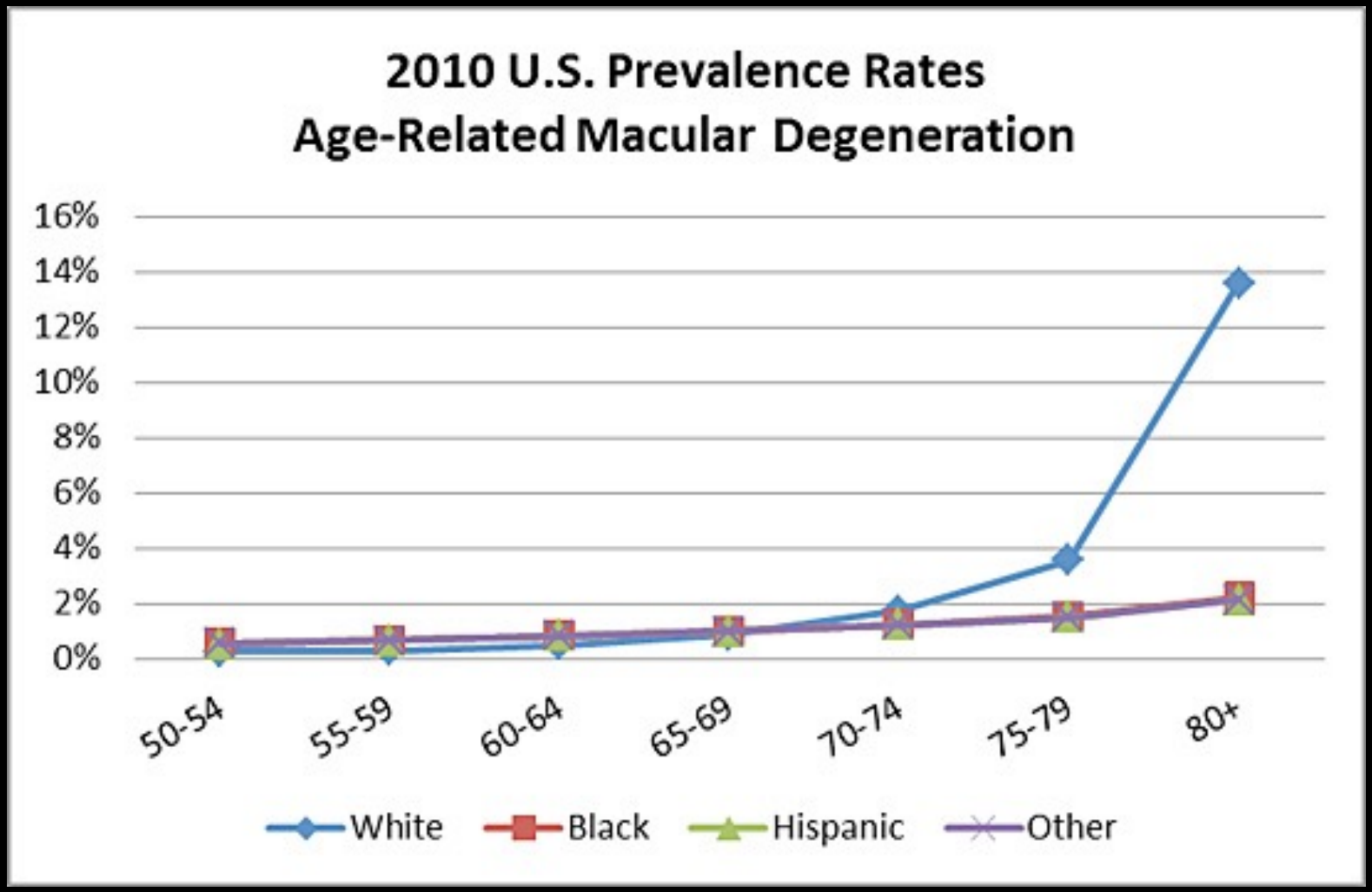
Things we cannot avoid





AMD

- 7.3 million patients (6.1%) 40 years or older have early AMD (large retinal drusen)
- 1.75 million (1.5%) have late AMD (GA or CNV)
- 30% of patients 75 and older have early AMD
- 7% have late AMD



AMD Statistics

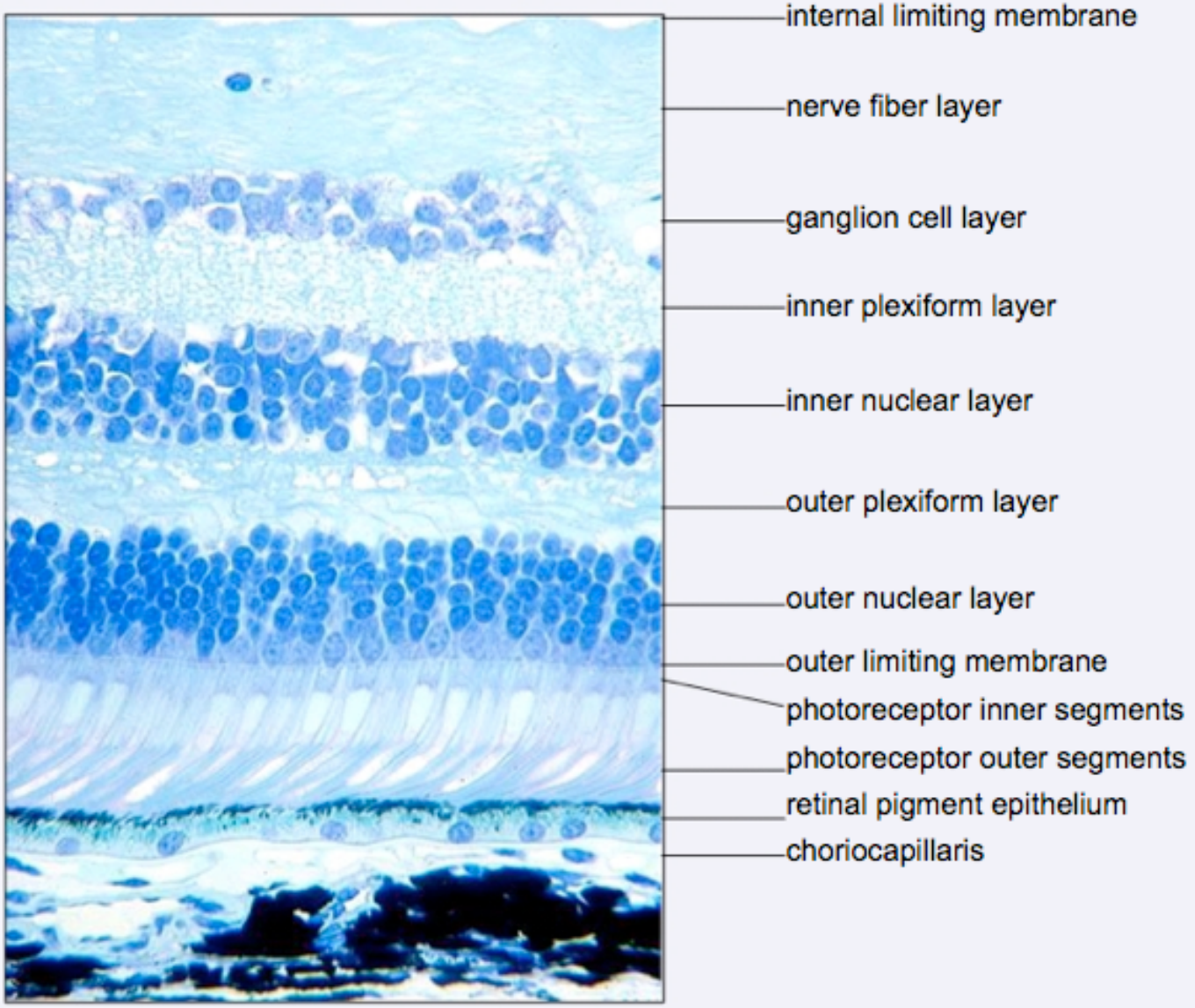
RISK FACTORS

- Questionable
  - Smoking
  - Family History
  - HTN
  - Cataract Surgery
  - Light Exposure in 20's and 30's
  - Alcohol
- None
  - Statins

Overview

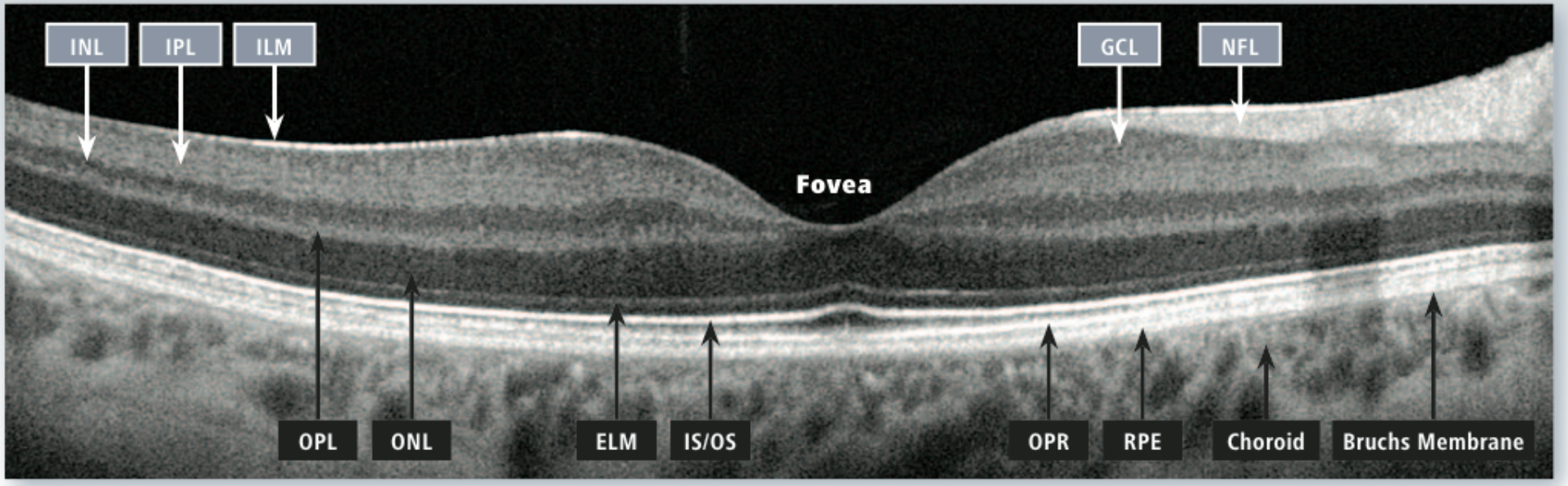
1. Current State of Wet Age-Related Macular Degeneration (AMD)

2. New Therapy in Wet AMD
   - Longer-Acting Treatments
   - Combination Treatments
   - Gene Therapy


internal limiting membrane
nerve fiber layer
ganglion cell layer
inner plexiform layer
inner nuclear layer
outer plexiform layer
outer nuclear layer
outer limiting membrane
photoreceptor inner segments
photoreceptor outer segments
retinal pigment epithelium
choriocapillaris

OCT INTERPRETATION

OPTICAL COHERENCETOMOGRAPHY



ILM: *Inner limiting membrane*
IPL: *Inner plexiform layer*
INL: *Inner nuclear layer*
OPL: *Outer plexiform layer*
ONL: *Outer nuclear layer*

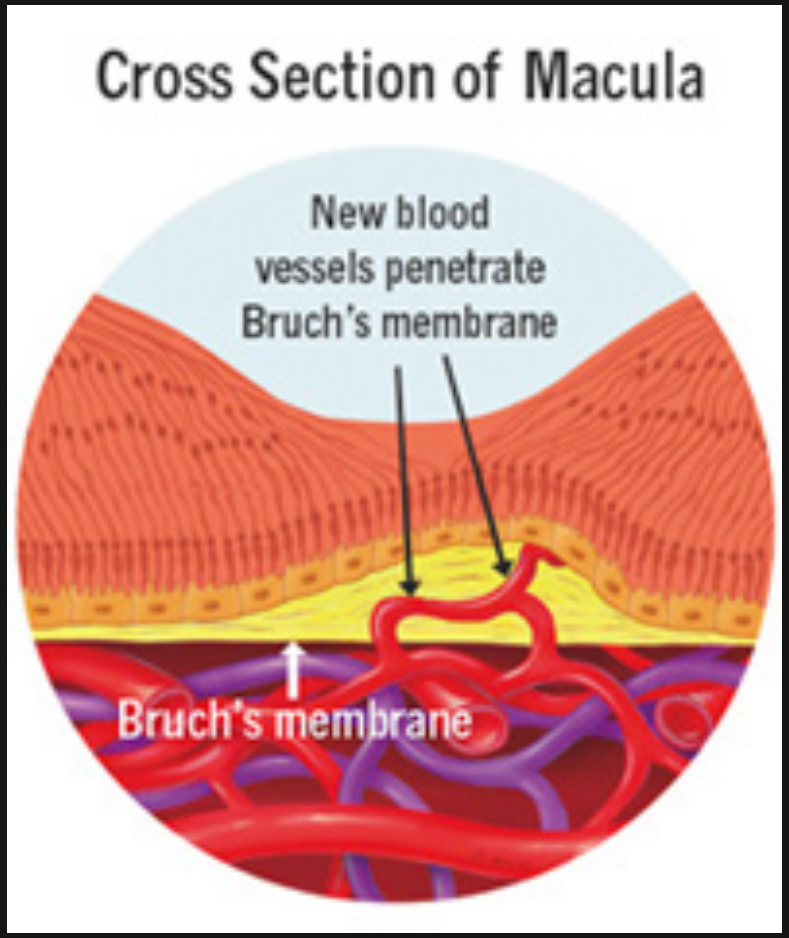
ELM: *External limiting membrane*
IS/OS: *Junction of inner and outer photoreceptor segments*
OPR: *Outer segment PR/RPE complex*

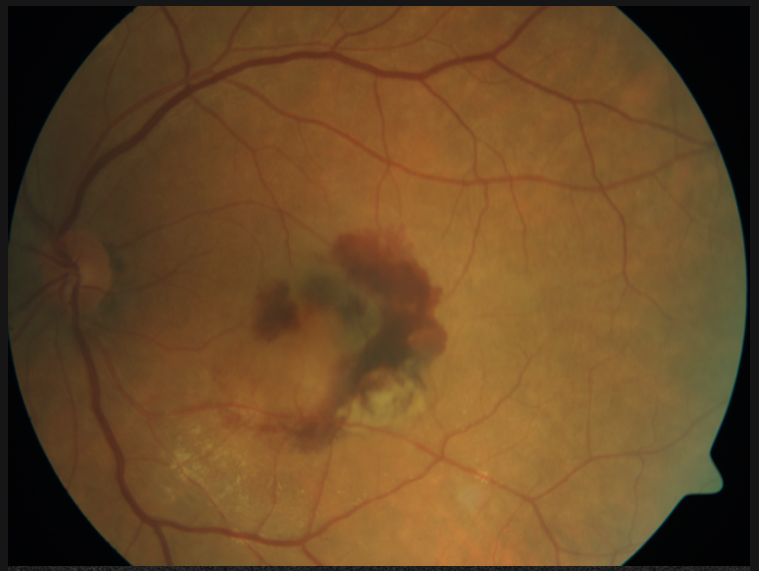
NFL: *Nerve fiber layer*
GCL: *Ganglion cell layer*
RPE: *Retinal pigment epithelium + Bruch´s Membrane*

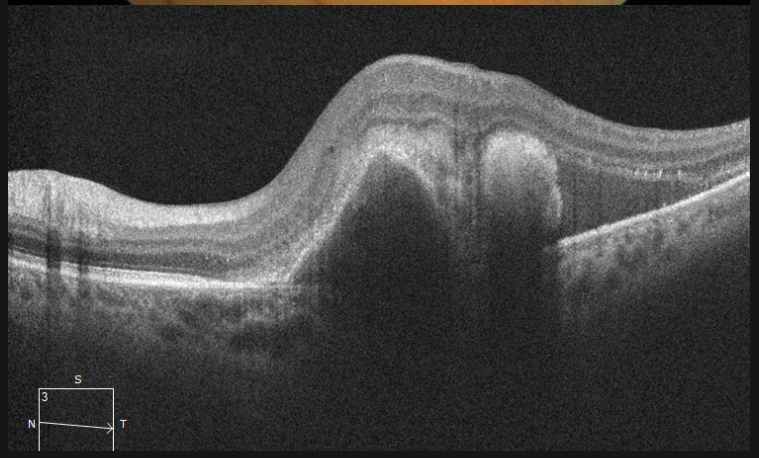
ANGIOGENESIS

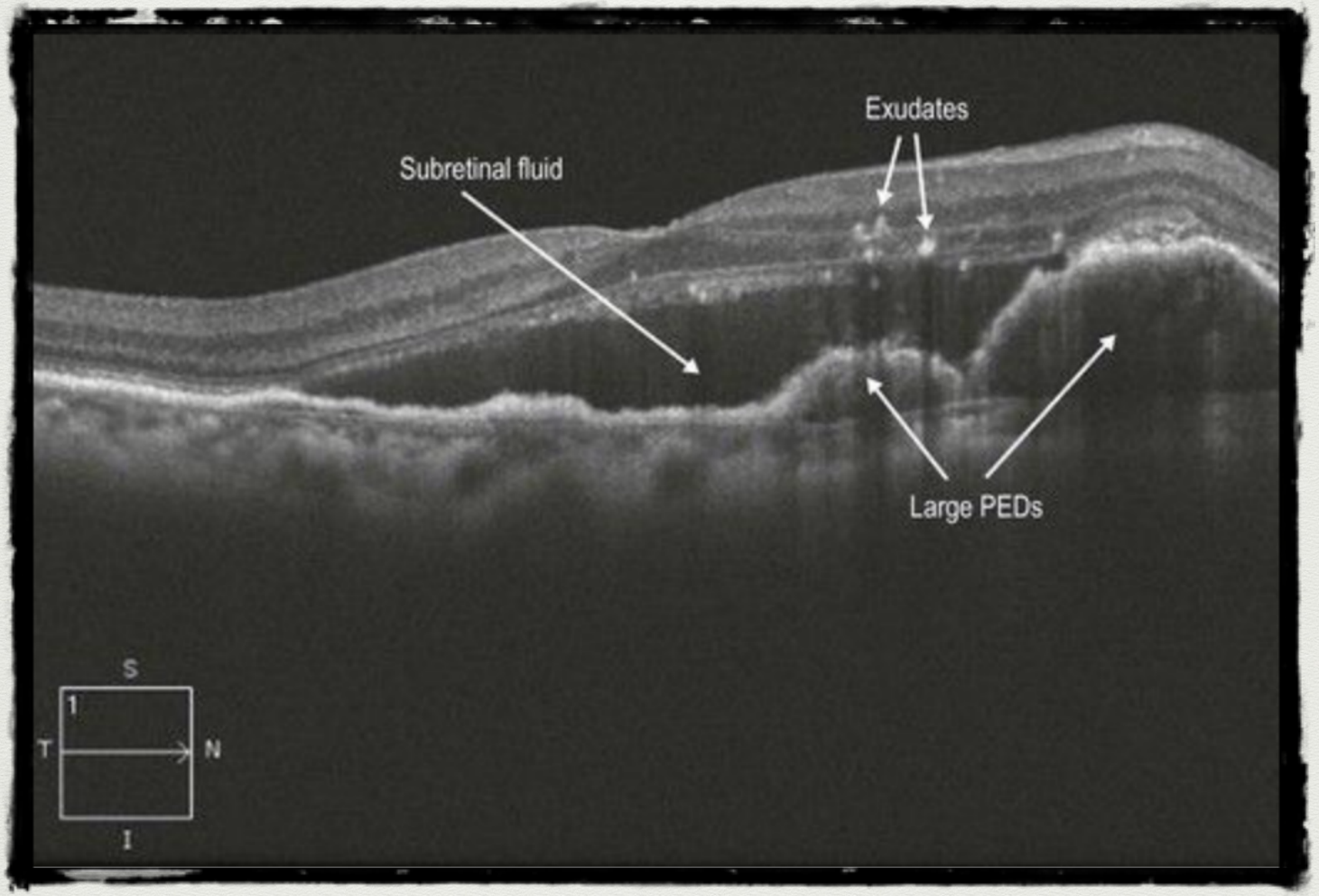
- Vascular component
- Extravascular component
- Finding a treatment combination that attacks a component in more than one way or both components simultaneously is the key

CNV


Cross Section of Macula
New blood vessels penetrate Bruch's membrane
Bruch's membrane

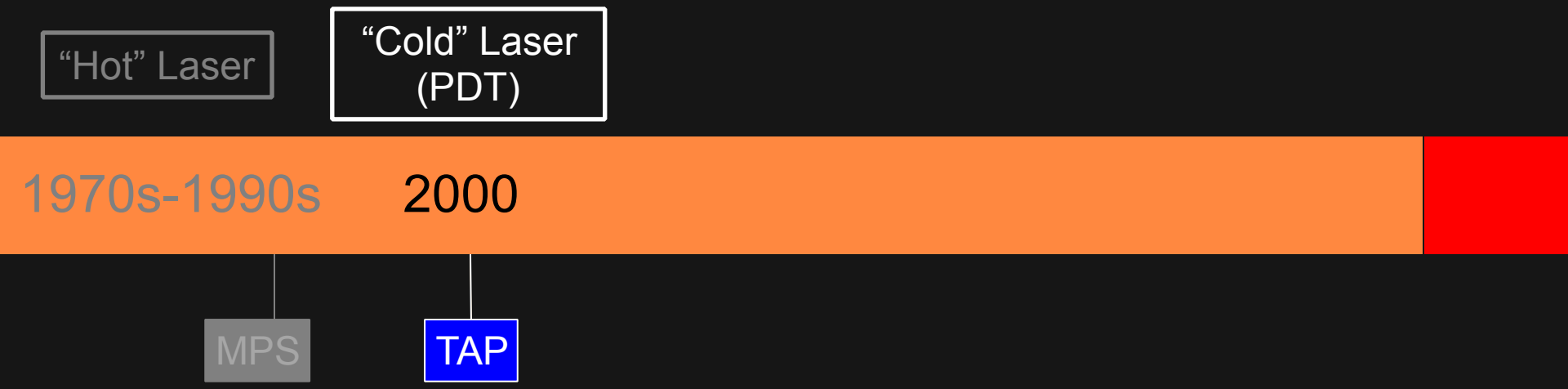



S
3
N
T

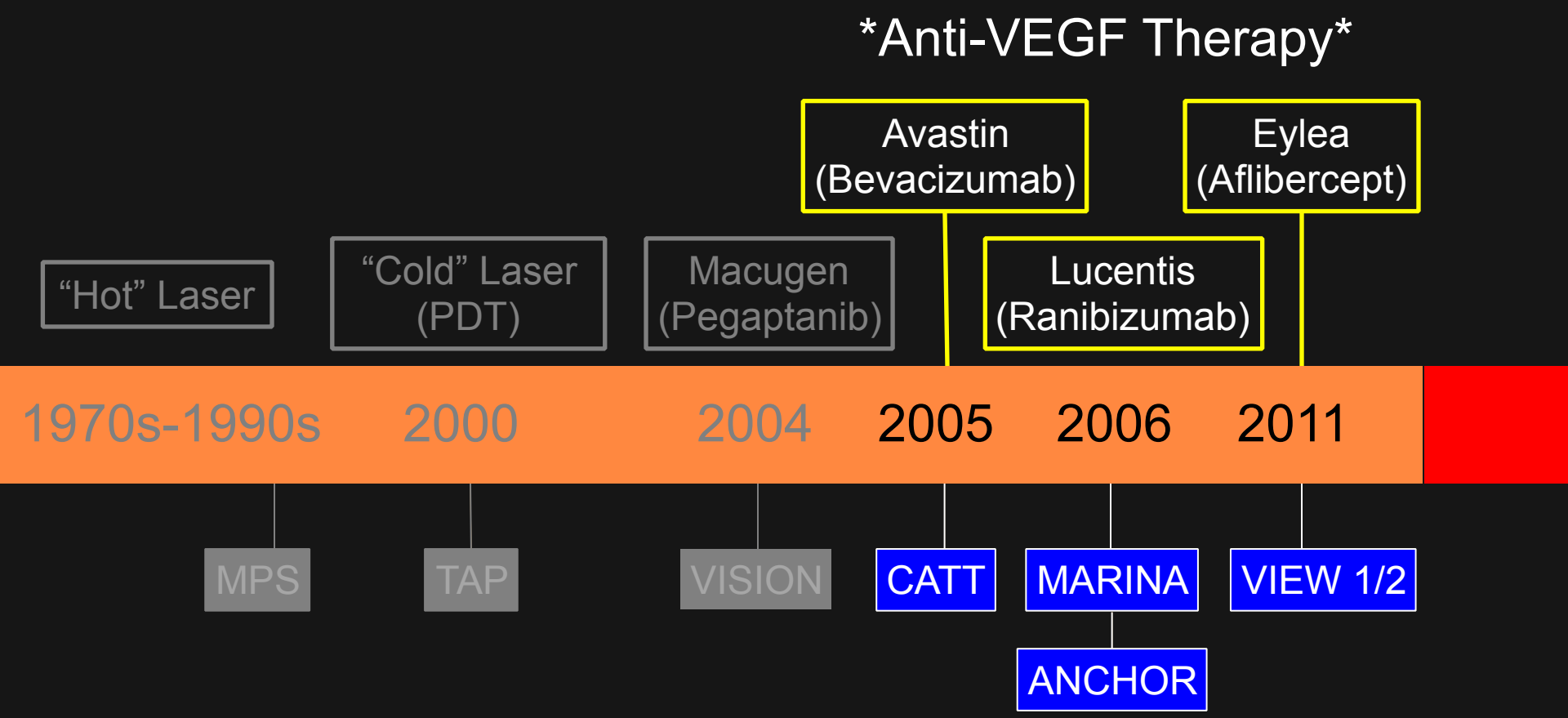

Exudates
Subretinal fluid
Large PEDs
S
1
T
N
I

Treatment for Wet AMD

Treatment for Wet AMD



Treatment for Wet AMD

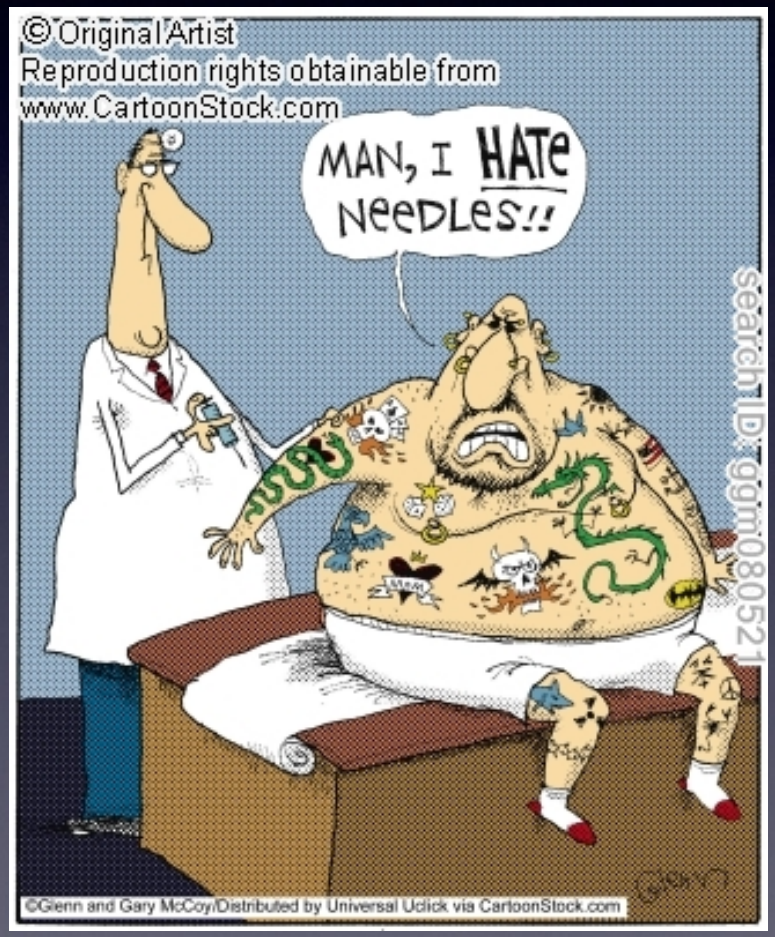


- Avastin 2005
  - Monoclonal **antibody**
  - blocks VEGF-A

- Lucentis 2006
  - Monoclonal **antibody fragment**
  - blocks VEGF-A

- Eylea 2011
  - **Fusion protein**
  - **blocks** VEGF-A isoforms and PlGF

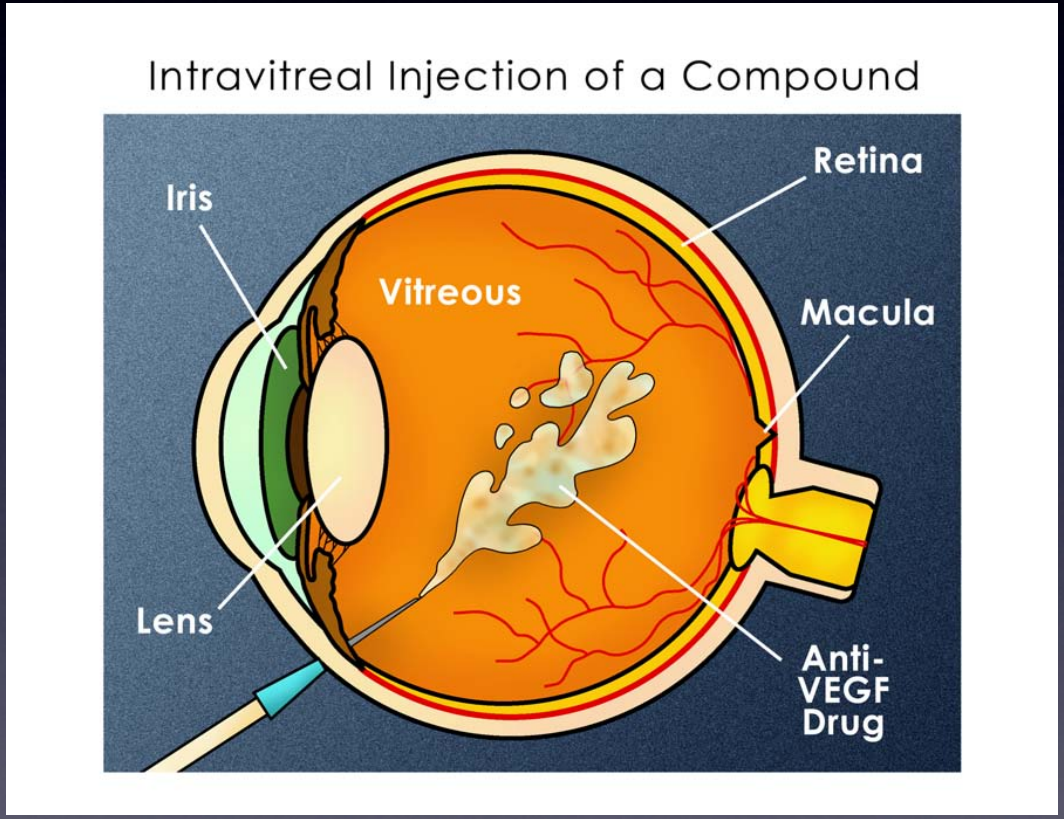
Intravitreal Injections



Intravitreal Injections Benefits

- Cornerstone of retina treatment
- Permit direct delivery of medication
- Very high dose
- Minimal if any systemic absorption
- Minimal risk of systemic side affects

IV-I

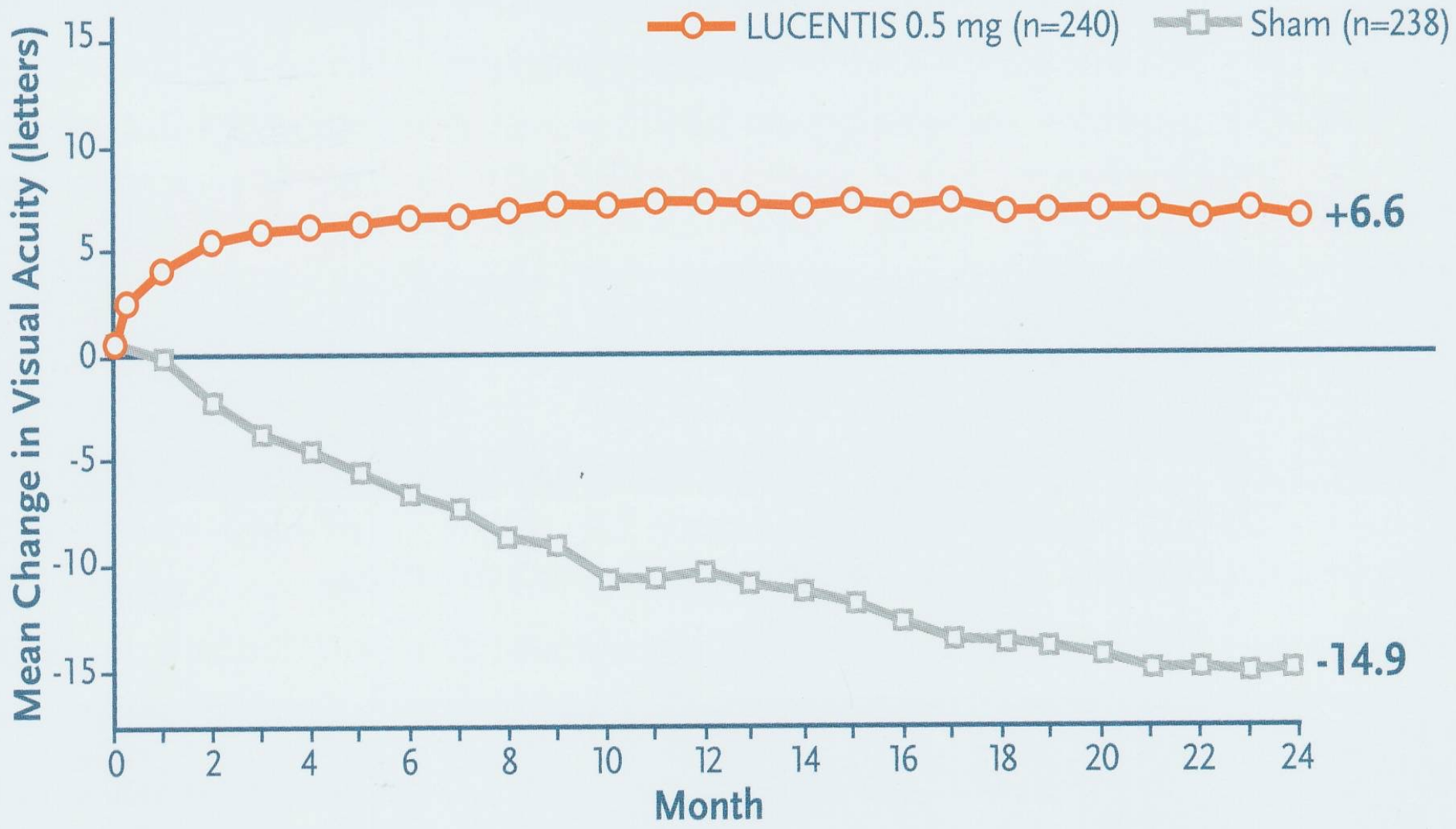

Intravitreal Injection of a Compound
Iris
Retina
Vitreous
Macula
Lens
Anti-
VEGF
Drug

LUCENTIS

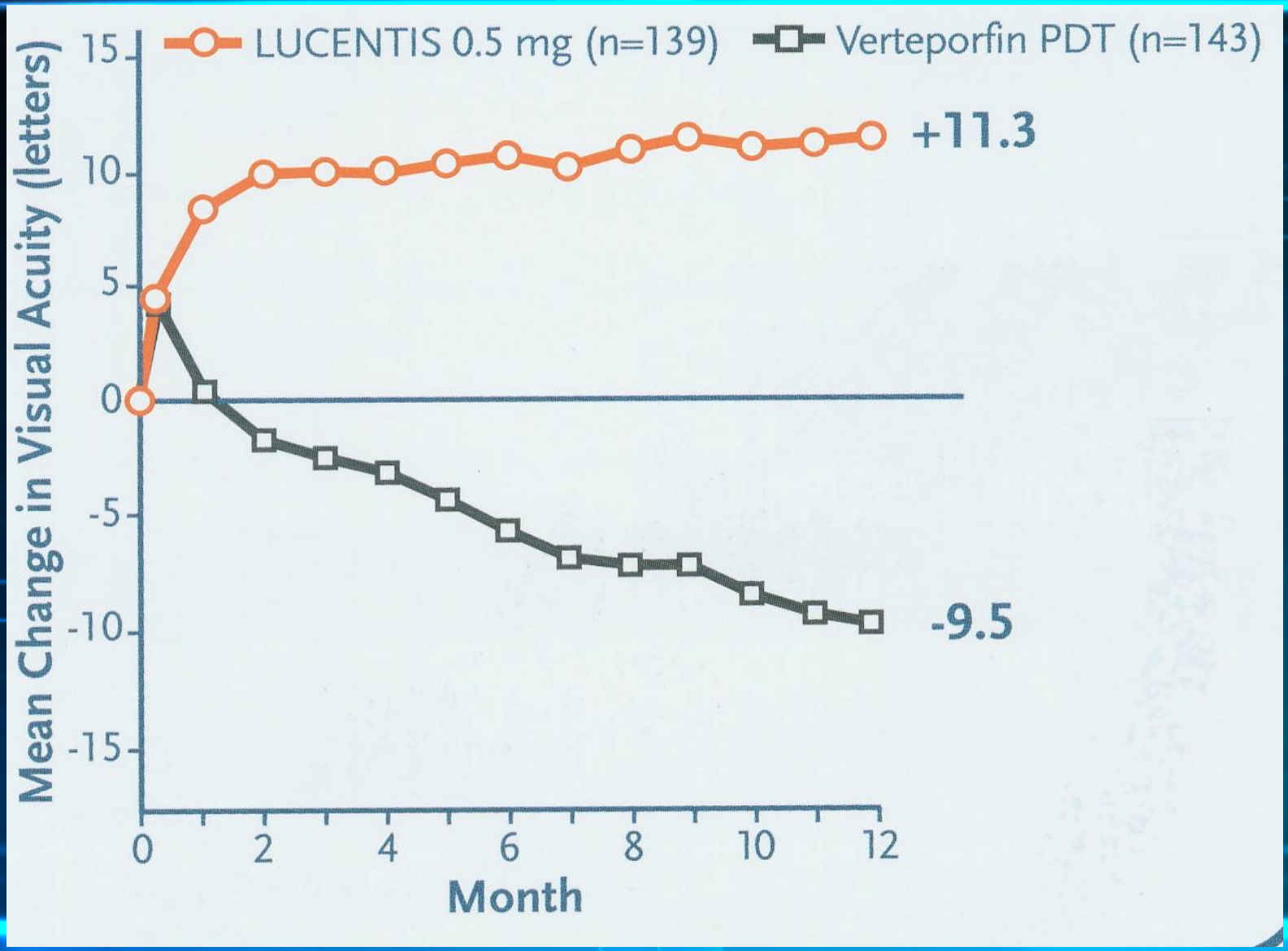
Binds to VEGF-A and prevents interaction with its receptors (VEGF-R1 and VEGF-R2) on the surface of endothelial cells

Lucentis blocks all isoforms of VEGF

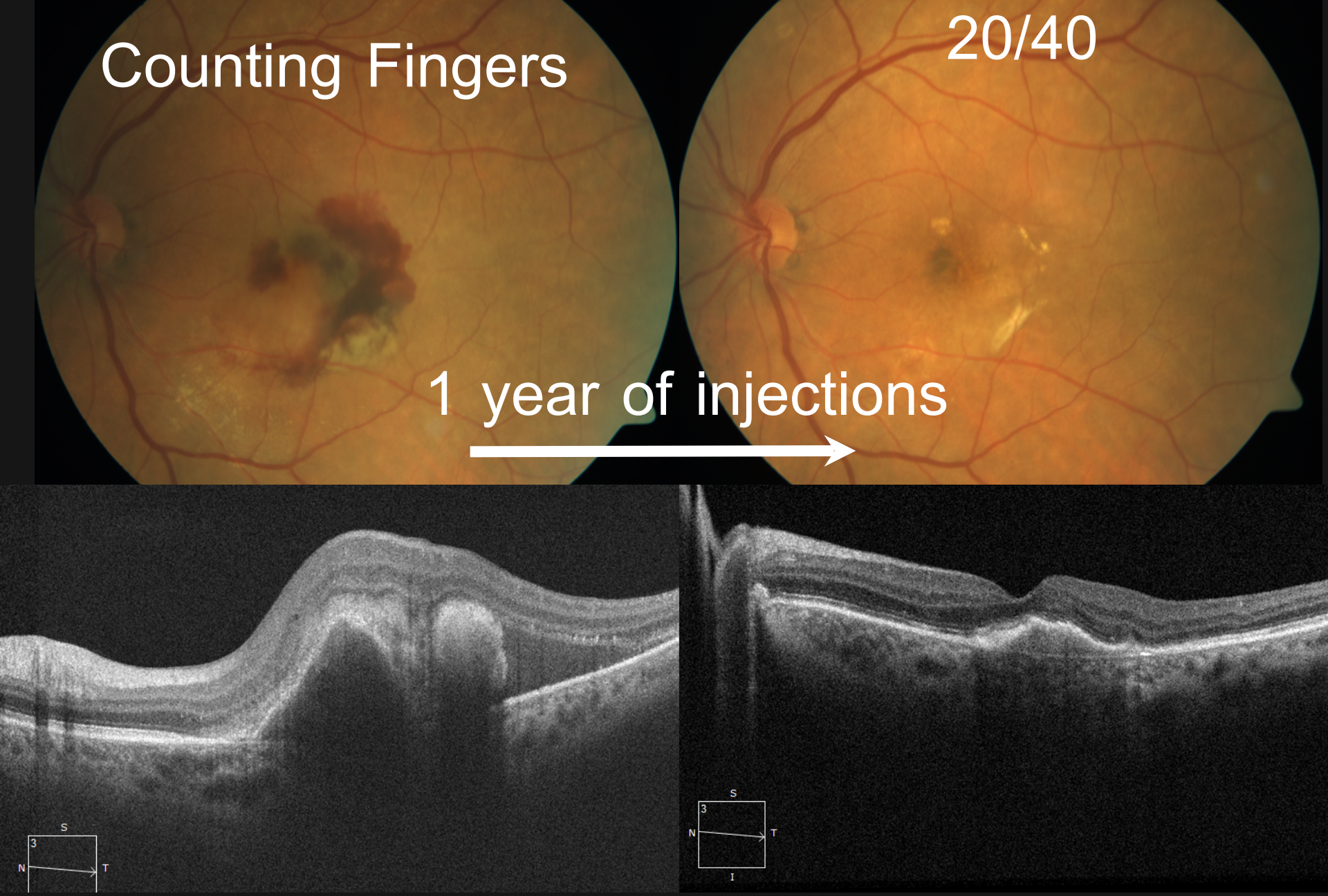
MARINA

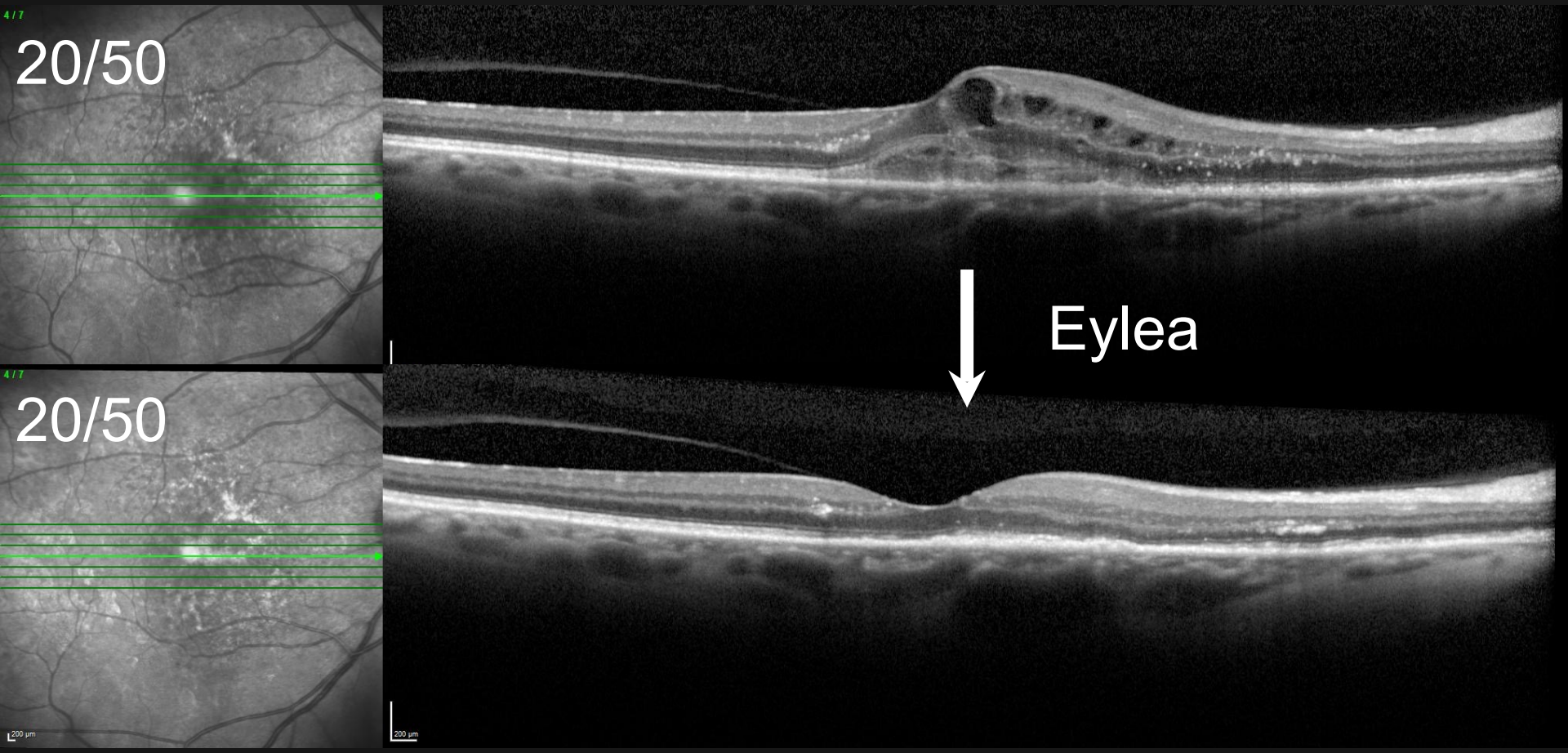

LUCENTIS 0.5 mg (n=240)
Sham (n=238)
Mean Change in Visual Acuity (letters)
15
10
5
0
-5
-10
-15
+6.6
-14.9
0
2
4
6
8
10
12
14
16
18
20
22
24
Month

ANCHOR


LUCENTIS 0.5 mg (n=139)
Verteporfin PDT (n=143)
+11.3
-9.5
Mean Change in Visual Acuity (letters)
15
10
5
0
-5
-10
-15
0
2
4
6
8
10
12
Month

Case Examples


Counting Fingers
20/40
1 year of injections
S
3
N
T
S
3
N
T
I


20/50
20/50
Eylea
200 µm
200 µm

Beyond Anti-VEGF
Future Treatments for AMD

• Anti-VEGF therapy reduces or eliminates "leakage" (fluid in or under macula).

Disadvantages:

– Anti-VEGF does not address associated scarring or fibrosis.

– Current anti-VEGF treatment requires frequent intraocular injections.

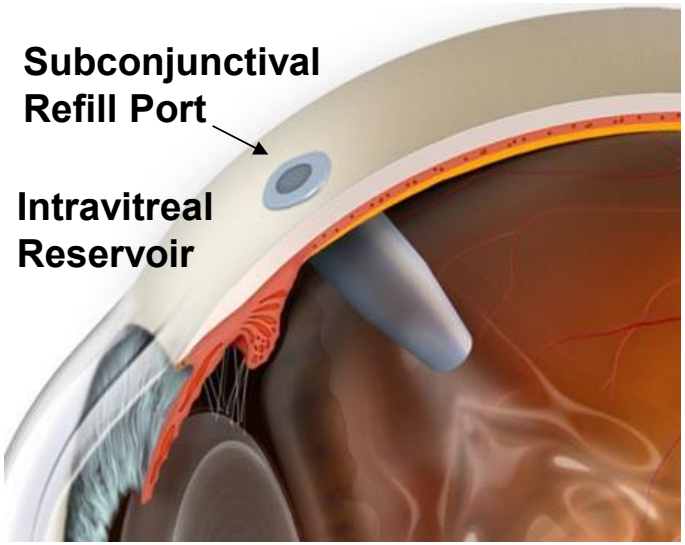
→→ These are unmet needs.

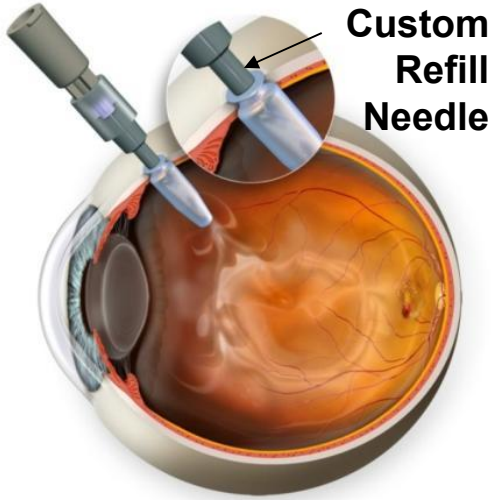
Port Delivery System LADDER clinical trial Currently Enrolling

- Refillable drug port delivery system (Genentech)
  - Surgically implantable/refillable port for Lucentis.
  - Allows for continuous medication release.
  - Refills can be done in the office.

Ranibizumab (RBZ) Port Delivery System (RPDS)

- **Refillable, Long-Term Drug Delivery Implant**
  - Durable Implant Placed in Pars Plana (Subconjunctival)
  - ~ 8 mm long, ~ 2.5 mm diameter
  - Implanted Using Standard Surgical Techniques, 3.2 mm Incision
  - No Scleral Sutures (~10-15 minute procedure)
  - Minimally Invasive Office-Based Refill Procedure
  - Sustained Intravitreal Drug Release Between Refills



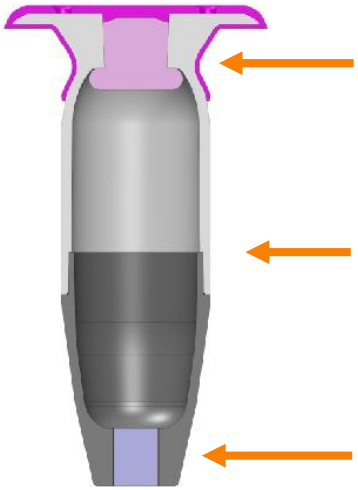


LADDER

Genentech
A Member of the Roche Group

Phase II RPDS Components

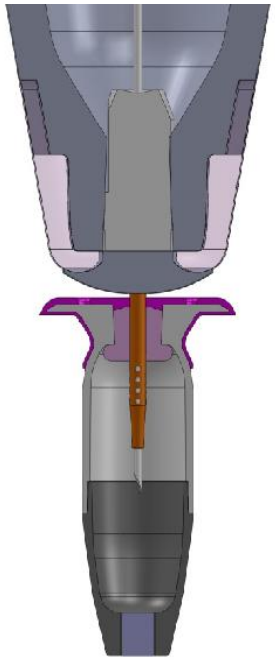
1. RPDS Implant



Self-Sealing Septum

Drug Reservoir

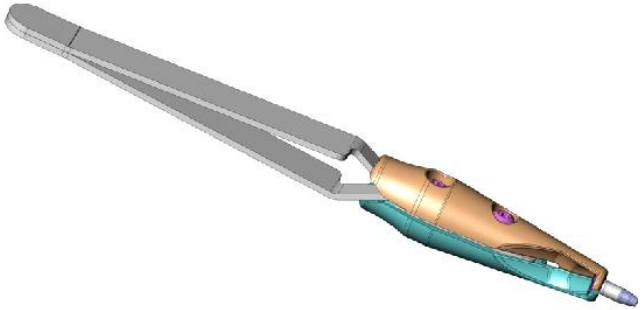
Release Control Element (RCE)



3. RPDS Custom Needle Assembly

Ensures
- Accuracy of Dosing
- Repeatable Device Performance

2. RPDS Implantation Tool



Facilitates Handling and Placement of Device

LADDER

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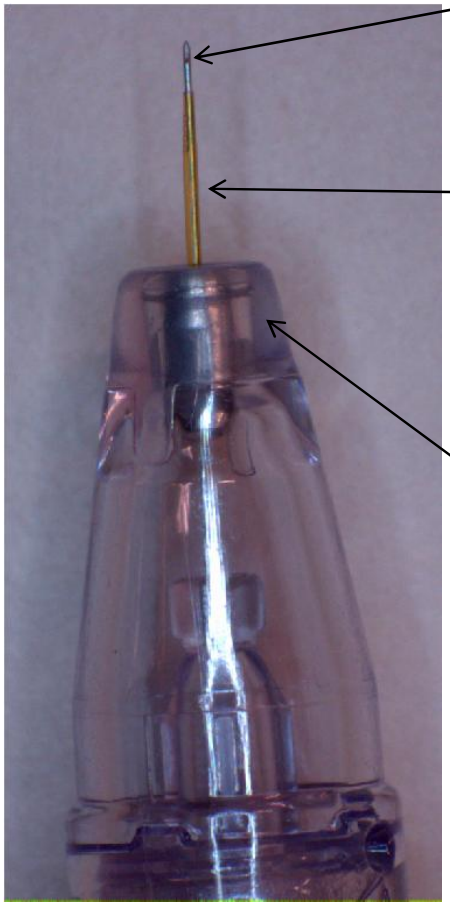
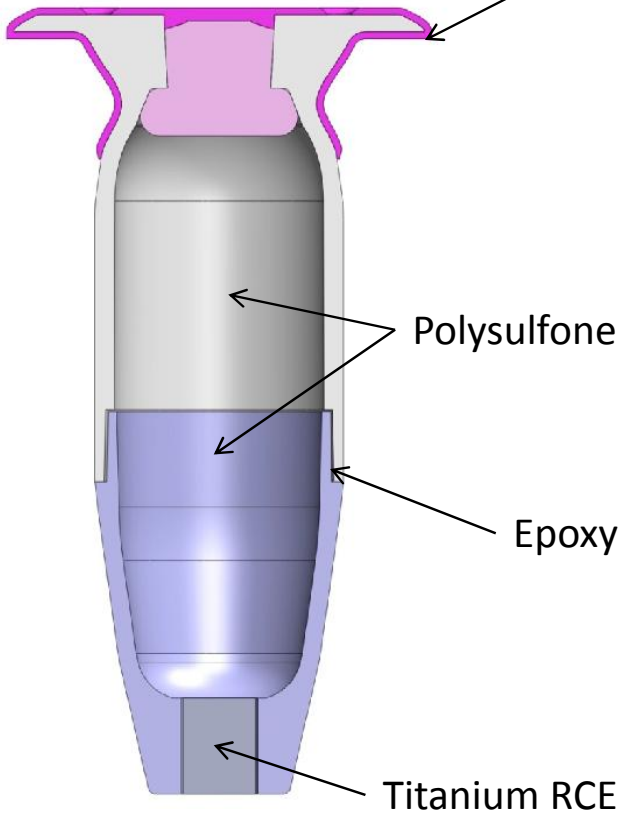
Phase 2 Refill Needle / Implant Details





LADDER

Genentech
A Member of the Roche Group

Gene Therapy

- Gene therapy is a treatment technique that uses a vector (typically an inert virus) to transfer a specific therapeutic gene of interest into a particular group of cells in the patient.
- Potential to provide longer-lasting therapy than what is currently available.
- Semi-permanent effect that may last years.

OPHTHOTECH

Fovista™ (Anti-PDGF) Combination Therapy In Wet AMD Therapy

Fovista anti-PDGF Currently Enrolling

- Fovista (Ophthotech)
  - Anti-PDGF in combination with anti-VEGF.
  - May cause regression of new blood vessels (CNV) → reduce scarring/fibrosis.
  - Given as an intravitreal injection in combination with anti-VEGF agent.

Problems with Anti-VEGF Monotherapy

- Majority of Patients Do Not Achieve Significant Visual Gain
- Majority of Patients Do Not Achieve Final Visual Acuity of 20/40 or Better
- 25-30% Lose Vision

Why Do Patients lose vision in wet AMD?

Role of "New Vessels"

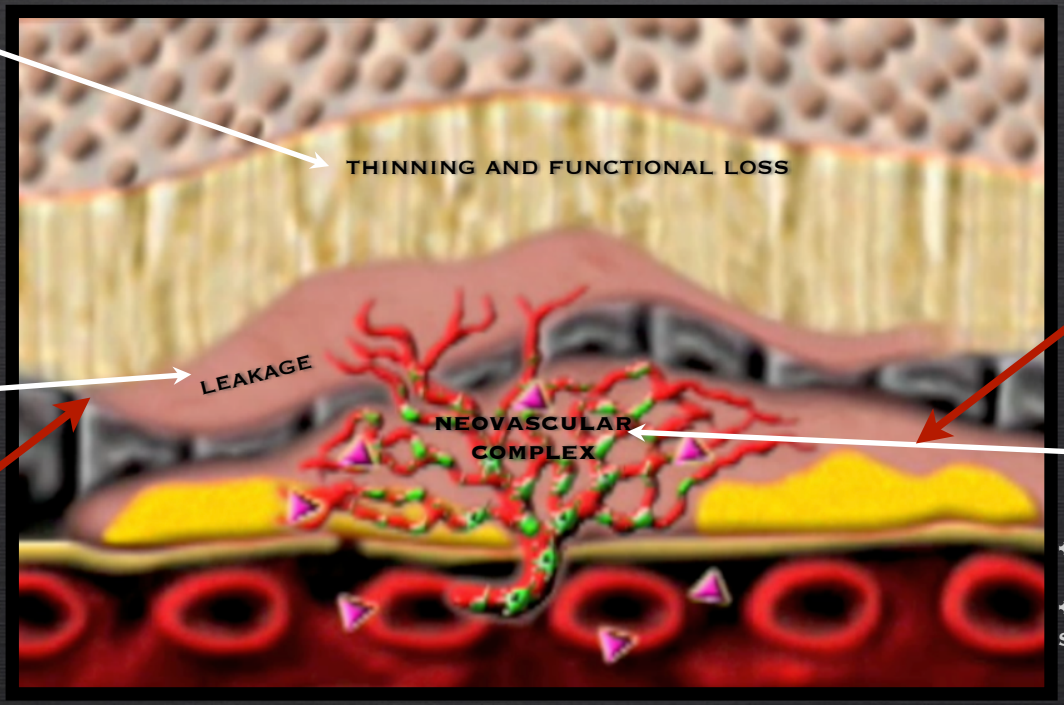
Photoreceptor Degeneration

Underlying "Dry AMD"

No Therapy Yet

Leakage

Anti-VEGF



Anti-PEDF

Neovascular ("New Vessels") Complex

- Distorts retinal anatomy
- Evolves into a destructive scar

As CNV Advances, it resembles mature Blood Vessels, Developing Pericytes, etc.

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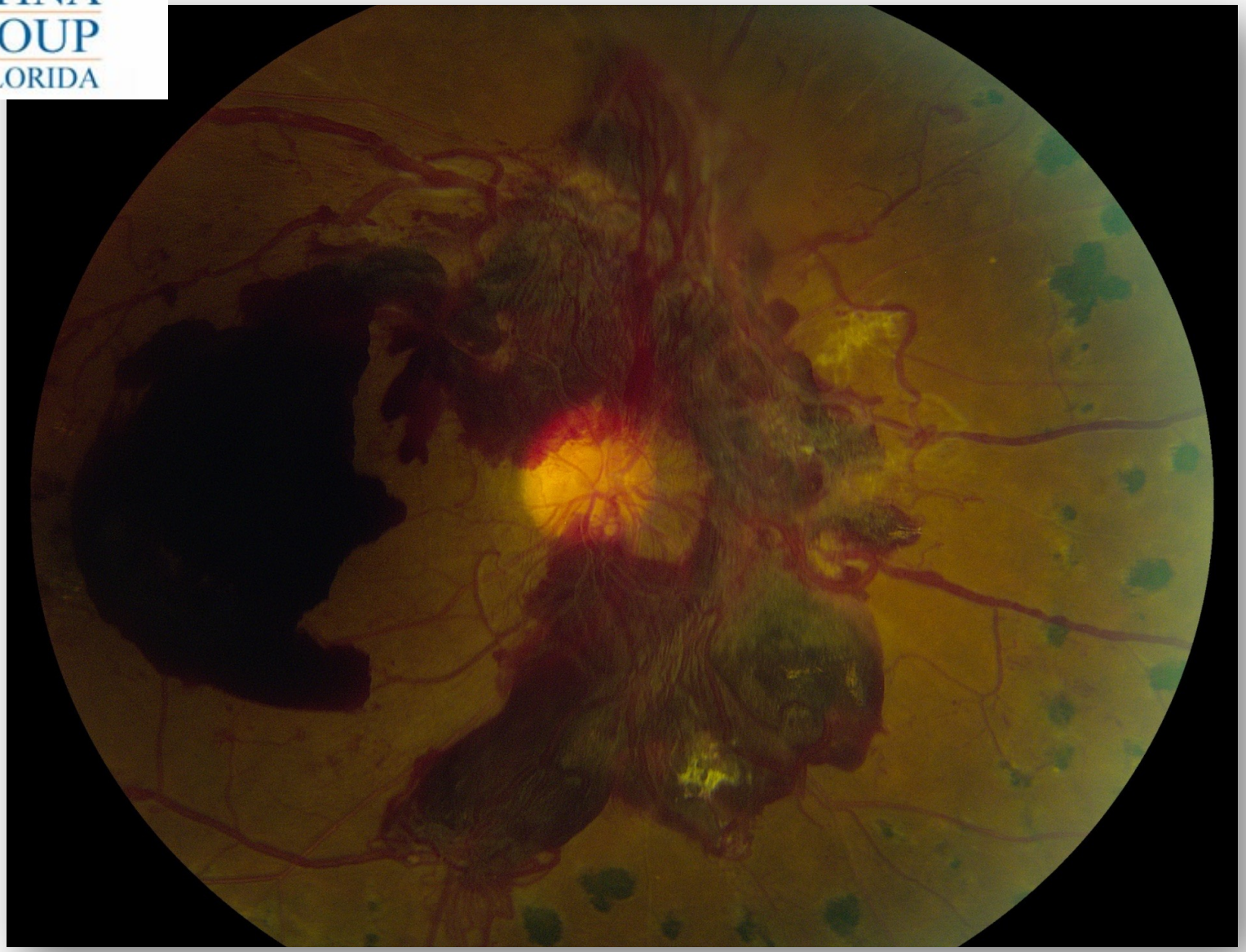
Bridging the Gap: Preserving Vision in Patients with Diabetes



THE IMPORTANT ROLE OF TEAM-BASED CARE IN PRESERVING VISION IN PEOPLE WITH DIABETES TO INCREASE:

- RATE OF ANNUAL DILATED EYE EXAMINATIONS
- EARLY TREATMENT

Special Considerations for Underserved Populations

- African Americans, Latinos, Pacific Islanders, and Native Americans have higher risk for DM, DME, and vision loss
- Economically disadvantaged and rural-living Americans have higher risk
- Poorly-educated Americans have higher risk
- Those who travel for work, eg, migrant workers and truck drivers

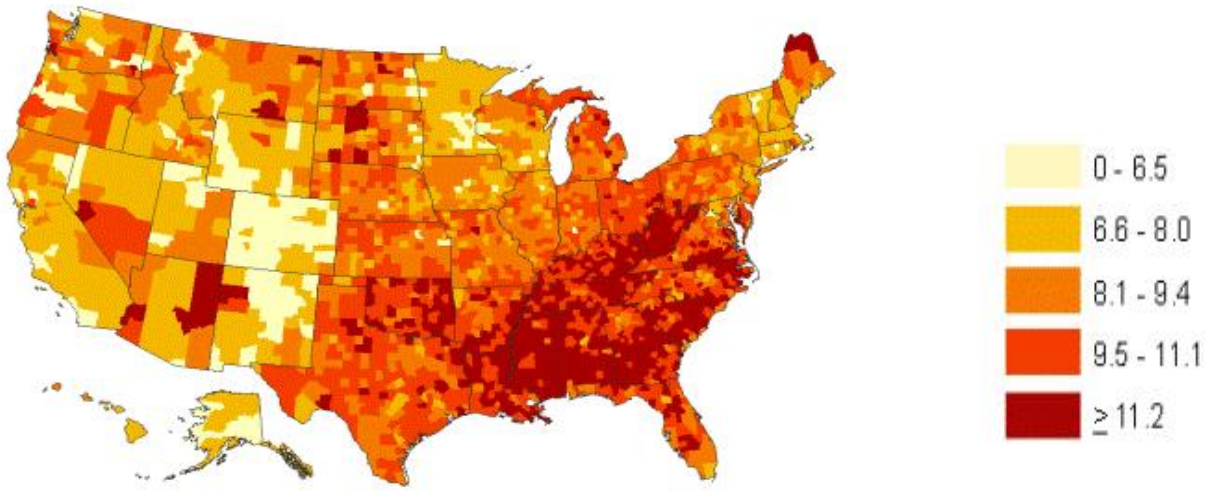
What to Tell the Eye Care Professional

- Type of diabetes
- Duration of diabetes
- Current diabetes therapy
- Control status (most recent HbA1c)

What to Expect in Return

- A consultation letter
  - Visual acuity
  - Presence/Absence of diabetic retinopathy
    - Severity, if present
    - Plan for therapy, if needed
  - Presence of any other relevant ocular disease
  - Motivation??

Diabetes: An Epidemic



2007 Percent of Adults with Diagnosed Diabetes

- **25.8 million people in the United States (~8.3% of the population)**
- **By 2020, prevalence is expected to rise to 15% of adults in the US (39 million)[2]**
- 6.3% of U.S. & 4% of world
- 25% of diabetics have some retinopathy
  - 5,000,000 in US
- Leading cause of visual loss & new-onset blindness 20 – 64

Diabetes is Associated With Serious Systemic Comorbidities

Prevalence of Microvascular and Macrovascular Complications in Diabetes Patients

Diabetic Retinopathy (DR)

28.5% of adults with diabetes ≥40 years old have DR.[1]

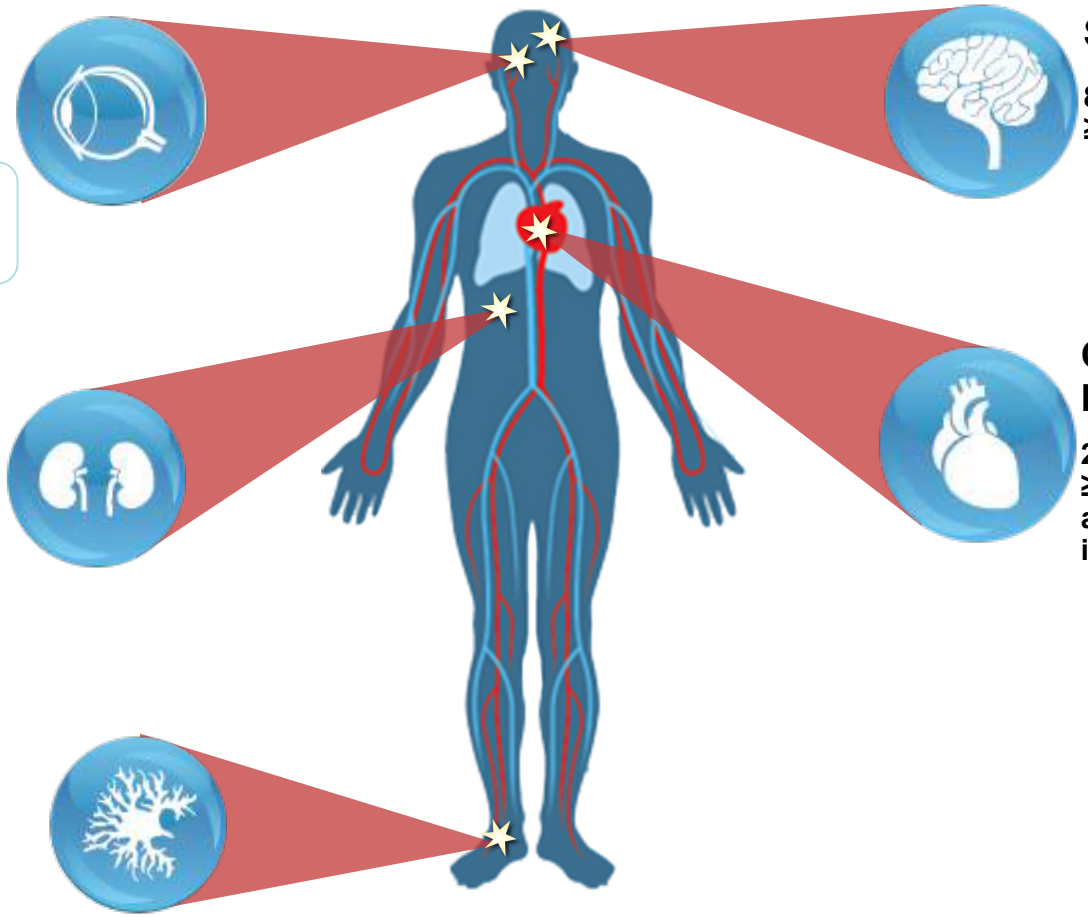
~13% of DR patients have DME[2]

Diabetic Nephropathy

~33% of self-reported diabetics have chronic renal disease[4]

Diabetic Neuropathy

60-70% of people with diabetes have some form of nervous system damage[1]



Stroke

8.5% of diabetes patients ≥35 years old[3]

Coronary Heart Disease

20.4% of diabetes patients ≥35 years old have CHD, angina, or had a myocardial infarction[3]

1. National Diabetes Fact Sheet, 2011 http://apps.nccd.cdc.gov/DDTSTRS/FactSheet.aspx. 2. NHANES database search by Genentech, Data on file.
3. CDC 2010, http://www.cdc.gov/diabetes/statistics/cvd/fig2.htm. 4. US Renal Data System, http://www.usrds.org/atlas.aspx.

Patient's Fear of Blindness

- "60% of Americans are more frightened of going blind than dying from heart disease, which is the leading killer of men and women"
- Losing one's eyesight "is the worst thing that can happen to me"
- The potential for blindness is a great motivator for patients to see an eye specialist

PRWeb. Americans fear blindness more than heart disease, survey finds. August 11, 2010. http://www.prweb.com/releases/2010SurgeResearchInc/08/prweb4372854.htm. Accessed October 15, 2014.

DME: Pathophysiology and Role of Vascular Endothelial Growth Factor (VEGF)

Retinal Microvascular Damage

↓

Retinal Hypoxia

↓

↑ **VEGF-A, HIF, EPO, etc.**

↓

↑ Permeability
↑ Neovascularization

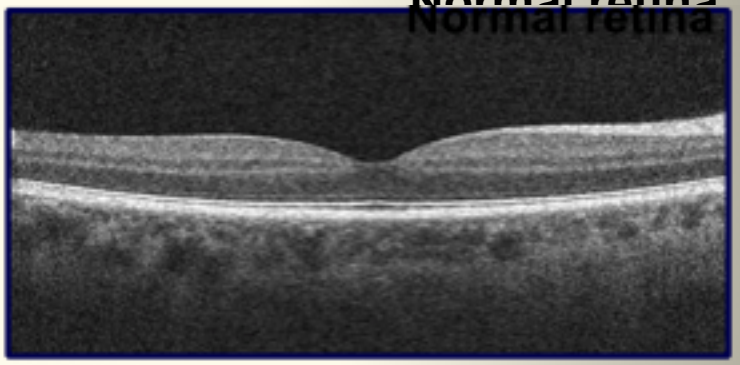
↓

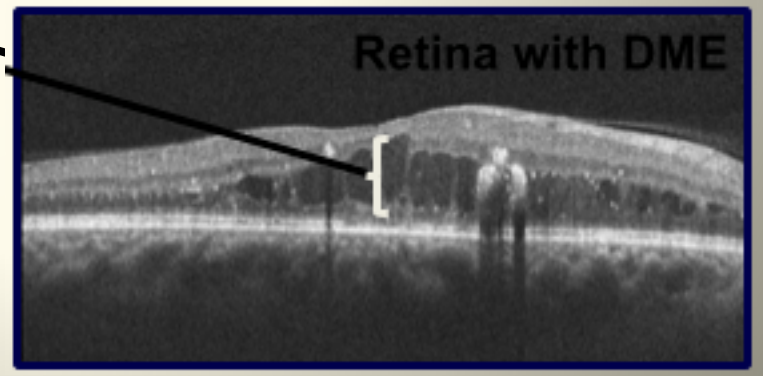
Vascular Leakage

↓

Diabetic Macular Edema

OCT Images





Boyer DS, Hopkins JJ, Sorof J, Ehrlich JS. *Ther Adv Endocrinol Metab*. 2013 Dec;4(6):151-169.

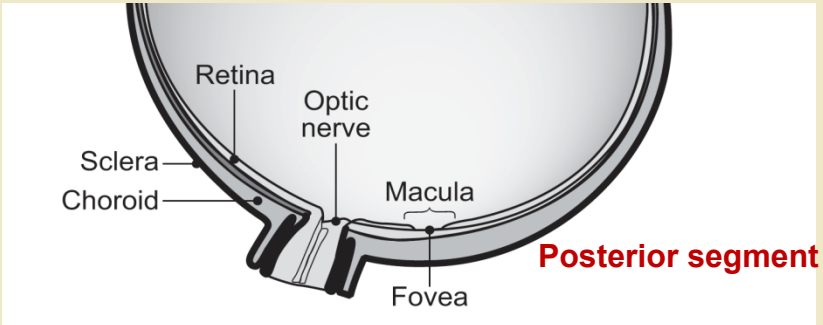
The Annual Dilated Eye Examination

The Standard 8-Part Eye Examination

- Visual acuity
- Pupil examination
- Visual fields
- Ocular motility
- Intraocular pressure
- External examination
- Anterior segment examination
- Posterior segment examination

Posterior Segment Examination By Eye Specialists For Retinopathy

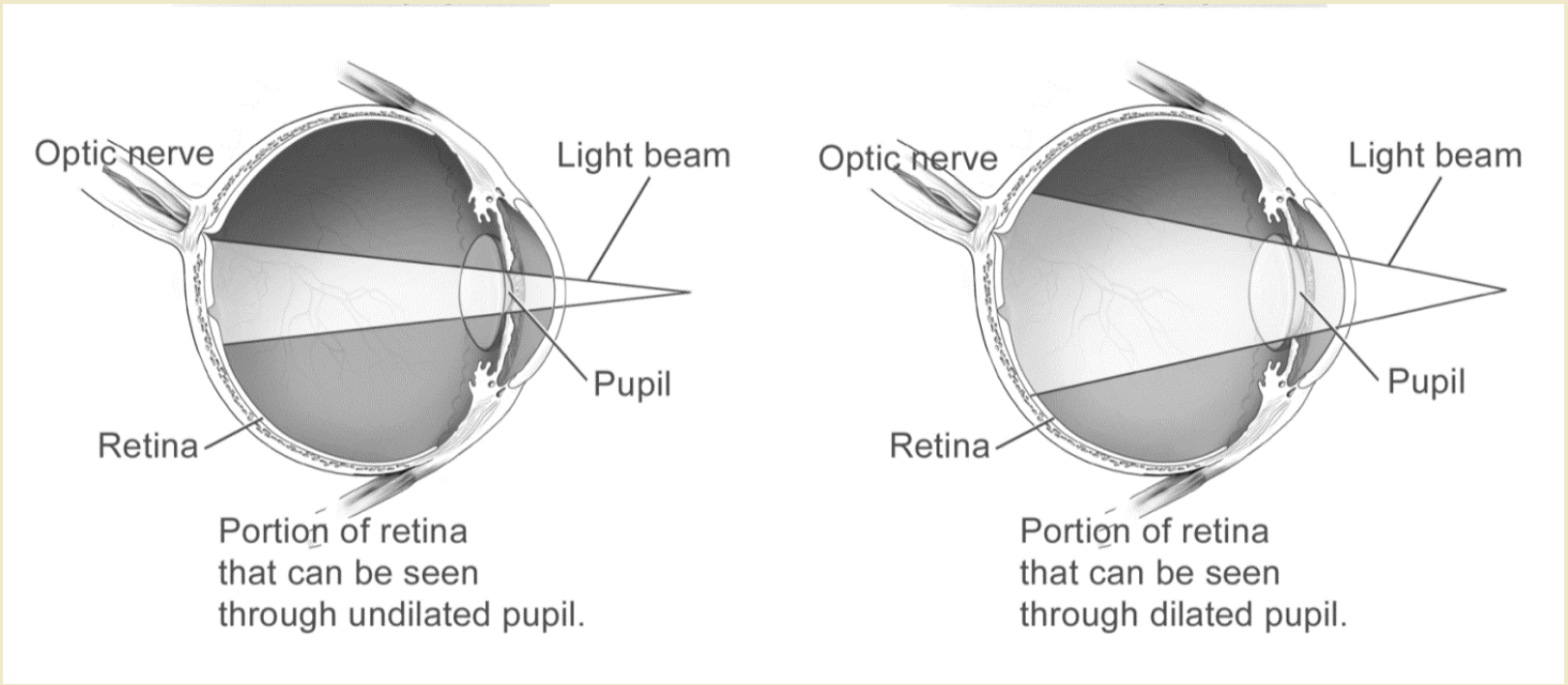
- Includes inspection of:
  - Optic nerve
  - Macula
  - Blood vessels
  - Peripheral retina
  - Vitreous



www.nei.nih.gov

- Can be performed undilated using a direct ophthalmoscope
  - Not a stereoscopic (3D) view
  - Limited view of peripheral retina
- Can be performed dilated using an indirect ophthalmoscope or using condensing lenses through the slit lamp
  - Gives a stereoscopic view
  - Permits complete retinal evaluation

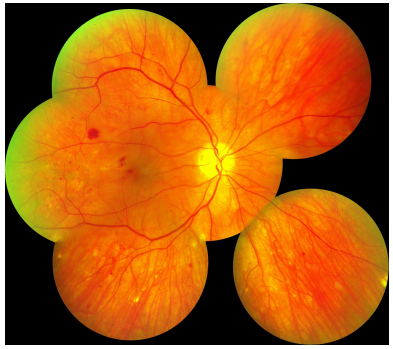
Why Are Dilated Examinations Important?



Diagnosis

- Capturing a retina image is only one part of the clinical diagnosis of DR and DME
- There are many ways to monitor retina health[1]

Color fundus photography



Optical coherence tomography

Image of normal retina

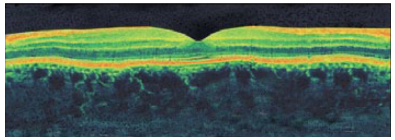
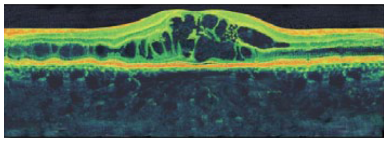
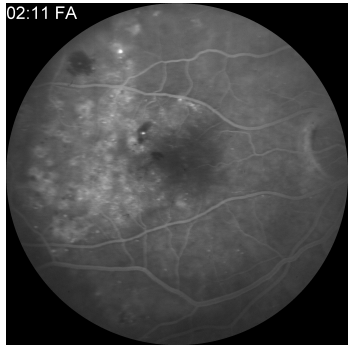


Image of retina with DME



Fluorescein angiography

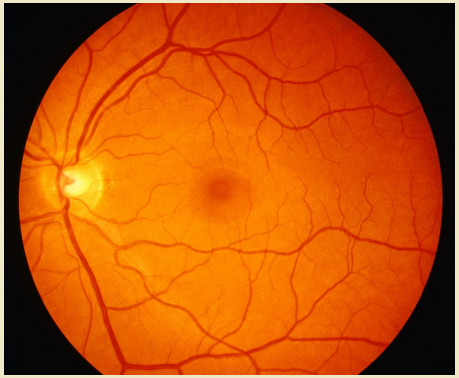


REFERENCE: 1. University of Iowa. Carver College of Medicine. Ophthalmology and visual sciences. http://www.medicine.uiowa.edu/eye/Ocular-Fundus-Photography/. Accessed May 5, 2013.

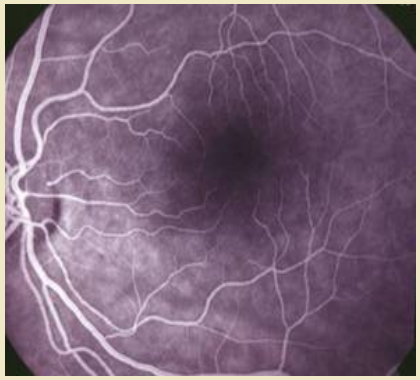
Posterior Segment Imaging

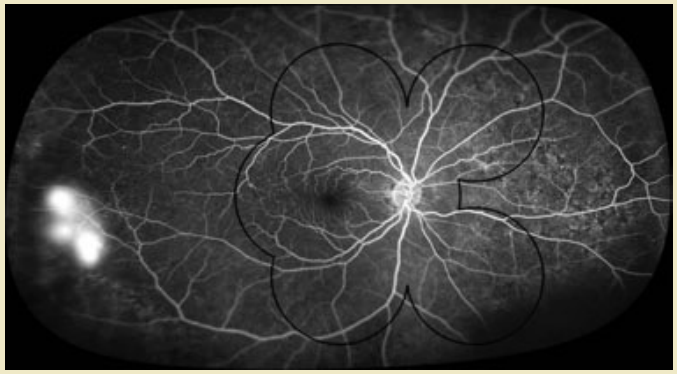
Standard

More invasive
Reveals vasculopathy

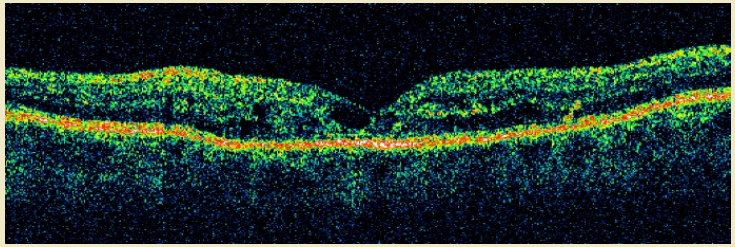


Fundus Photograph





Fluorescein Angiography – standard and widefield

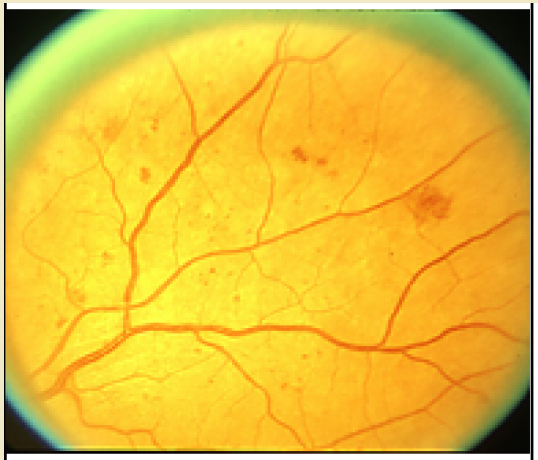
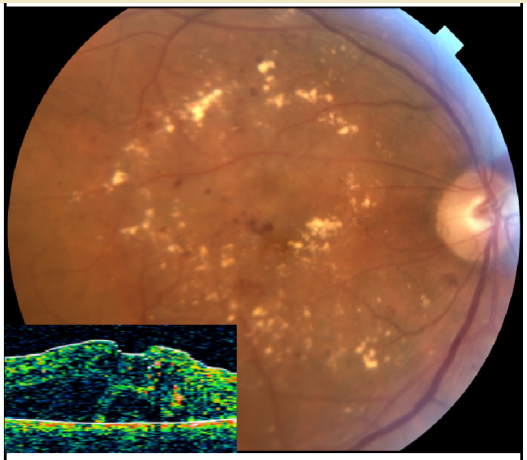
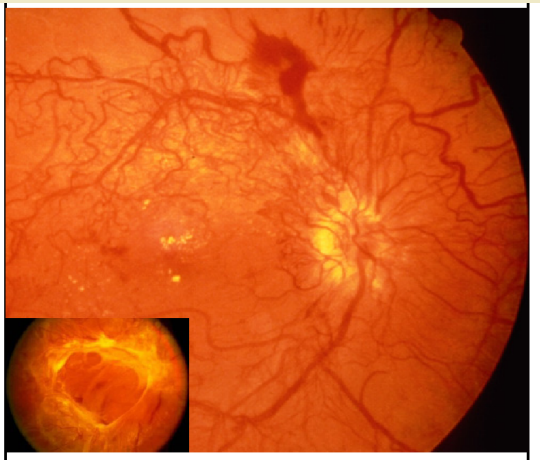


Optical Coherence Tomography

Fundus and OCT mages courtesy of David M Brown, MD

Widefield image: Witmer MT, Kiss Szilard. Rev Ophthalmol. March 8, 2012.
http://www.revophth.com/content/d/retina/c/32799/

Classification of Diabetic Retinopathy

Nonproliferative DR	Diabetic Macular Edema	Proliferative DR
		
Microvascular damage • Chronic, occurring over years • Typically no significant vision loss, but progresses to DME and/or PDR • Similar damage occurs in other end-organ vascular beds	**Swelling in central retina** • Accounts for most vision loss • Co-exists with NPDR and PDR	**End stage** • Neovascularization of retina • High risk of severe visual loss

More common
Less severe

Less common
More severe

Edema can be present in both NPDR and PDR

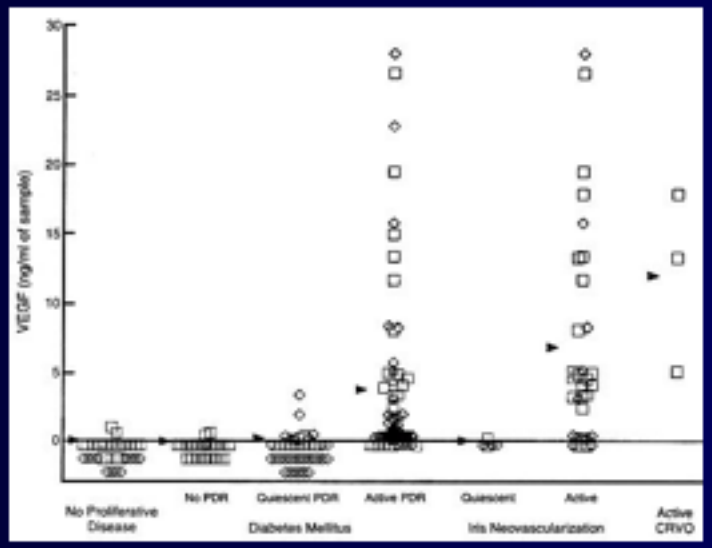
DME accounts for most of the vision loss

Diabetic Macular Edema: Risks

- DME **triples** the risk for visual impairment
- Associated with a **5X** increase in blindness compared with patients with DM
  who do not have DME

Klein R et al. *Ophthalmology.* 1984;91(12):1464–1474.

Elevated VEGF Levels in DME



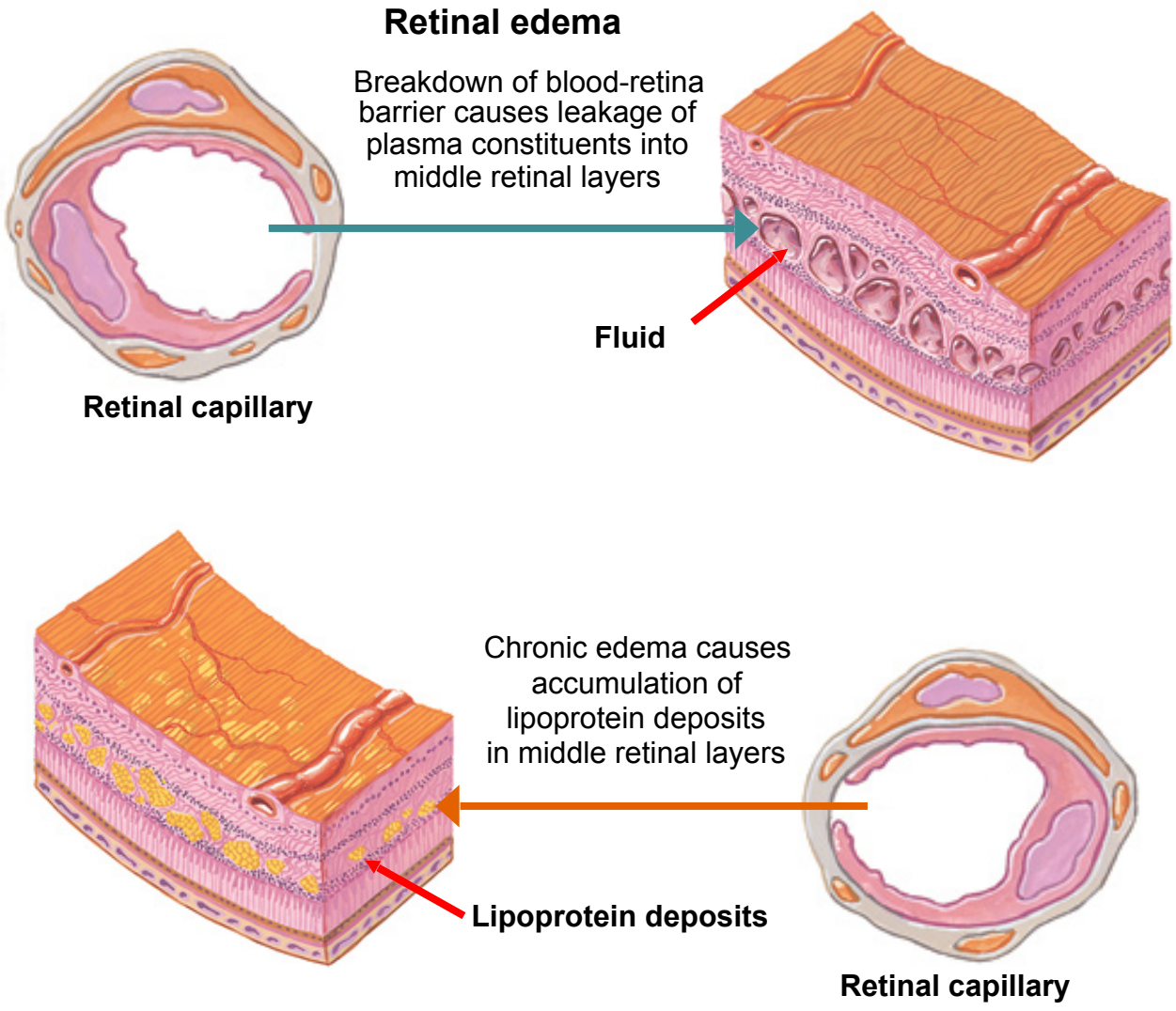
VASCULAR ENDOTHELIAL GROWTH FACTOR IN OCULAR FLUID OF PATIENTS WITH DIABETIC RETINOPATHY AND OTHER RETINAL DISORDERS

NEJM 1994

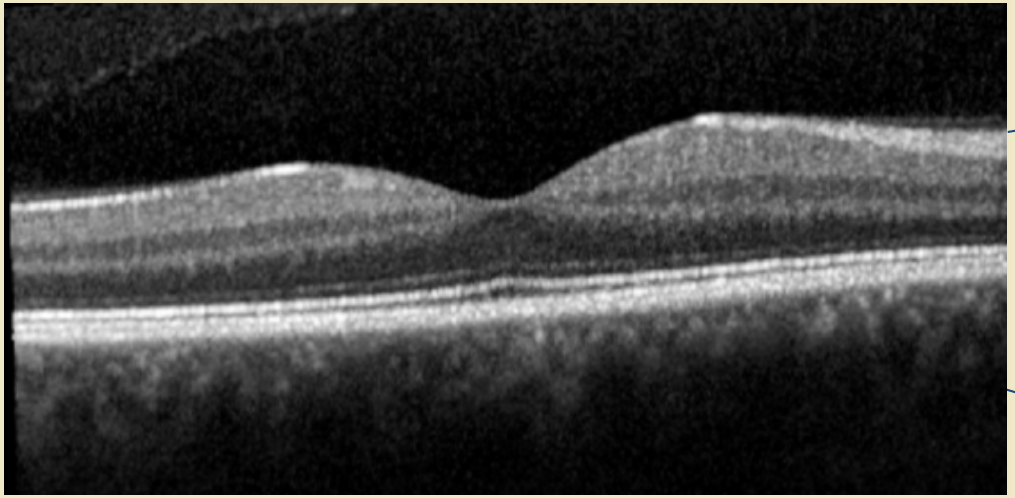
- Aqueous VEGF concentrations in DME eyes elevated 5-fold compared with controls[4]

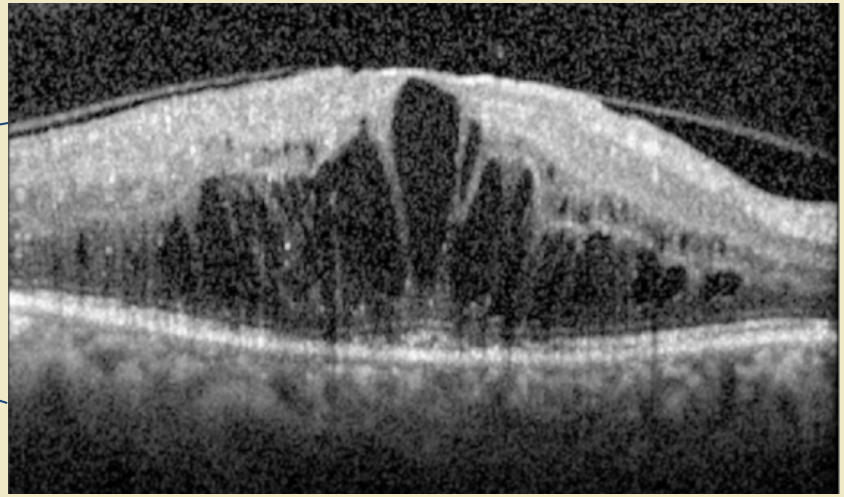
14. Funk M, Schmidinger G, Maar N, et al. *Retina.* 2010;30:1412–9.

Diabetic Macular Edema (DME)



Diabetic Macular Edema



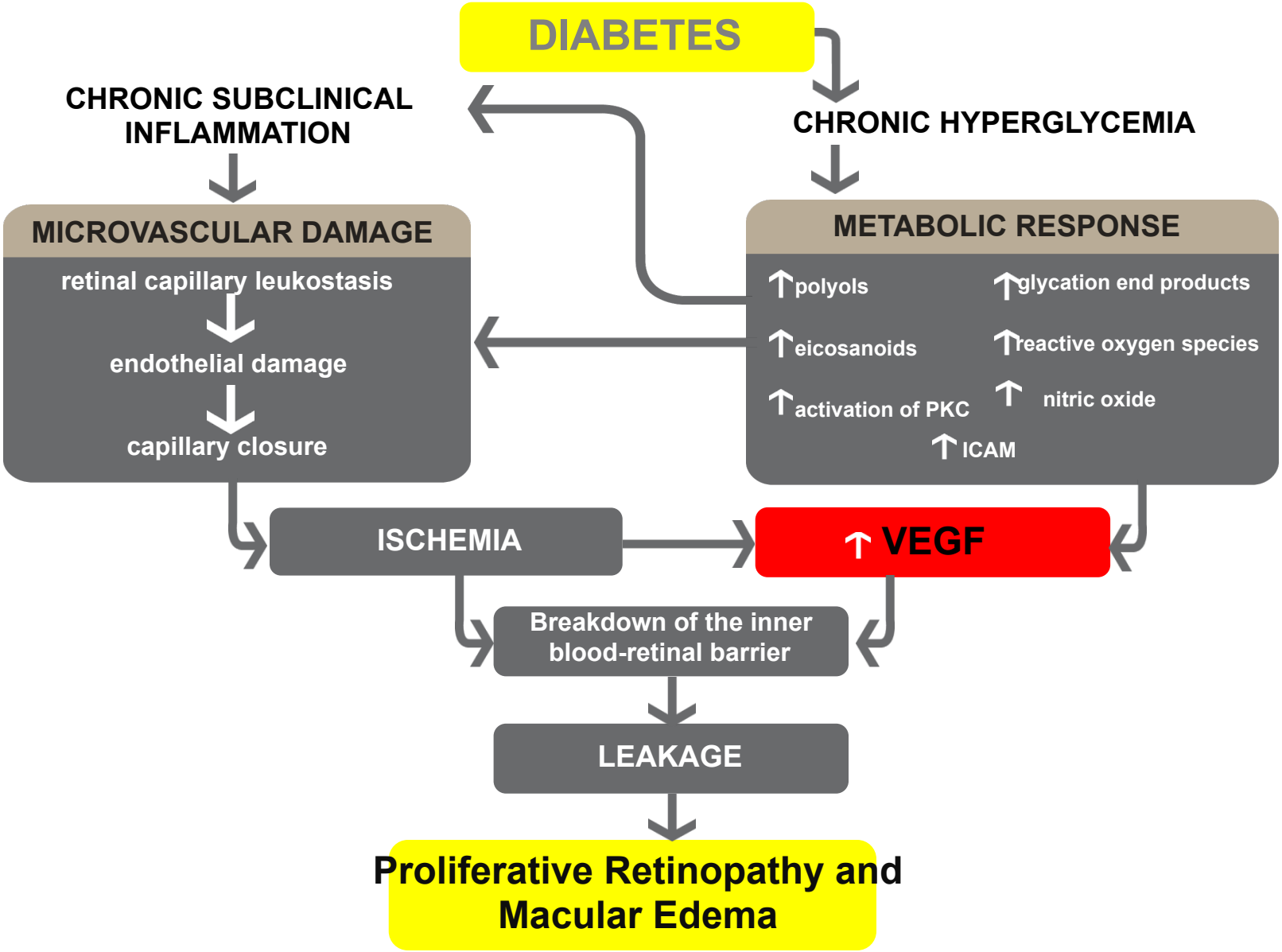


Normal Macula:
In the normal retina, light passes through 9 layers to reach the photoreceptors

Diffuse Edema:
Increased thickness of the retina affects the ability of light to travel through the tissue to photoreceptors

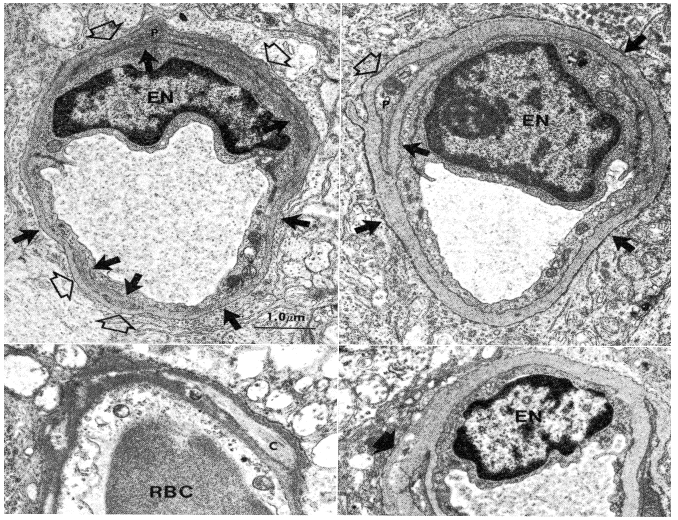
Photos courtesy of David Brown, MD

Pathophysiology

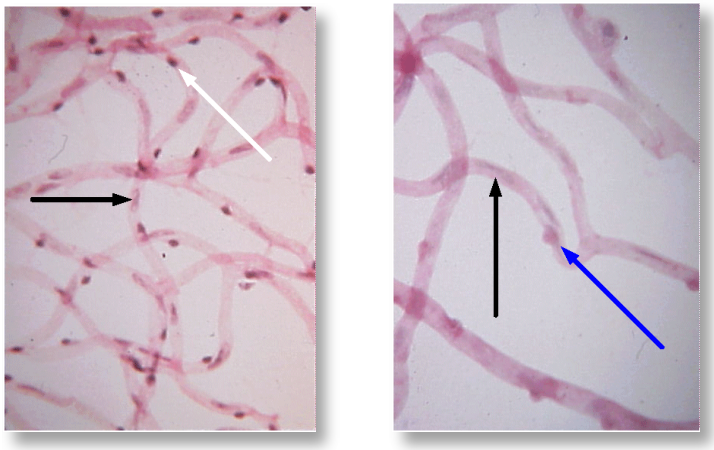


Pathophysiology of Diabetic Retinopathy

- Capillary pericyte loss
- Endothelial cell loss
- Nonfunctional acellular capillaries
- Capillary basement membrane thickening
- Microaneurysm formation
- Neovascularization



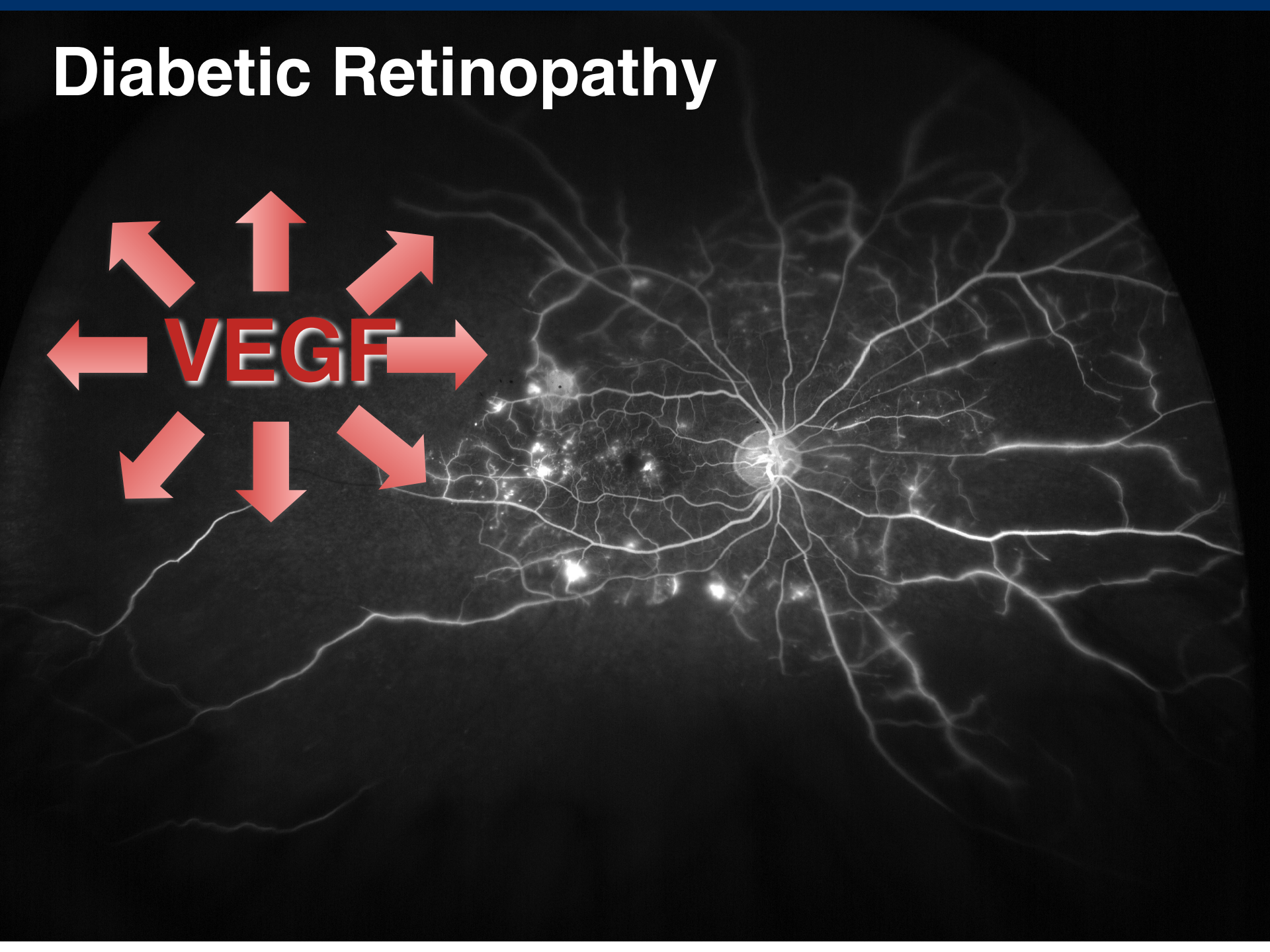
Normal vessels



Diabetic vessels

Frank RN. Etiologic mechanisms in diabetic retinopathy. In: Ryan SJ, ed. *Retina*, Schachat AP and Murphy RP, eds vol. 2 *Medical Retina*, St. Louis, 1994, Mosby. 1253-126.5. *Photos copyright acknowledgement to publication*.

Diabetic Retinopathy



Patients with diabetic macular edema may not have symptoms[1]

Don’t wait for vision loss before you refer patients for a retina (dilated) eye exam

- Symptoms and pain are often both absent in the early stages[1]
- Vision loss can occur suddenly, and regular examinations are crucial to ensure treatment is obtained[2]

Symptoms of DME include[1]

BLURRED VISION

DOUBLE VISION

PATCHES OF VIS

REFERENCES: 1. National Eye Institute. Facts about diabetic retinopathy. http://www.nei.nih.gov/health/diabetic/retinopathy.asp. Accessed May 5, 2013. **2.** University of Michigan. Diabetic retinopathy. http://www.kellogg.umich.edu/patientcare/conditions/diabetic.retinopathy.html. Accessed May 5, 2013.

Patients should get an annual retina (dilated) eye exam

American Academy of Ophthalmology: recommended eye examination schedule (including dilated eye exam) for patients with diabetes[1]

Diabetes type	Recommended time for first examination	Recommended follow-up*
Type 1	3-5 years after diagnosis	**Yearly**
Type 2	At time of diagnosis	**Yearly**
Prior to pregnancy (Type 1 or Type 2)	Prior to conception and early in the first trimester	• No DR to mild or moderate NPDR: every 3-12 months • Severe NPDR or worse: every 1-3 months

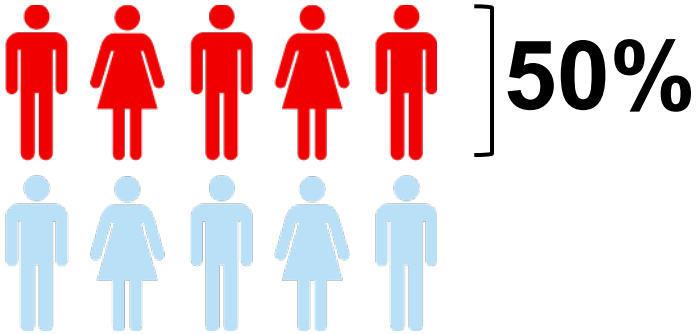
It's important for patients to understand there are different types of eye exams they need, eg, dilated eye exam, retina eye exam, or diabetes eye exam.

*Abnormal findings may dictate more frequent follow-up exams.

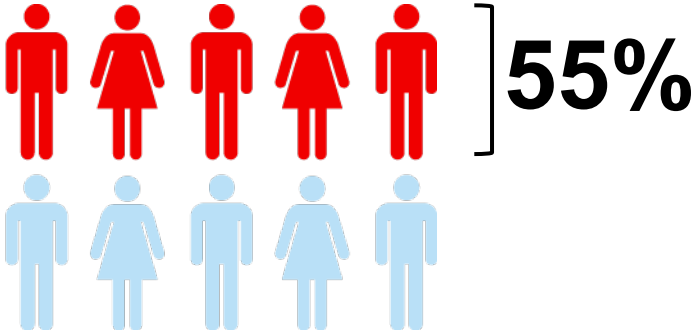
REFERENCE: 1. Preferred Practice Pattern® Guidelines, Diabetic Retinopathy. San Francisco, CA: American Academy of Ophthalmology; 2008. http://one.aao.org/CE/PracticeGuidelines/ppp.aspx.

Many patients with diabetic retinopathy and diabetic macular edema remain untreated or undiagnosed

Patients with vision-threatening DR who did not have timely follow-up exams[1]



Patients unaware they have DME[2]



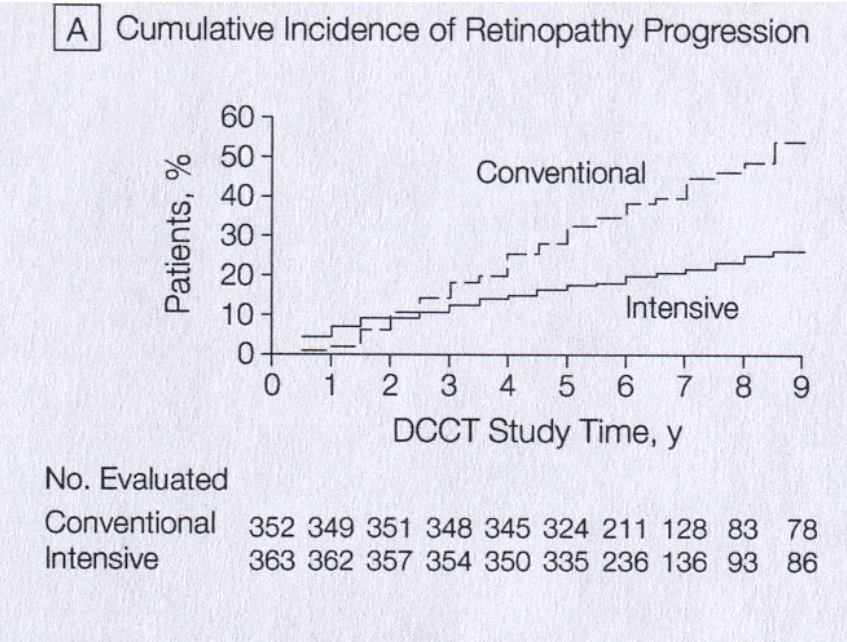
REFERENCES: 1. Soliman AZ, et al. ARVO, 2011. Poster A37. **2.** Data on file. Genentech, Inc. South San Francisco, CA.

Where We Can Make a Difference in Vision Preservation

- Hyperglycemia – key modifiable risk factor
- Hypertension management
- Hyperlipidemia management
- Annual eye exams and timely treatment of DR/DME

Diabetes Control & Complications Trial (DCCT)

- Intensive blood glucose control:
  - 76% risk reduction in the development of any retinopathy
  - 54% risk reduction of retinopathy progression for those who had retinopathy at baseline



The DCCT Research Group. *N Engl J Med.* 1993;329:977-986. *Figure copyright NEJM.*

Other Modifiable Risk Factors

- Dyslipidemia
  - Positive association between severity of retinopathy and lipid profiles (total and LDL-cholesterol, LDL/HDL)[1]
  - High triglycerides & high LDL associated with subsequent progression of retinopathy over 2 yrs[2]
  - ETDRS: baseline risk factors for PDR include high triglycerides[3]
- Hypertension – risk factor for pathogenesis of DR[4]
  - Barbados Eye Study: Antihypertensive treatment halved the risk of developing DR over 9 years[5]

1. Kissebah AH et al. *Lancet.* 1975;1:1104-1108.
2. Orchard TJ et al. *Diabetes Care.* 1990;13:741-747.
3. Davis MD et al. *Invest Ophthalmol Vis Sci*. 1998;39:233-252.
4. West KM et al. *Diabetes.* 1980;29:501-508.
5. Leske MC et al. *Ophthalmol.* 2005;112:799-805.

Other Systemic Issues & Retinopathy

- Renal function[1] and fluid balance can potentially play a role in worsening of diabetic retinopathy and macular edema
- Plasma VEGF increases with poor glycemic control[2]

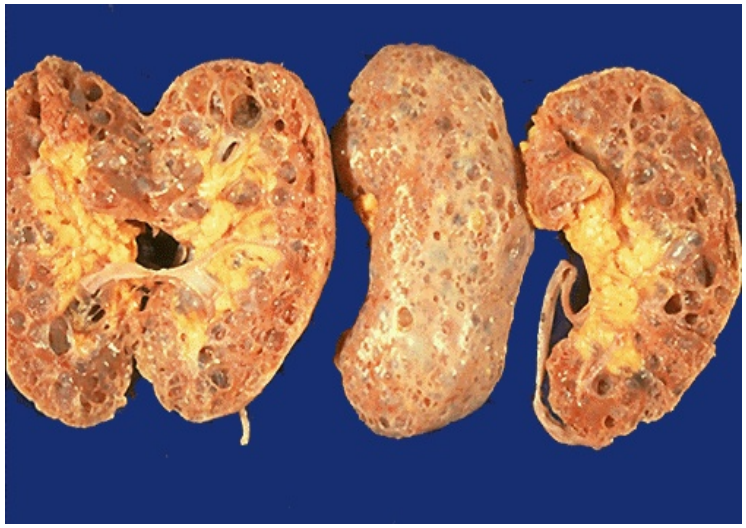


Photo source: to come

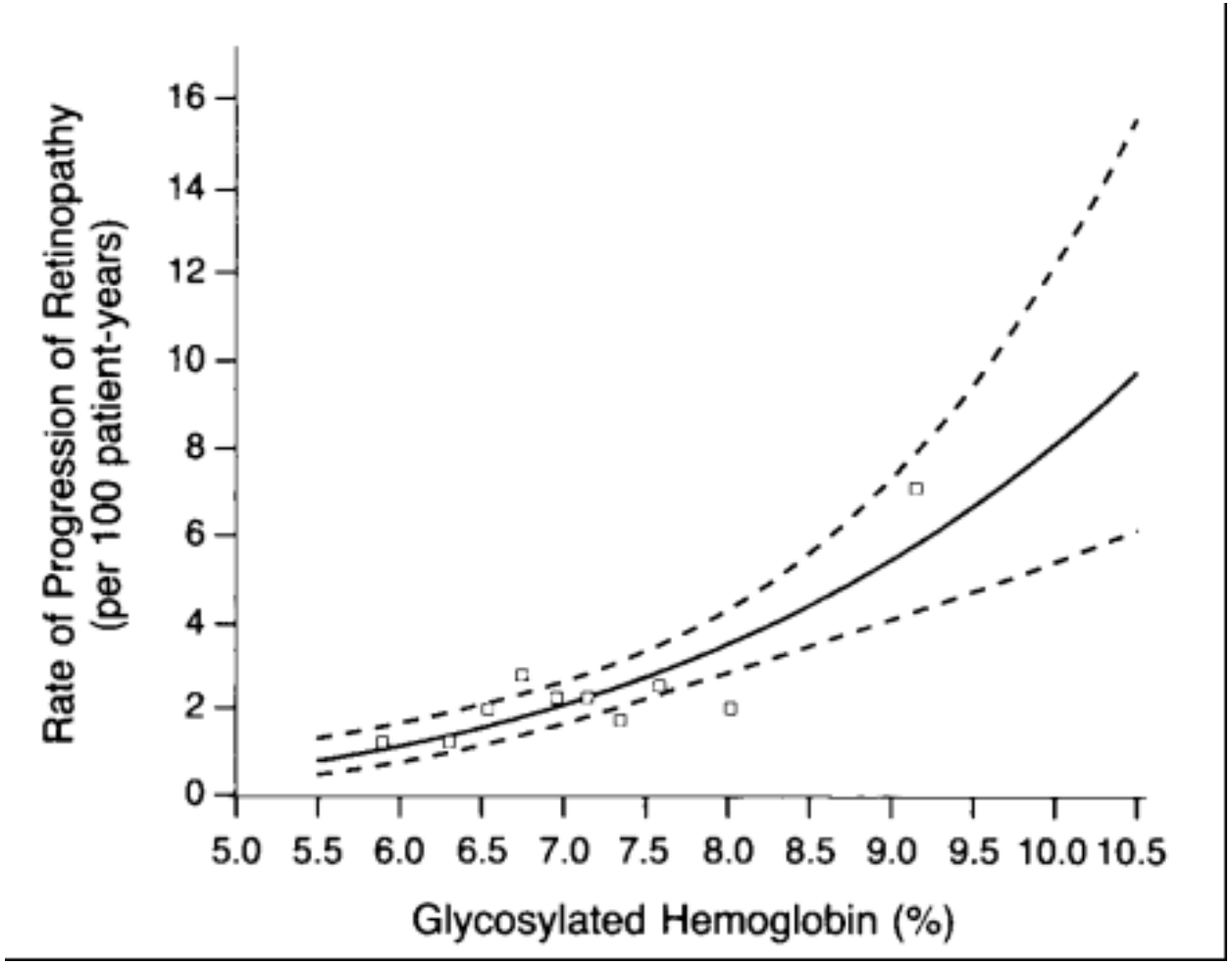
1. Chase HP et al. *JAMA*. 1989;261:1155–1160.
2. Kakizawa H. *Metabolism.* 2004;53:550-555.

Considerations for Pregnancy – DCCT

- Women with type 1 DM must be followed closely during pregnancy and into the first postpartum year
- Effect of pregnancy is relatively transient
- Most changes revert to pre-pregnancy levels after a year or more
- Pregnancy does not affect ultimate long-term rate of progression of mild to moderate retinopathy

The DCCT Research Group. *Diabetes Care.* 2000;23:1084-1091.

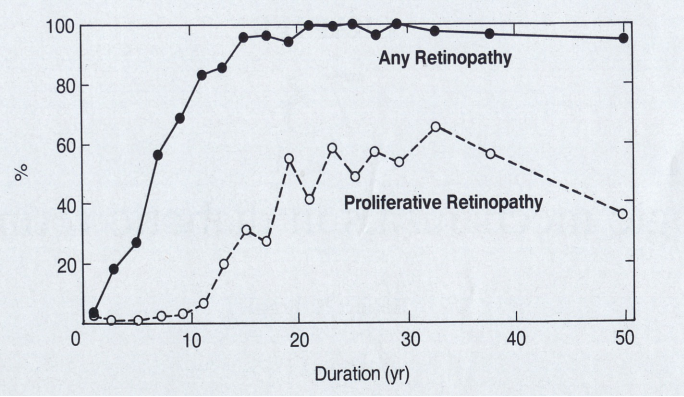
Importance of Hemoglobin A1C



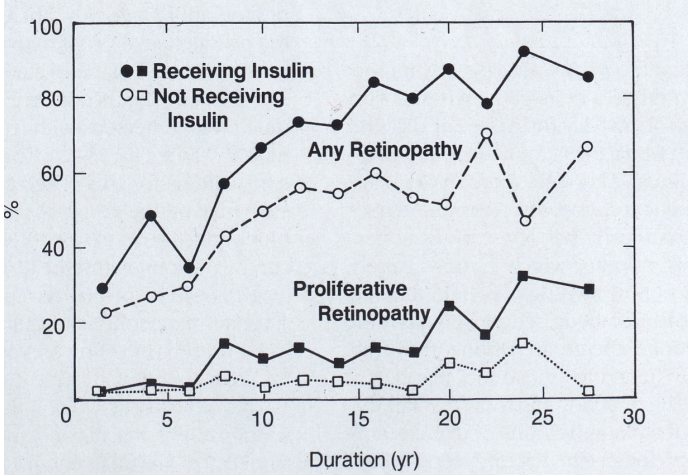
DCCT Research Group. *N Engl J Med*. 1993;329:977-86.

Prevalence of Proliferative Retinopathy

- Type I DM
  - 15 years' duration: 30%



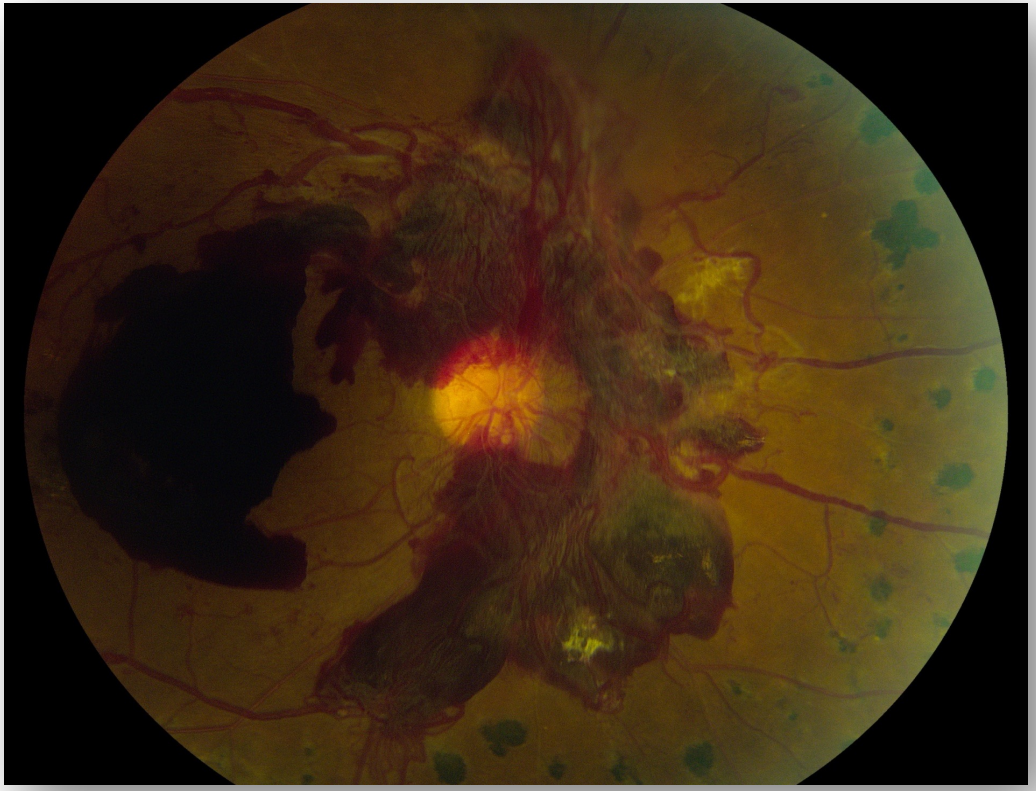
- Type II DM
  - Receiving insulin:
    - » 15 years' duration: 15%-20%
  - Not receiving insulin:
    - » 15 years' duration: 5%-10%



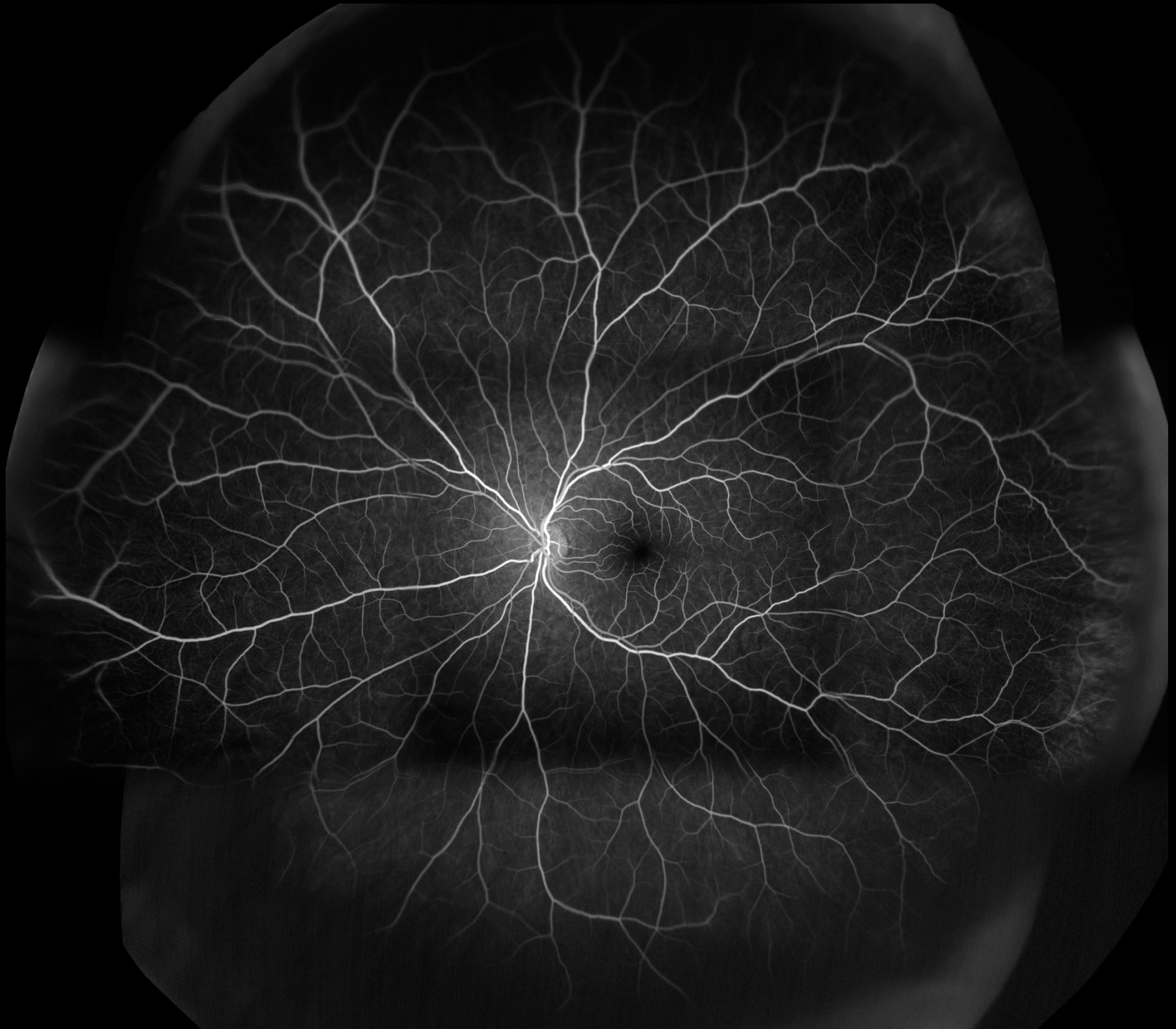
Redrawn from Klein R, Klein BEK, et al. *Arch Ophthalmol* 102:520-526, 1984 in Frank RN. Etiologic mechanisms in diabetic retinopathy. In Ryan SJ, ed: *Retina*, Schachat AP and Murphy RP, eds. vol. 2 *Medical Retina*, St. Louis, 1994, Mosby, p. 1253-1265.

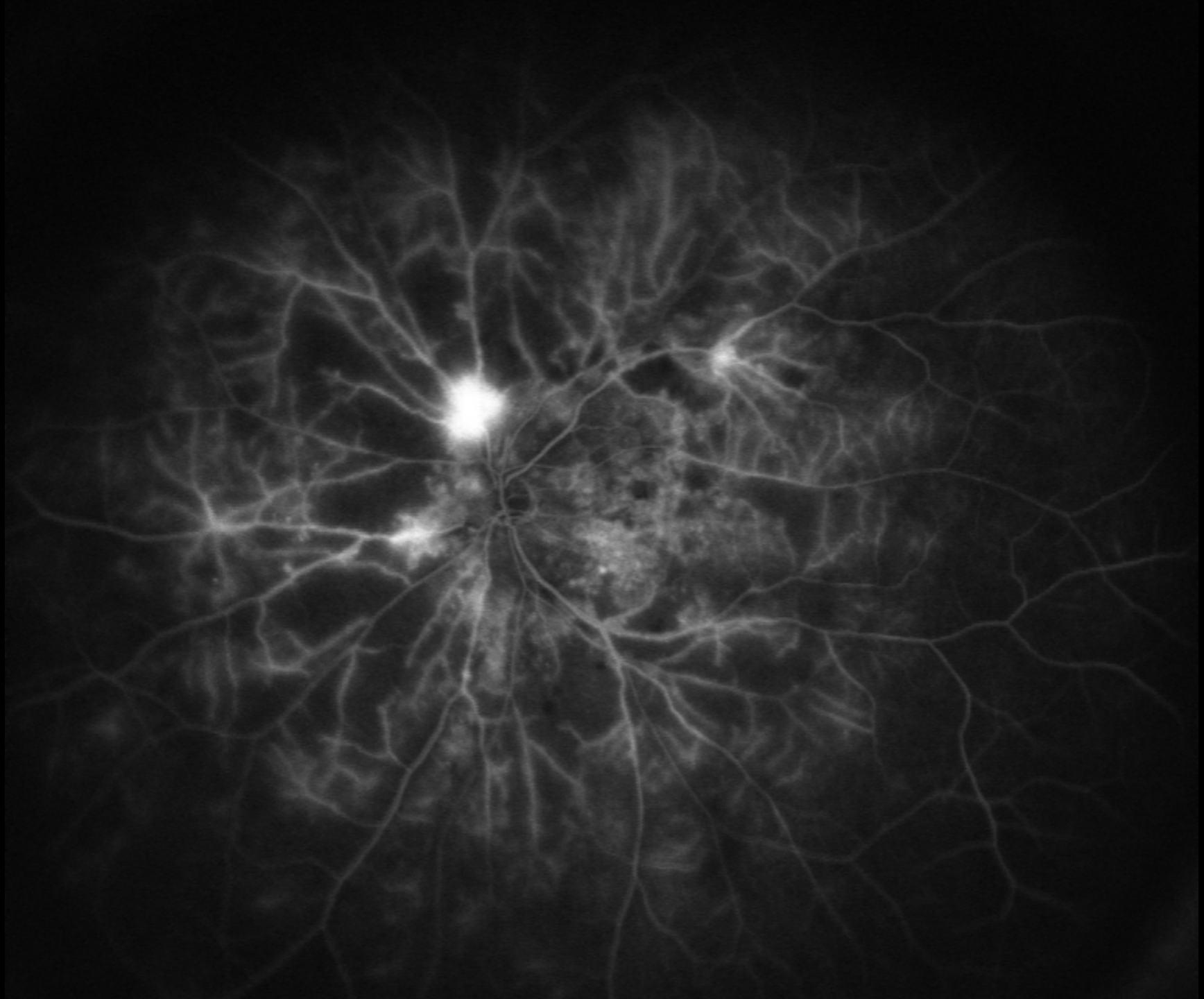
Treatment Considerations – Laser Therapy

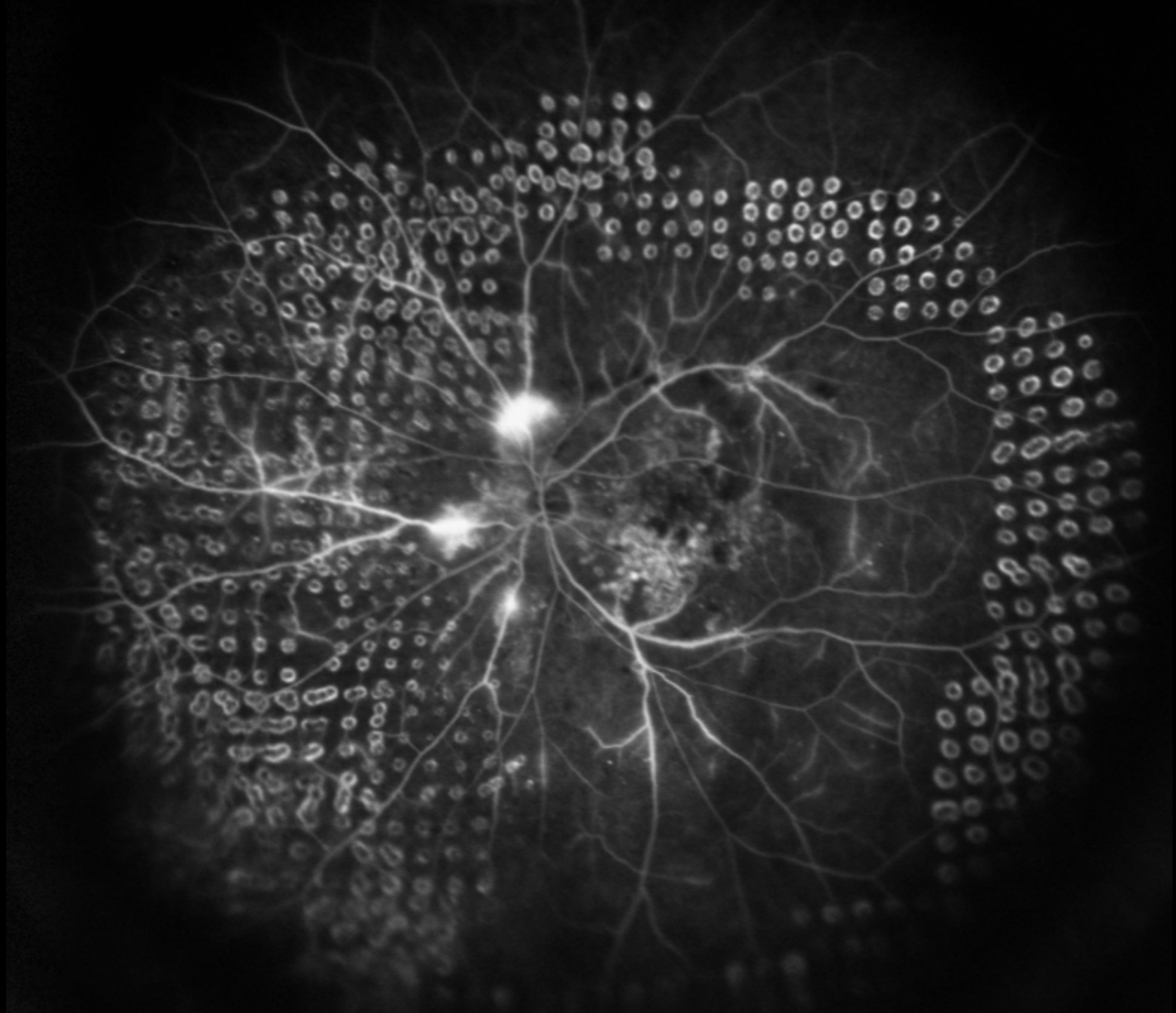
- Laser photocoagulation initially established as standard therapy for proliferative diabetic retinopathy by:
  - Diabetic Retinopathy Study (1976)[1]
  - Panretinal photocoagulation still used to treat PDR



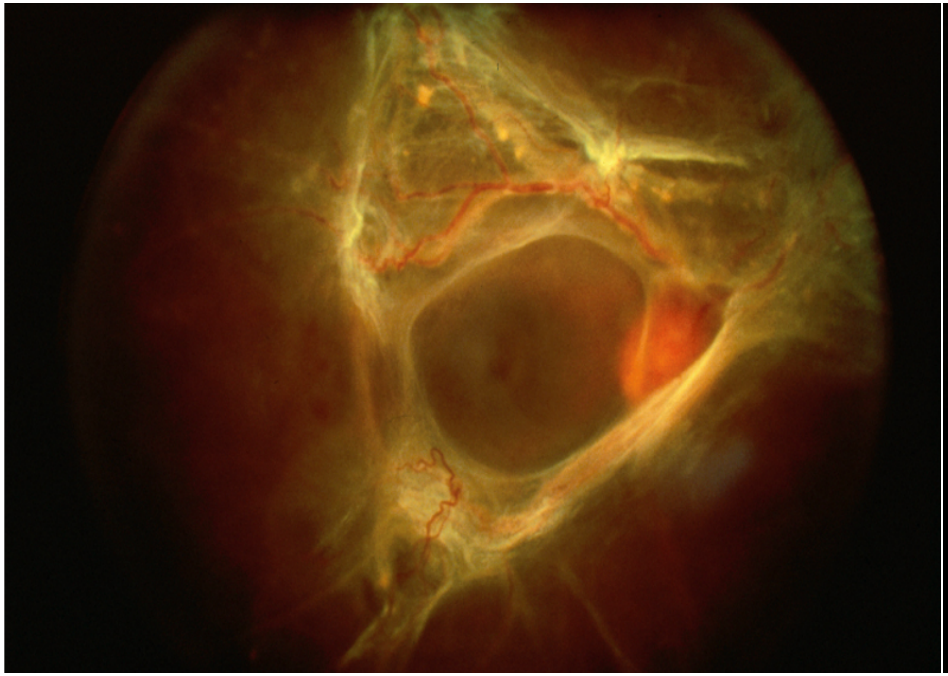
1. DRS Research Group. *Am J Ophthalmol*. 1976;81:383-396. .

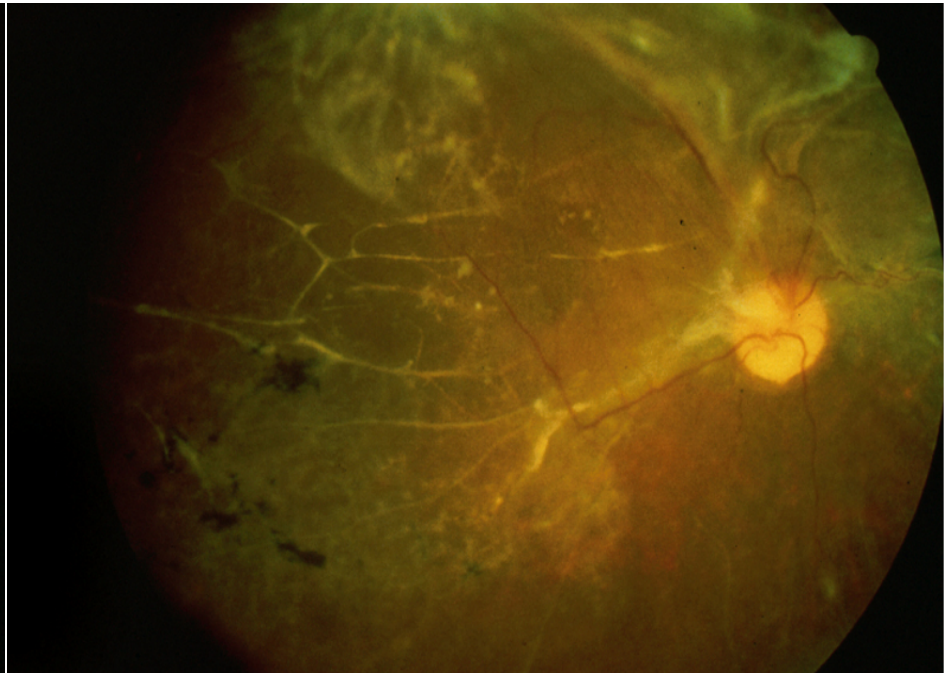






Vitrectomy





DME Treatment

- Diabetic Macular Edema
  - Laser
  - Steroids
  - Anti-Vascular Endothelial Growth Factor (Anti-VEGF) Drugs

Early Treatment Diabetic Retinopathy Study

Clinical Sciences

Expedited Publication

Photocoagulation for Diabetic Macular Edema

Early Treatment Diabetic Retinopathy Study Report Number 1

Early Treatment Diabetic Retinopathy Study Research Group

• Data from the Early Treatment Diabetic Retinopathy Study (ETDRS) show that focal photocoagulation of "clinically significant" diabetic macular edema substantially reduces the risk of visual loss. Focal treatment also increases the chance of visual improvement, decreases the frequency of persistent macular edema, and causes only minor visual field losses. In this randomized clinical trial, which was supported by the National Eye Institute, 754 eyes that had macular edema and mild to moderate diabetic retinopathy were randomly assigned to focal argon laser photocoagulation, while 1,490 such eyes were randomly assigned to deferral of photocoagulation. The beneficial effects of treatment demonstrated in this trial suggest that all eyes with clinically significant diabetic macular edema should be considered for focal photocoagulation. Clinically significant macular edema is defined as retinal thickening that involves or threatens the center of the macula (even if visual acuity is not yet reduced) and is assessed by stereo contact lens biomicroscopy or stereo photography. Follow-up of all ETDRS patients continues without other modifications in the study protocol.

(*Arch Ophthalmol* 1985;103:1796-1806)

For editorial comment see "Photocoagulation Therapy for Diabetic Eye Disease" *JAMA*, Dec 6, 1985.

The Early Treatment Diabetic Retinopathy Study (ETDRS) is a National Eye Institute–supported, multicenter, randomized clinical trial designed to evaluate photocoagulation and aspirin treatment in the management of patients with nonproliferative or early proliferative diabetic retinopathy. The ETDRS was designed to address the following three major questions:

1. When in the course of diabetic retinopathy is it most effective to initiate panretinal photocoagulation?
2. Is photocoagulation effective in the treatment of diabetic macular edema?
3. Is aspirin treatment effective in altering the course of diabetic retinopathy?

This first report deals only with question number 2.

Previous studies have suggested that photocoagulation may be beneficial in the treatment of diabetic macular edema.[1-7] These studies did not provide conclusive evidence because of one or more of the following reasons: (1) Patients were not randomized. (2) Visual acuity was measured without prior refraction and/or was not measured by a "masked" observer. (3) There were confounding effects of advanced proliferative diabetic retinopathy and/or panretinal photocoagulation. (4) The number of patients was small. (5) Treatment techniques were incompletely described. (6) Evaluation of possible photocoagulation effects on visual function other than visual acuity was not reported. Because of these limitations, clinical guidelines for the treatment of macular edema were difficult to formulate.[8,9]

In the ETDRS, the effects of *focal* photocoagulation for macular edema are being evaluated in a prospective, large-scale, randomized clinical trial involving 29 centers (including 23 clinical centers). This first ETDRS report presents the data that support the conclusion that focal photocoagulation for macular edema is beneficial.

PATIENTS AND METHODS

From April 1980 to August 1985, the ETDRS research group enrolled 3,928 diabetic patients with early proliferative retinopathy, moderate to severe nonproliferative retinopathy, and/or diabetic macular edema in each eye. Patients with "high-risk" proliferative retinopathy[10] (moderate or severe optic nerve neovascularization or any neovascularization with hemorrhage) were not eligible for the study, because immediate panretinal photocoagulation already has been recommended for such patients.[11] Patients with other significant ocular disease or visual acuity worse than 20/200 were also ineligible. Prior to

Accepted for publication Sept 27, 1985.

A complete listing of the participants in this research study appears at the end of this article.

Reprint requests to the Biometry & Epidemiology Program, National Eye Institutes, Bldg 31, Room 6A24, 9000 Rockville Pike, Bethesda, MD 20892.

Vision Gain

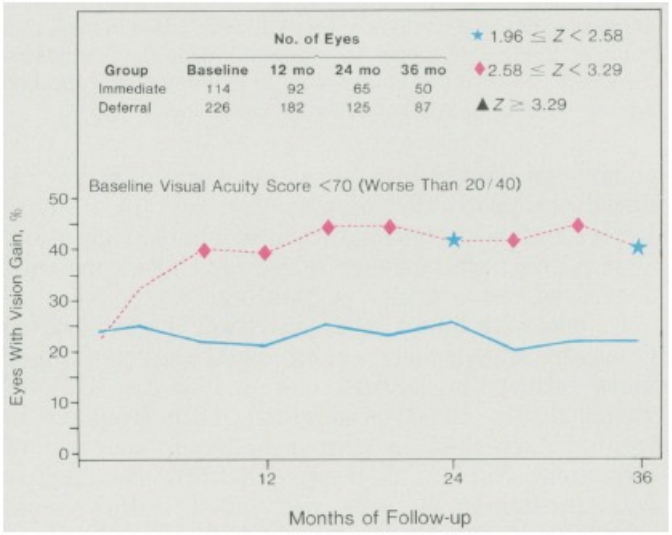


Fig 7.—Comparison of percentage of eyes that experienced visual gain of six or more letters (equivalent to more than one-line gain) in eyes with macular edema and mild to moderate diabetic retinopathy assigned to either immediate focal photocoagulation (broken line) or deferral of photocoagulation (solid line).

ETDRS Research Group. *Am J Ophthal* 1985;103:1796-1806.

Macular Laser for DME

- Standard of care since 1985
- No impact on underlying disease progression
- Reduces risk of vision loss, but few patients experience visual improvement

Focal Laser

Grid Laser

Courtesy of Dr Donald D'Amico

Advances in DME Treatment

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

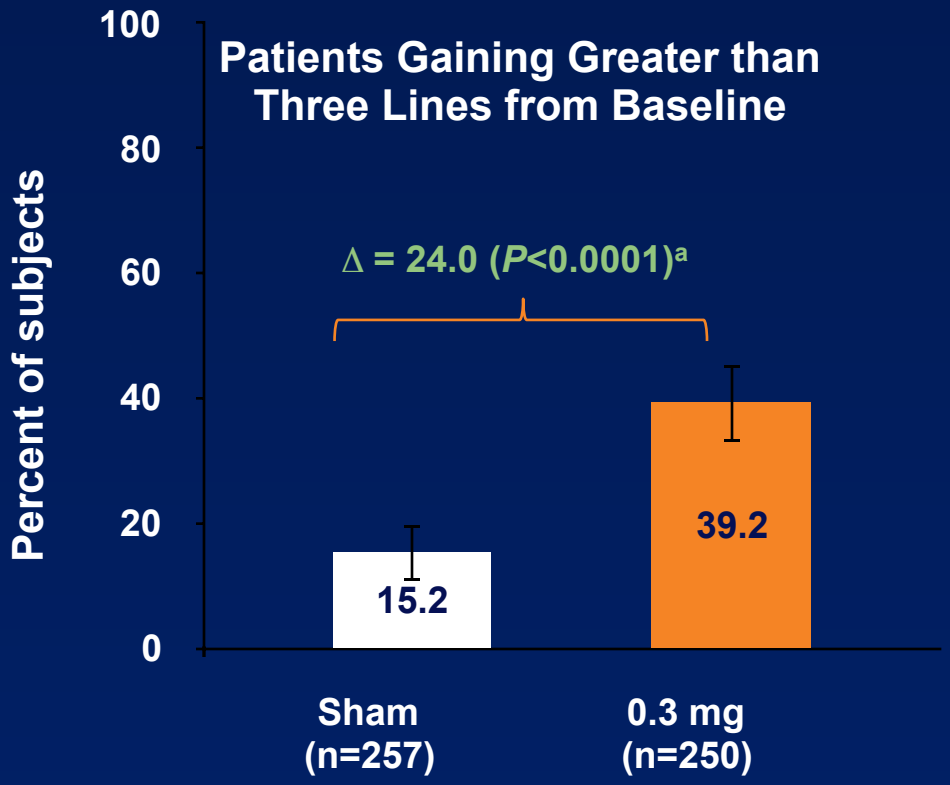
Inflammation-targeted therapy

- Steroid injections
- Dexamethasone steroid implant for long-term

Anti-VEGF Key Studies

- RISE/RIDE: 2 parallel phase III, multicenter, double-masked, sham-injection controlled, randomized studies
- VISTA/VIVID: 2 parallel phase III, multicenter, double-masked, sham-injection controlled, randomized studies

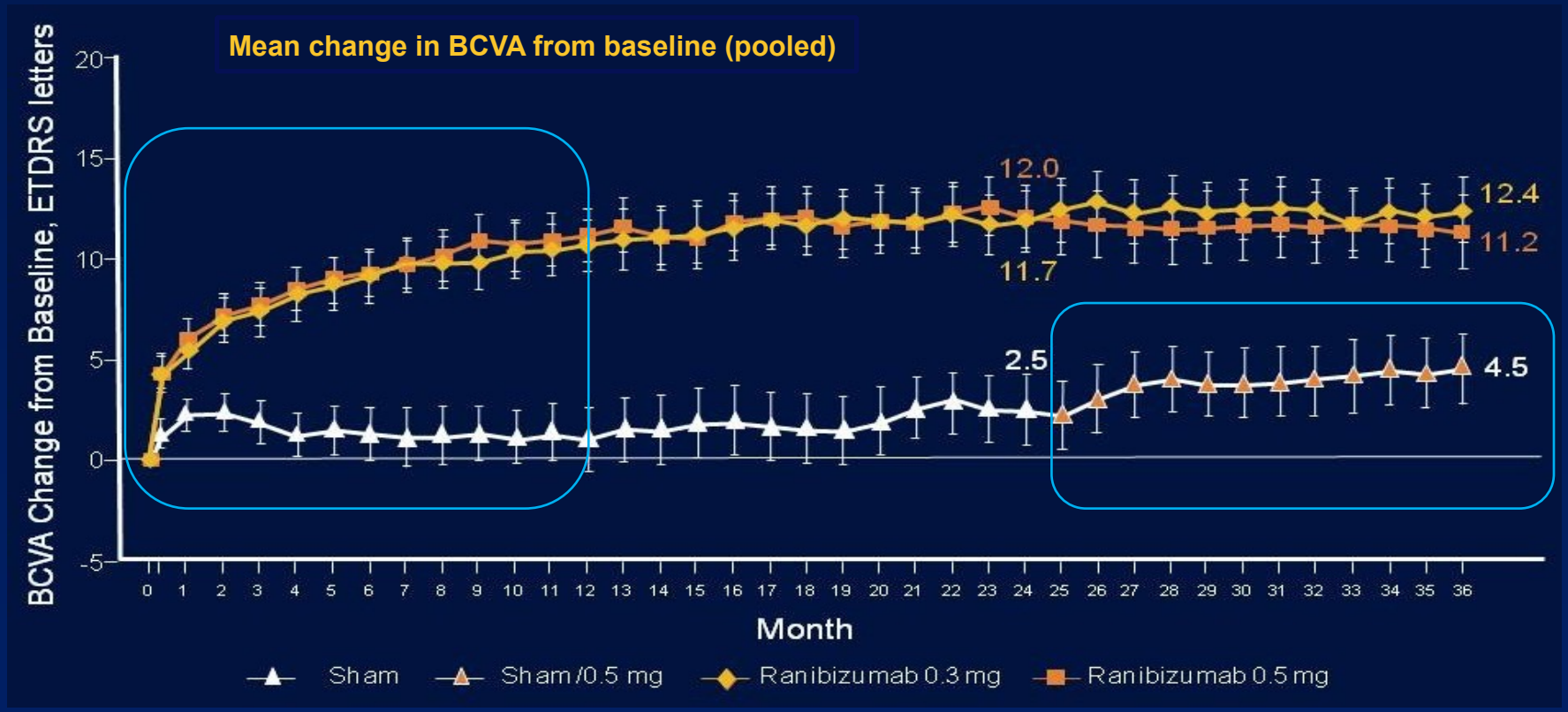
Subjects Gaining ≥15 ETDRS Letters From Baseline at Month 24 (Primary Endpoint)



[a]Cochran-Mantel-Haenszel chi-squared test (stratified).
The LOCF imputation method was used. Vertical bars are 95% confidence intervals. Reported percentages and differences vs sham are unadjusted, test and *P* value are adjusted for baseline VA (≤55, >55 letters), baseline HbA_{1c} (≤8%, >8%), and prior treatment for DME (yes, no).
LUCENTIS FDA Briefing Book.

RIDE/RISE

Effects of Treatment Delay

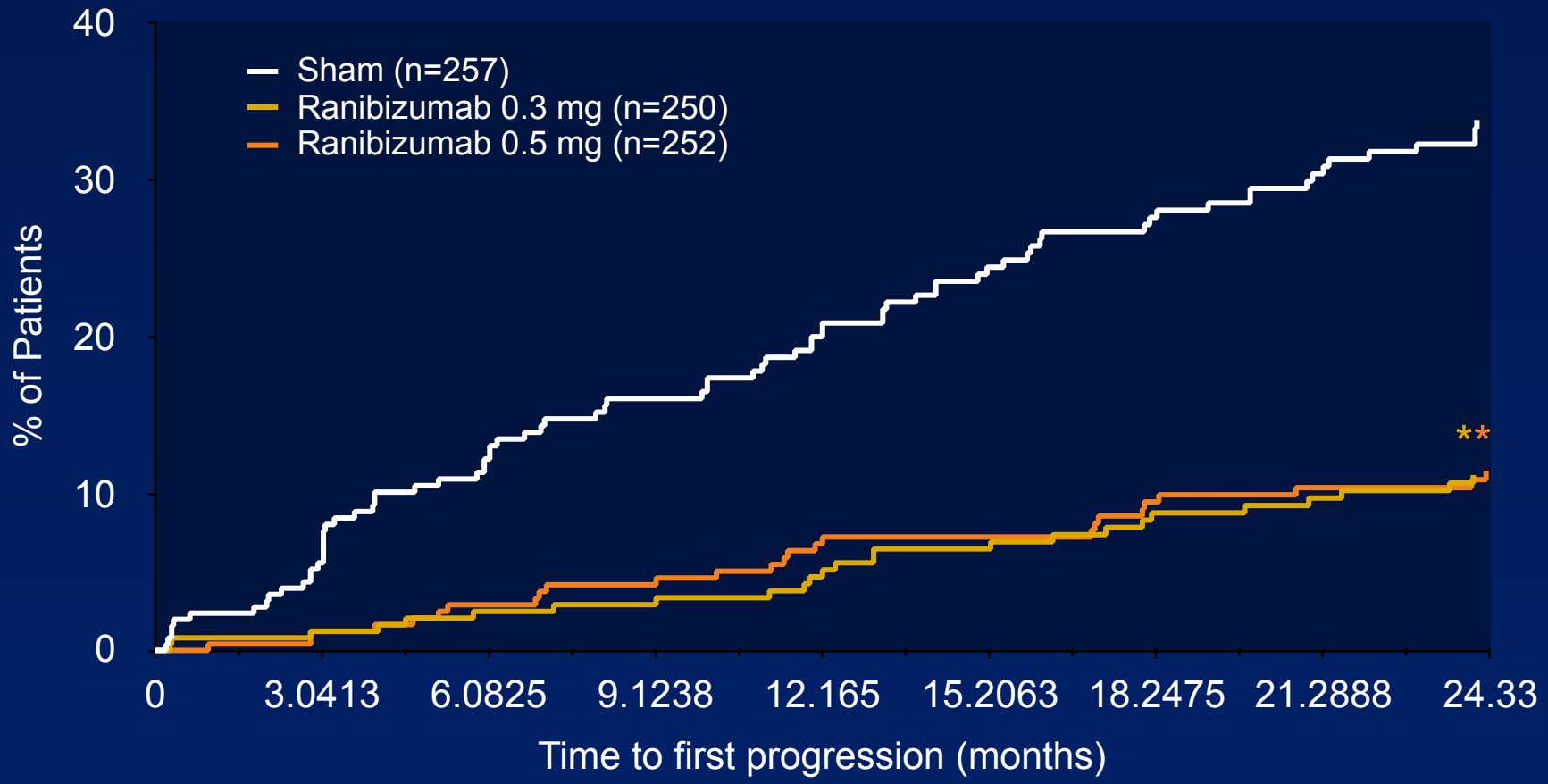


- **Delayed treatment reduced magnitude of VA benefits of anti-VEGF therapy**

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

RIDE/RISE

Time to Development of PDR[1]
(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. AE=adverse event; DR=diabetic retinopathy; PDR=proliferative diabetic retinopathy. *P<.001 vs sham.

1. Ip et al. *Archives of Ophthalmology.* 2012. [Epub ahead of print].

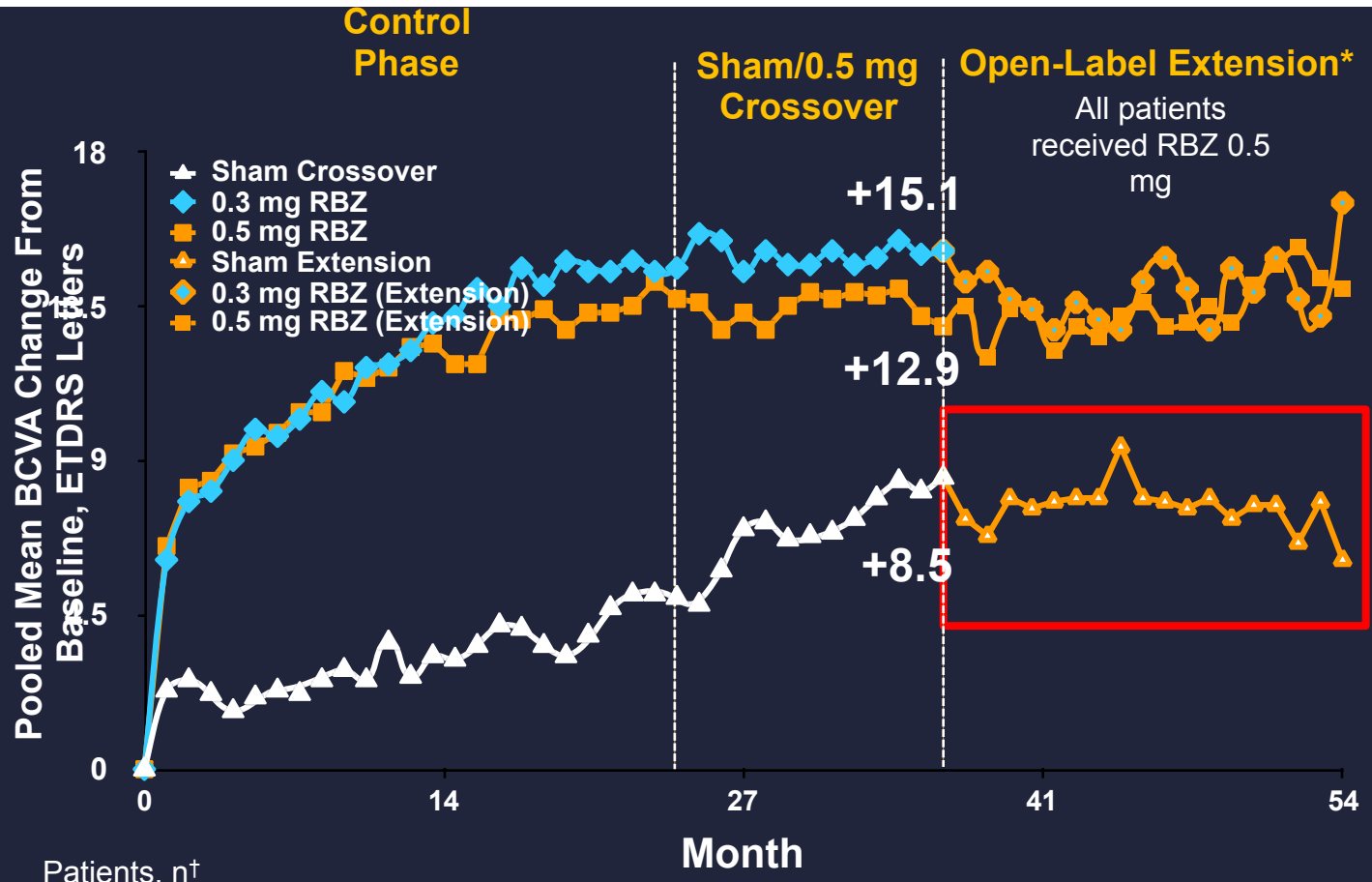
Anti-VEGF Key Studies: Aflibercept

- VIVID-DME and VISTA-DME: Similarly designed, assessed safety and efficacy of aflibercept in the treatment of DME
- Treatment groups: intravitreal aflibercept monthly, every 2 months (after 5 initial monthly injections), or laser photocoagulation

http://bmctoday.net/retinatoday/2013/10/article.asp?f=vivid-vista-1-year-results-show-aflibercept-superior-to-laser-for-dme.

Early Treatment is Important: Delayed Treatment Never Catches Up

RIDE/RISE Open-Label Extension



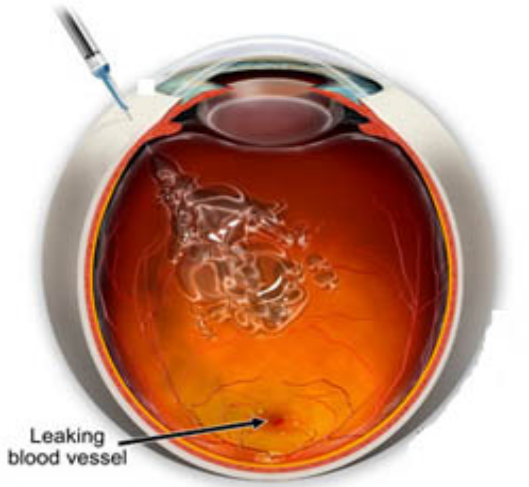
Patients, n†

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

Brown D, ASRS 2014

Counseling and Minimizing Patient Treatment Burden

- Monthly injections may present a significant burden to patient, particularly those who are working-age
- Treatment may go on for several years
- Combination therapy has potential benefits in reducing frequency of injections
- Customized therapy will help to facilitate outcomes



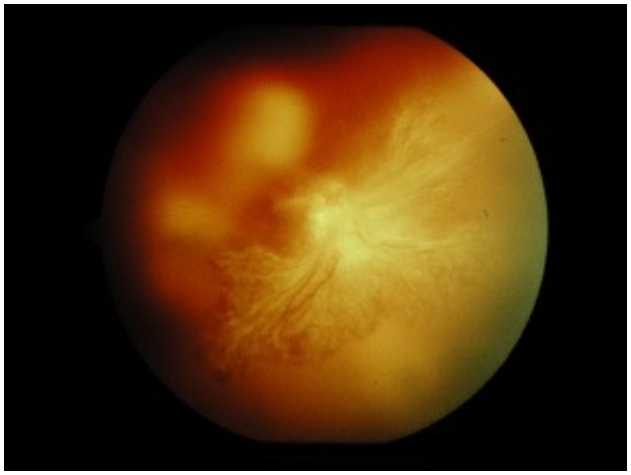
Vitrectomy

- Surgical options include possibility of vitrectomy
  - May be useful for patients with PDR who do not respond to photocoagulation, are not able to undergo photocoagulation due to vitreous hemorrhage, or other select situations[1]
  - May be beneficial for some patients with clinically significant macular edema, such as those with vitreomacular traction[2]
  - Complications of vitrectomy include recurrent vitreous hemorrhage, retinal detachment, rubeosis iridis, severe visual loss, endophthalmitis, cataract[3]

1. Diabetic Retinopathy Vitrectomy Study Report 5. *Arch Ophthalmol*. 1990;108(7):958-964.
2. Mohamed Q et al. *JAMA*. 2007;298:902.
3. AAO Preferred Practice Patterns. 2012.

Take Home Points

- Intensive glycemic control is one of the most important factors for decreasing the onset and progression of diabetic retinopathy
- Other systemic issues play a role:
  - Pregnancy
  - Lipid control
  - Hypertension
  - Renal function and fluid balance
  - Plasma VEGF
- Highly effective treatment options exist to prevent significant vision loss
- Consideration of interaction between glitazones and diabetic eye disease is important



Diabetic retinopathy

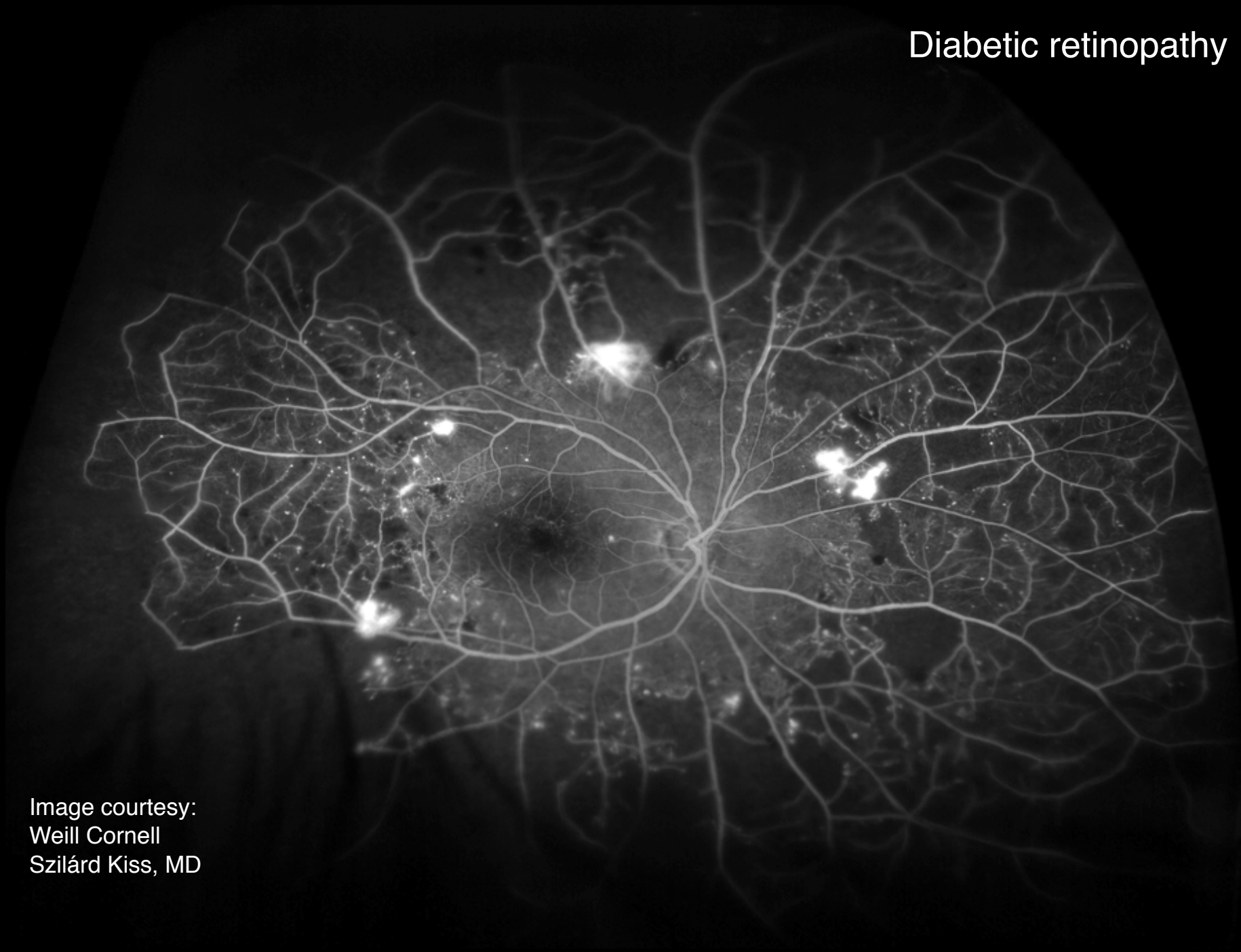


Image courtesy:
Weill Cornell
Szilárd Kiss, MD

CONCLUSIONS

Diabetic Retinopathy is preventable through strict glycemic control and annual dilated eye exams by an ophthalmologist.

Thank you!!!