SUNCOAST SEMINAR

Presented by the
Pinellas Optometric Association

Course Syllabus

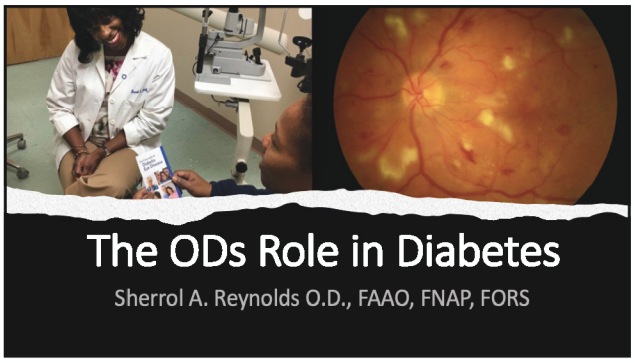
Suncoast Seminar 2024
Schedule of Events

Saturday, April 27, 2024

7:45 am – 8:15 am	**Registration** **Continental Breakfast** - *sponsored by Eye Institute of West Florida* **Exhibit Hall** open
8:15 am – 9:55 am	**Co-Managing the Light Adjustable Lens (90938-PO)** T. Hunter Newsom, M.D., Brian Szabo, D.O., and Eric Fazio, O.D.
9:55 am – 10:40 am	**Break** - *sponsored by Updegraff Vision* **Exhibit Hall** open
10:40 am – 12:20 pm	**Emerging Trends in Macular Disease (TQ) (90790-TD)** Sherrol A. Reynolds, O.D.
12:20 pm – 1:10 pm	**Lunch** - s*ponsored by St. Luke's Cataract & Laser Institute* **Exhibit Hall** open
1:10 pm – 1:20 pm	**Lighthouse of Pinellas Update**
1:20 pm – 1:30 pm	**F.O.A. Update**
1:30 pm – 3:10 pm	**Eye on Systemic Disease (TQ) (90791-SD)** Sherrol A. Reynolds, O.D.
3:10 pm – 3:30 pm	**Break -** *sponsored by Sight360*
3:30 pm – 5:10 pm	**The ODs Role in Diabetes (TQ) (86739-TD)** Sherrol A. Reynolds, O.D.

Sunday, April 28, 2024

7:30 am – 8:00 am	**Registration** **Continental *Breakfast*** - *sponsored by Next Vision Instruments*
8:00 am – 9:40 am	**Neural Pearls (TQ) (89379-NO)** Joe Sowka, O.D.
9:40 am – 10:00 am	**Break** – *sponsored by Suncoast Seminar*
10:00am – 11:40 am	**Prevention of Medical Errors (89825-EJ)** Joe Sowka, O.D.
11:40 am – 12:00 pm	**Break** – *sponsored by Suncoast Seminar*
12:00 pm – 1:40 pm	**Florida Jurisprudence (89275-EJ)** Joe Sowka, O.D.



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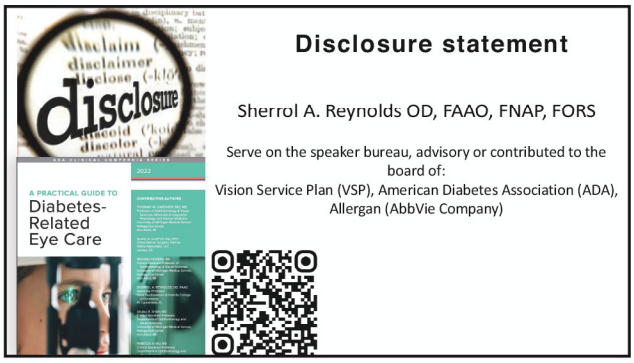

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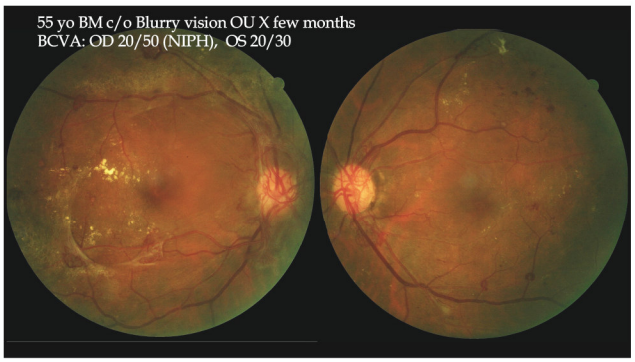

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Poll Question #1

Approximately what percentage of T2DM patients have retinopathy at time of diagnosis?

A. 5%
B. 15%
C. 20%
D. 33 %
E. I don't know

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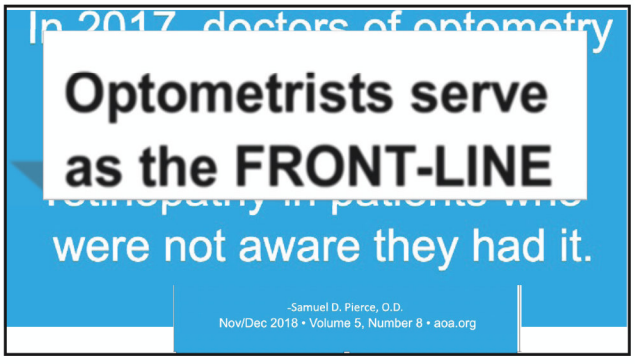

5

Why we are here today

- Diabetes retinopathy is the leading cause of blindness in adults aged 20-74 worldwide.
- Diabetic macular edema (DME) is the leading cause of vision loss among patients with DR

AGENDA:

- Provide the most up-to-date information on diabetes and diabetes-related retinal disease (DRD).
- Discuss the ODs role in Diabetes.
- Discuss the latest in imaging technologies for early detection of DRD.
- OD's role coordination of care for patients with DRD.

6

Diabetes Prevalence Expected to Double Globally by 2050

June 22, 2023
Hayden E. Klein

Article

New estimates predict that type 2 diabetes prevalence will more than double in the next 30 years, from 529 million peo in 2050.

The number of people living with diabetes is expected to more than double globally by 2050, according to research published today in *The Lancet*.

New estimates predict the number will jump from 529 million people living with diabetes in 2021 to at least 1.3 billion in 2050. Researchers also do not expect any countries to see a drop in age-standardized diabetes rates over the next 3 decades.

Centers for Disease Control and Prevention. National Diabetes Statistics Report website. https://www.cdc.gov/diabetes/data/statistics-report/index.html Accessed October 9, 2023
American Diabetes Association. Diabetes Care 2023;46(Supplement_1):S203–S215
International Diabetes Federation Atlas: 10th edition.
Available from https://www.idf.org/aboutdiabetes/what-is-diabetes/facts-figures.html; Accessed 9 October 2323

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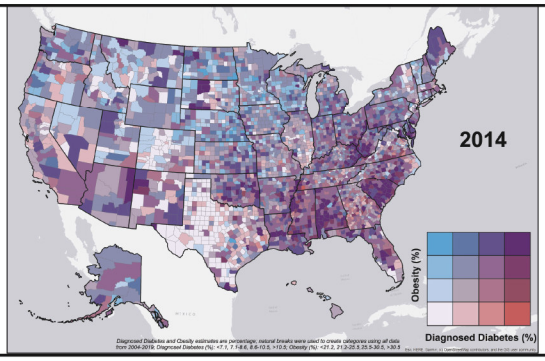

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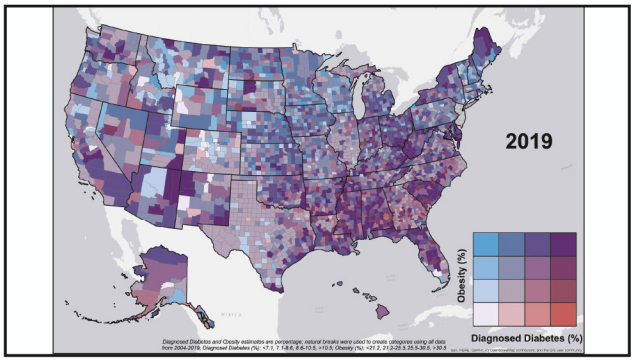

9

TYPES OF DIABETES

Type I Diabetes	• Autoimmune destruction of pancreatic β-cells results in significantly decreased insulin secretion • Exogenous insulin (injection) is necessary to sustain life • Represents only 5-10% of all DM • Can occur at any aga, with myriad oof acute symptoms
Type 2 Diabetes	• Results from insulin resistance at cellular receptor sites, as well as decreased insulin secretion (or absolute loss • Represents ~90% of all DM • Commonly seen in patients over 40 years; incidence increases with age and obesity
Gestational Diabetes	• β-cell dysfunction and insulin resistance during pregnancy • Occurs in ~4% of all pregnancies in second and third trimester • **40-60% risk of developing Type II DM within 5 years postpartum**
Less common forms	• **Genetic defects of β-cell function: latent autoimmune diabetes in adults (LADA), monogenic forms (maturity-onset diabetes of the young (MODY), exocrine pancreatic diseases, endocrinopathies, drug- or chemical-induced, Other rare forms** • **Often misdiagnosed as type 1 or 2 diabetes**
Prediabetes	• Higher than normal blood sugar level. It's not high enough to be considered type 2 diabetes

American Diabetes Association. Diabetes Care. 2024 Jan 1;47(Suppl 1):S52-S76.

10

RISK FACTORS FOR DIABETES

- Age
- Family history/ Genetics
- Specific ethnic backgrounds
  - African American
  - Native American
  - Hispanic
  - Asian American
  - Pacific Islander
- Sedentary lifestyle
- Obesity
- Pertinent medical history
  - Obesity/non-alcoholic fatty acid liver disease
  - Cardiovascular disease
  - Hypertension
  - High cholesterol
  - Polycystic ovarian syndrome (POS)
  - Psychiatric illness
  - Gestational DM
  - Impaired fasting glucose/impaired glucose tolerance
  - Smoking

11

Emerging risk factors for diabetes

Sleep disturbances (Apnea)

Air pollution

Workplace stress

Bisphenol A (BPA)exposure
- BPA detrimental effect on pancreatic β cells- beta-cell dysfunction, inflammation, and oxidative stress

Malnutrition

The Association between Vitamin D Deficiency and Diabetic Retinopathy in Type 2 Diabetes: A Meta-Analysis of Observational Studies. Nutrients. 2017 Mar; 9(3): 307.

12

Emerging risk factors for diabetes

- Medical nutrition therapy (MNT): has a direct effect in preventing or slowing diabetes complications including DR.
- Supplements may also have an effect on the prevention and progression of DR (vitamins A, B, C, and D; fiber; taurine; alpha-lipoic acid; lutein/zeaxanthin; others)
- Vitamin D deficiency
  - Low levels linked with high HbA1C levels (test showing blood sugar levels over weeks-months)
  - Low vitamin D levels (< 20 ng/mL) have been found to be associated with increased severity of DR

Br J Ophthalmol. 2016 Feb;100(2):227-34
J Steroid Biochem Mol Biol 2017 Oct;173:280-285.

13


COVID-19 in people with diabetes: understanding the reasons for worse outcomes

- Risk of Death from COVID-19 Four Times Greater for Those with Diabetes
- Nearly 40% of people who have died with COVID-19 had diabetes

Individuals with Diabetes are Up to Four Times More Likely to Develop Long COVID-19

www.thelancet.com/diabetes-endocrinology Vol 8 October 2020

14

Fast Progression of Diabetic Retinopathy with SARS-CoV-2 Infection

Authors: *Yigit C. Akduman,[1] William J. Anderson,[1] Sandeep Saxena[2]

1. Saint Louis University, St. Louis, Missouri, USA
2. King George's Medical University, Lucknow, India
*Correspondence to yiakduman@gmail.com

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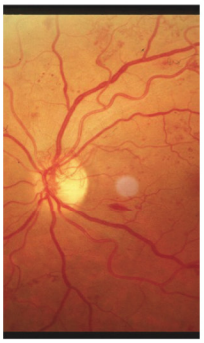
Received: 09.11.20
Accepted: 15.01.21
Keywords: Diabetic retinopathy, macular oedema, neovascularisation, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, vitreous haemorrhage.
Citation: EMJ Diabet. 2021; DOI/10.33590/emjdiabet/20-00254

Abstract

COVID-19 is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and has been shown to affect a multitude of organ systems. It is often associated with vasculitis or thromboembolic disease with resultant tissue hypoxia. This report presents a case of fast progression diabetic retinopathy in the case of a SARS-CoV-2 infection. The findings conclude that patients with diabetes should be more frequently monitored for emergence or progression of diabetic retinopathy if they present with COVID-19.



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16

Newly discovered genetic markers help pinpoint diabetes risks, complications

Date: February 19, 2024

Source: University of Massachusetts Amherst

Summary: In the largest genome-wide association study to date on Type 2 diabetes, a team of international researchers has located 1,289 genetic markers associated with Type 2 diabetes (145 of which are newly identified) and generated risk scores for diabetes complications.

17

Science News *from research organizations*

Blood test could determine diabetes risks

Date: February 21, 2024

Source: Edith Cowan University

Summary: A blood test could potentially be used to assess a patient's risk of type 2 diabetes, a new study has found.

- Inflammatory biomarker currently used to predict the risk of type 2 diabetes is **high-sensitivity C-reactive protein (CRP)**
- A study by ECU researcher Dan Wu investigated the connection between systematic inflammation, assessed by joint cumulative high-sensitivity CRP and another biomarker called monocyte to high-density lipoprotein ratio (MHR)
- concomitant increases in MHR and CRP presented significantly higher incidence rates and risks of diabetes

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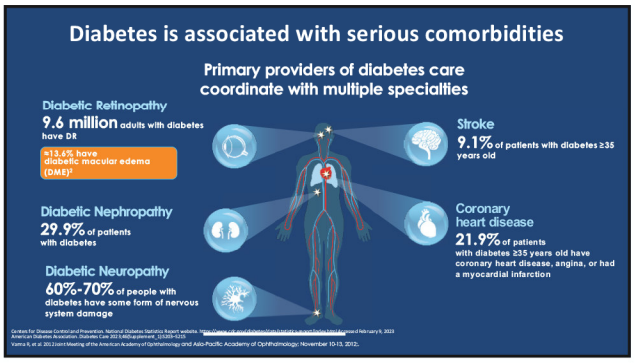

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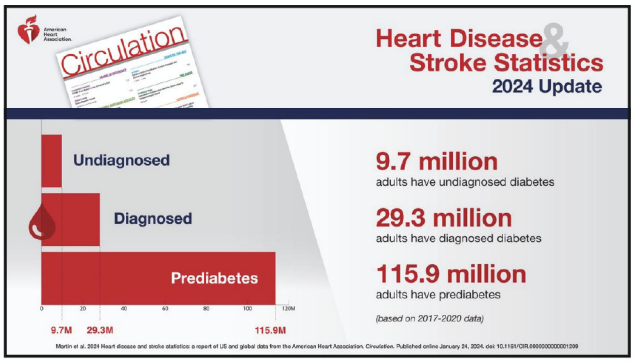

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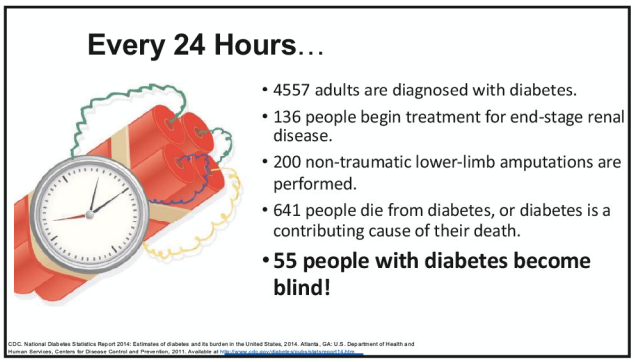

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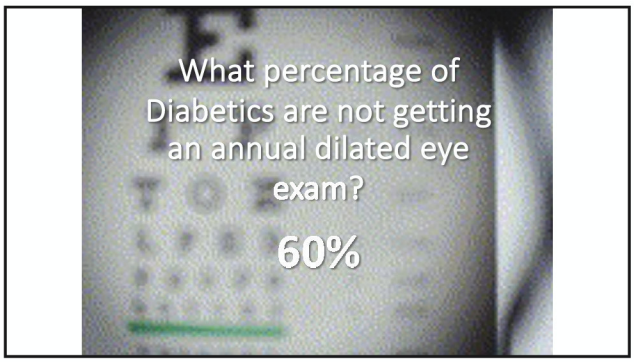

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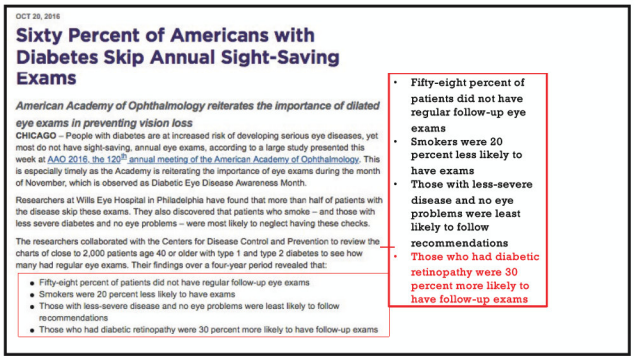

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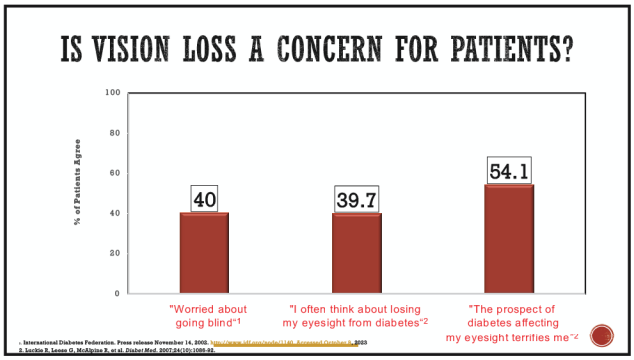

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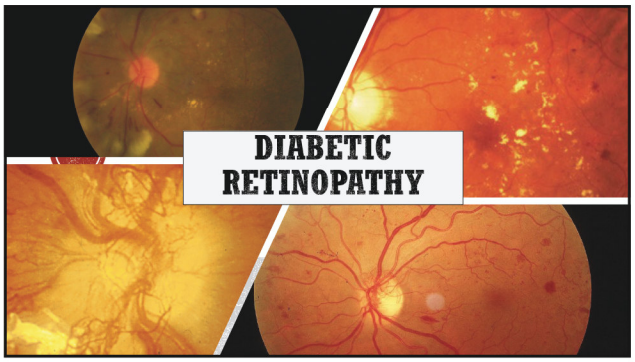

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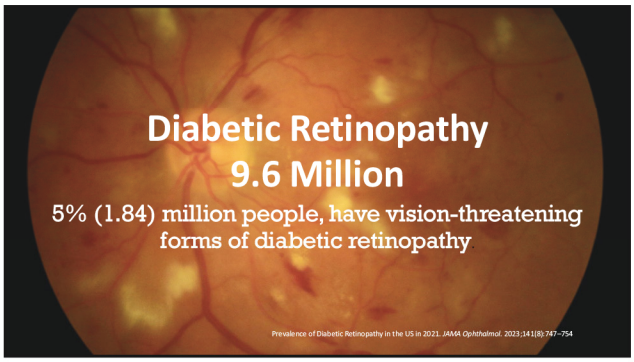

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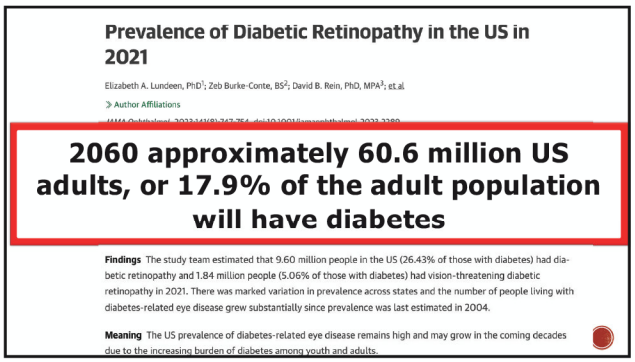

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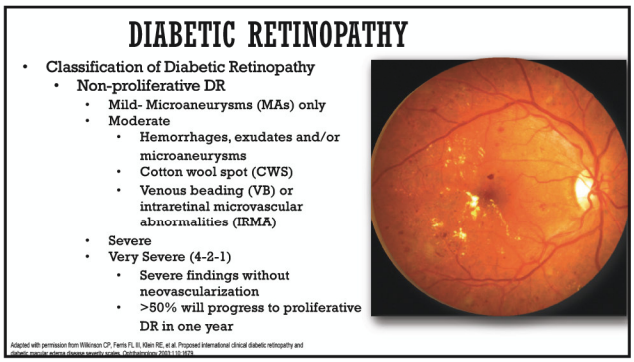

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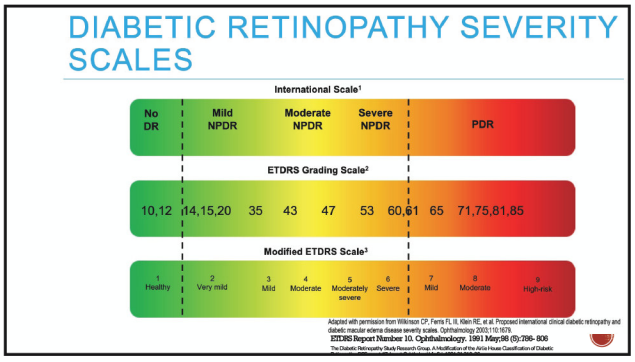

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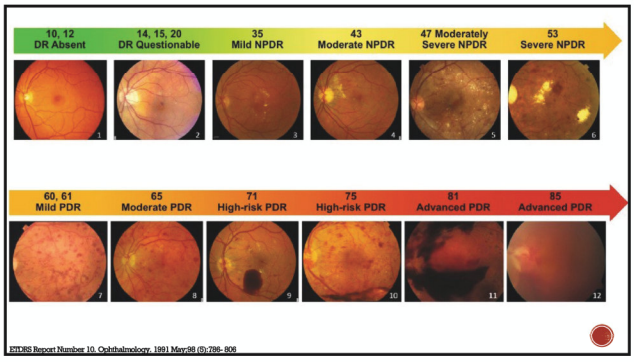

30

Disease Severity	Definition	Management	Natural History
No retinopathy	Diabetic retinopathy absent	12 months	
Mild NPDR	MAs only	12 months	*5% risk of progression to proliferative diabetic retinopathy (PDR) within one year.
Moderate NPDR	MAs plus, exudates, cotton wool spots, retinal hemorrhages, intraretinal microvascular abnormality, venous beading	Three to six months *Depends on severity of signs, stability, systemic factors, and patient's glycemic control	*Up to 27 % risk of progression to proliferative diabetic retinopathy (PDR) within one ye ar.
Severe NPDER (4-2-1) rule	Severe retinal hemorrhages in four quadrants, or venous beading in at least two quadrants, or moderately severe intraretinal microvascular abnormality in at least one quadrant	Two to three months	*Proliferative diabetic retinopathy in up to 50% within a year

American Optometric Association. Evidence-based Clinical Practice Guideline: Eye Care of the Patient With Diabetes Mellitus. www.aoa.org/optometrists/tools-and-resources/evidence-based-optometry/evidence-based-clinical-practice-guidlines/cpg-3-eye-care-of-the-patient-with-diabetes-mellitus. Accessed October 8, 2023

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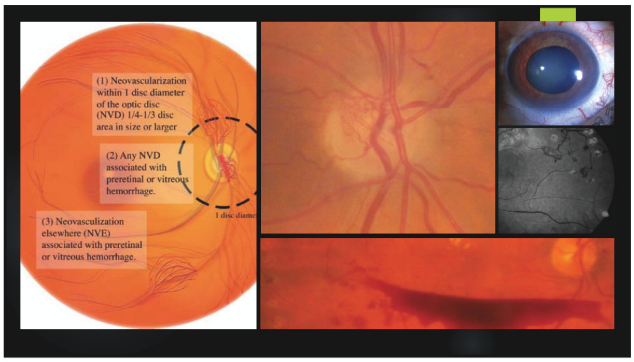


32

Proliferative Diabetic Retinopathy

PDR	Neovascularization Vitreous Hemorrhage		Retina referral within one week
	High Risk: 1. NVD > 1/4-to-1/3-disc area 2. Any NVD associated with vitreous or preretinal hemorrhage 3. Any NVE associated with vitreous or preretinal hemorrhage		Retina referral within one day to two days

American Optometric Association. Evidence-based Clinical Practice Guideline: Eye Care of the Patient With Diabetes Mellitus. www.aoa.org/optometrists/tools-and-resources/evidence-based-optometry/evidence-based-clinical-practice-guidlines/cpg-3-eye-care-of-the-patient-with-diabetes-mellitus. Accessed October 8, 2023

33

Diabetes Eye Disease Risk

Duration of diabetes is a major risk factor associated with the development of DR.

Total glycemic exposure (A1C over time) is the key alterable risk factor associated with the development of DR.

Obesity/BMI is an alterable risk factor for the development of DR.

The ABCs of diabetes: A1C, blood pressure, cholesterol, and smoking cessation are alterable risk factors associated with the development of DR

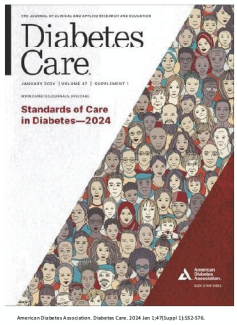
A A1C levels

B Blood pressure

C Cholesterol

S Stop smoking

34



American Diabetes Association. Diabetes Care. 2024 Jan 1;47(Suppl 1):S1-S276.

New in 2024

- HbA1c near normal 6%
- CGM in patients on Insulin
  - Time in Range (TIR)
  - Target range: 70–180 mg/dL
  - Recommended TIR for most: >70%
- Stricter BP targets (≤130/80)
- New lipid management recommendations- LDL <70 mg/dL in general and <55 mg/dL for those with preexisting atherosclerotic CVD
- Higher weight loss targets (up to 15%) based on the efficacy of and access to newer medications such as high-dose semaglutide and tirzepatide
- Screen for Sleep Apnea
- Social Determinant of Health (SDOH)

35

Glycemic Control

- Long-term benefits of meeting glycemic targets, including for eye health
  - **Optimizing glycemic control (near normal 6%)**
  - Small reductions add up (effect of a 1% reduction on A1C in reducing microvascular and macrovascular complications)

A1C	DCCT 9—7%	UKPDS 8—7%
Retinopathy	63%	17–21%
Nephropathy	54%	24–33%
Neuropathy	60%	—
Macrovascular Disease (stroke, MI)	41%	16%

DCCT Research Group; Nathan DM, Genuth S, Lachin J, et al. N Engl J Med 1993;329:977–986
UK Prospective Diabetes Study Group. Lancet 1998;352:854–865
American Diabetes Association. Diabetes Care 2023;46(Supplement_1):S203–S215

36

What is the average AIC in the US?

Patient Perceptions of Current Disease Control in Poorly Controlled Diabetes

- Average A1c was 9.9 (S.D. 1.7)%; no differences were noted based on income, education, disease duration, or complication history.
- 23.7% described their disease control as "good" or "excellent" in spite of an average A1c of 9.5%
- 50.0% had an A1C value of 7.0% or higher.

Appendix Table 9. Distribution of A1C levels among adults with diagnosed diabetes aged 18 years or older, overall and by age group, United States, 2013–2016.

A1C	Total	18–44 years	45–64 years	≥65 years
<5.5%	34.2 (30.4–38.1)	38.7 (30.5–47.6)	30.5 (25.9–35.5)	36.9 (31.9–42.3)
5.5%–6.9%	15.8 (13.2–18.8)	14.7 (9.3–22.4)	14.8 (11.5–18.9)	17.4 (13.1–22.9)
7.0%–7.9%	22.3 (19.5–25.4)	12.9 (8.8–18.5)	22.3 (19.0–26.0)	25.6 (20.8–31.0)
8.0%–8.9%	13.2 (10.7–16.2)	12.9 (7.6–21.1)	13.7 (10.0–18.5)	12.6 (9.8–16.1)
9.0%–9.9%	4.6 (3.3–6.5)	4.5 (2.4–8.4)	5.9 (3.9–8.9)	3.1 (1.8–5.3)
≥10.0%	9.9 (8.1–12.1)	16.3 (10.8–23.9)	12.7 (9.5–16.9)	4.3 (2.9–6.5)

Note: Estimates are crude percentages and 95% confidence intervals.
Data source: 2013–2016 National Health and Nutrition Examination Survey.

37

A1C is the gold standard

- American Diabetes Association emphasizes an incremental benefit to further lowering the A1C in selected individuals with no significant hypoglycemia to reach values as close to normal (<6.0%) as possible.
- Average of blood glucose ± (= glycation)
  - The "mean" by CGM can vary significantly in patients with same A1C
  - **A1C is unreliable in patients with anemia, hemoglobinopathies, or iron deficiency.**
  - **Evidence shows that A1C differs among ethnic groups.**
- HbA1c does not reveal glucose variability that has predictive power for DR and other diabetes complications

American Diabetes Association. Diabetes Care 2023;46(Supplement_1):S203–S215
Davies T, Nirel R, Bettelheim T, et al. Diabetes Care 2017;40:1631–1640
Christy AL, Manjrekar PA, Babu RP, Hegde A, Rukmini MS, Iran Biomed J 2014;18:88–93
Wolffenbuttel BH, Herman WH, Gross JL, Chamnadegam M, Jiang HH, Hardin DS. Diabetes Care 2013;36:2931–2936

38

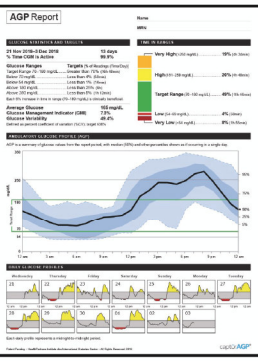
Continuous glucose monitoring (cgm)

- Sensor measures interstitial glucose levels continuously throughout the day.
- Wirelessly sends glycemic data to a monitor or smartphone app.
- May be connected to an insulin delivery system (hybrid closed-loop system, automating basal insulin delivery).
- Standardized reports allow patients and providers to identify glycemic trends and easily review the percentage of time spent above, in, or below a target glycemic range.

39

Time in Range (TIR)

- A new parameter to evaluate blood glucose control
- Indicates the percentage time a person's glucose value was within the target range during a defined period
- Target range: **70–180 mg/dL**
- Recommended TIR for most: **>70%**

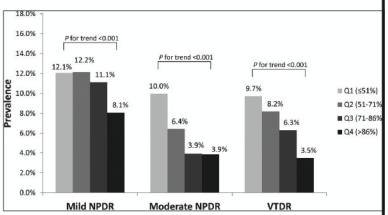


American Diabetes Association. Diabetes Care 2023;46(Supplement_1):S203–S215

40

Time in range (TIR) and Complications

- The higher the TIR range percentage- the lower the risk of developing complications
- The lower the TIR range percentage, the higher the risk of developing complications
- Lu et al., 2018: patients with more advanced DR had significantly less TIR and higher measures of glycemic variability than those with less severe or no DR. TIR was significantly associated with prevalence of all stages of DR.

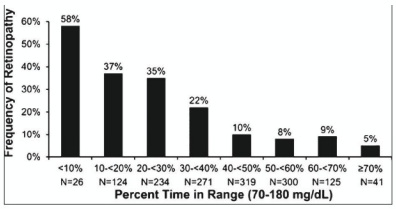


NPDR, nonproliferative diabetic retinopathy; VTDR, vision-threatening diabetic retinopathy.

41

Association of TIR and DRD

- Beck et al., 2019: analysis of data from the 1993 landmark Diabetes Control and Complications Trial.
- Computed TIR from 7-point blood glucose data that had been collected quarterly.
- Risk of DR was significantly higher in the conventional insulin therapy group than in the group receiving intensive insulin therapy.
- **For every 10% lower TIR, the hazard rate of retinopathy progression increased by 64%.**



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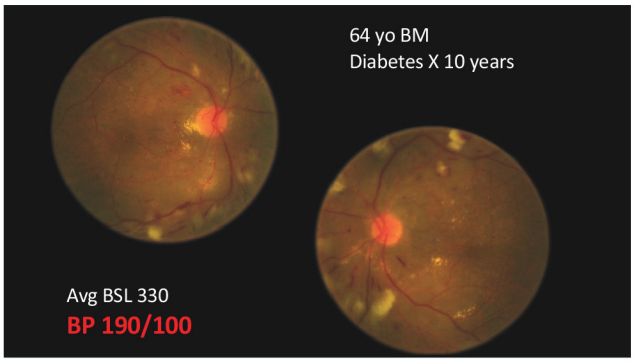

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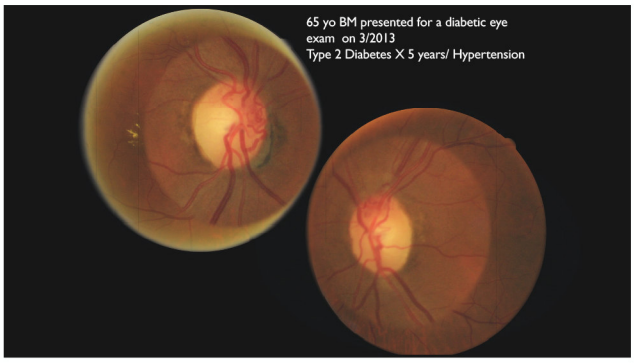
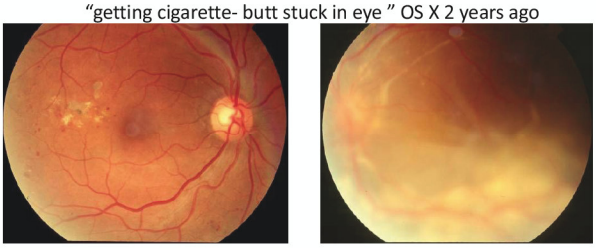


44

The Case of the Cigarette Attack

66-year-old Black male: H/o Type 2 DM X 5 years. (+) Trauma OS- "getting cigarette- butt stuck in eye " OS X 2 years ago



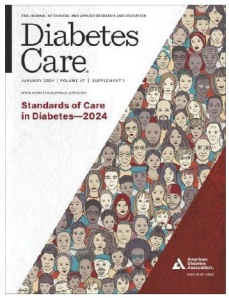
45

Asymmetric Diabetic Retinopathy

- Asymmetric retinopathy occur in 5-10% of diabetic patients increase risk of stroke
  - 2-4 times higher than people w/o diabetes
- Associated with carotid artery stenosis both ipsilateral and contralateral to the eye with worse DR
- Eyes with lower IOP may have increased risk of sight-threatening DR due to increased blood flow in compromised retinal capillary bed
- Protection also associated with prior chorioretinal scarring and high myopia

Brit J Diab Vasc Dis 2001; 1(1):80-87
Ophthalmology 1990; 97(7):869-74
Retina. 2017 Jul;37(7):1270-1276

46



Long-term benefits of optimized blood pressure and serum lipid control to reduce the risk or slow the progression of DR

- On-treatment target blood pressure goal **is ≤ 130/80 mmHg**
- ACE inhibitors and ARBs
- Obtain a lipid profile at initiation of statins or other lipid-lowering therapy
  - New lipid management recommendations- LDL <70 mg/dL in general and <55 mg/dL for those with preexisting atherosclerotic CVD
  - Simvastatin + Fenofibrate therapy lowers the risk of DR progression by 35% compared to simvastatin alone in patients with T2DM and high cardiovascular risk

American Diabetes Association. Diabetes Care. 2024 Jan 1;47(Suppl 1):S52-S74.

47

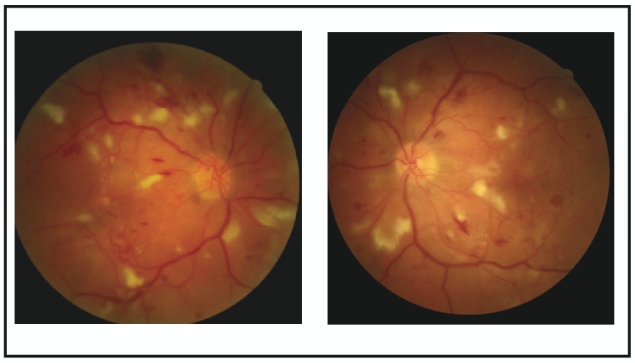
Can Statins Cause Diabetes Mellitus?

-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors

What Statin Is Best for People With Diabetes?

Diabetologia. 2015;58:1109-1117

48



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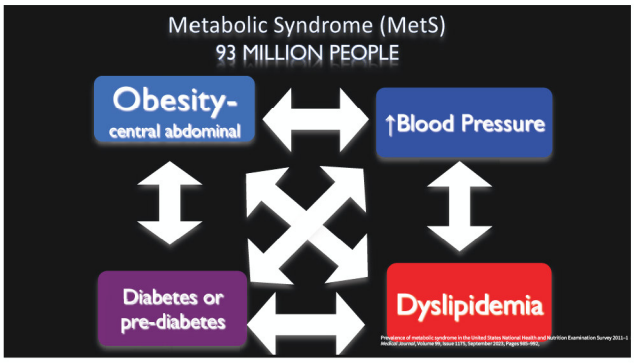


50

Cardioprotective Medications

- Semaglutide, a glucagon-like peptide-1 receptor agonist, has been shown to reduce the risk of adverse cardiovascular events in patients with diabetes
- FDA Approves ORAL GLP-1 as First-Line Tx
- Oral semaglutide (Rybelsus®) was approved 1/12/23 as first-line medical Tx for T2DM
- PIONEER-6 cardiovascular outcomes trial (CVOT)
  - Showed a 20% risk reduction in MACE and 51% reduction in CV death over 72 weeks when added to usual care (all patients > 50 with CVD or > 60 with CV risk factors)
- SGLT2 Inhibitors –Invokana® (canagliflozin); Farxiga® (dapagliflozin); Jardiance® (empagliflozin)
  - Significantly reduce the risk of being hospitalized for congestive heart failure (CHF) and Reduce MI, Stroke, Heart Failure, End-stage Renal Disease and CV Death by 19-50%

Effect of Oral Semaglutide on Cardiovascular Parameters and Their Mechanisms in Patients with Type 2 Diabetes: Rationale and Design of the Semaglutide Anti-Atherosclerotic Mechanisms of Action Study (SAMAS). Diabetes Ther. 2022 Apr;13(4):795-810

51

52

Exercise and Diabetes: Diabetes Prevention Program (DPP)

3,234 study participants were overweight and had prediabetes

Two groups:

- Lifestyle intervention group- diet, exercise, and behavior modification
- 850 mg of Metformin twice a day

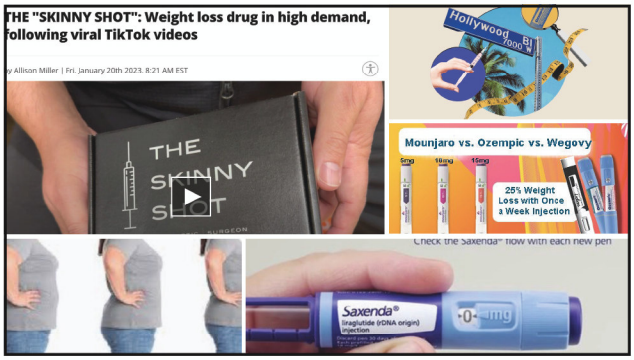
Result:

- **Lifestyle intervention group- reduced their risk of developing diabetes by 58%**
- Metformin reduced their risk of developing diabetes by 31%.

NATIONAL Diabetes PREVENTION PROGRAM

N Engl J Med 2002; 346:393-403

53



54

- **Wegovy, Ozempic: Once a Week Injections-Potent Weight Loss Meds**
- Ozempic: Semaglutides (0.5mg, 1 mg or 2mg)
- Glucagon-like peptide 1 receptor agonists (GLP-1 RA)
- Promotes the pancreas to release insulin
  - only when glucose values are elevated
  - makes people feel fuller faster so they tend to eat less,
  - Reduces the amount of glucose made by the liver.
- 25% weight loss from baseline
- Wegovy- higher dose (2.4mg)

- **Mounjaro (tirzepatide) injection**
- Activates both the glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptor
- 5milligrams, 10 milligrams and 15 milligrams
- Average Weight Loss of 60 Pounds Reported
- 10/2023- FDA Approved

55

Cardioprotective Medications

Weight-loss drug Wegovy can be marketed for heart benefits after FDA label update

By Meg Tirrell, CNN
3 minute read · Updated 5:53 PM EST, Fri March 8, 2024

56

Complications

- Pancreatitis- Inflammation of the pancreas
- Low blood sugar (hypoglycemia)
- Serious allergic reactions
- Kidney problems (kidney failure)
- Severe stomach problems (stomach paralysis)
- Gallbladder problems

57

December 14, 2022 | 2 min read SAVE

Nearly half of adults with type 2 diabetes saw remission with calorie restriction, timing

Percentage of adults with type 2 diabetes achieving remission:

	Intervention	Controls
At 3-month follow-up	47.2%	2.8%
At 12-month follow-up	44.4%	0%

DIABETES AND INTERMITTENT FASTING
TYPE 1, TYPE 2, & PREDIABETES

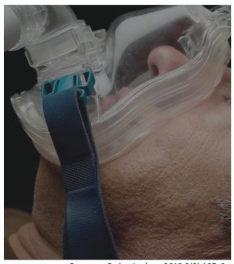
Effect of an Intermittent Calorie-restricted Diet on Type 2 Diabetes Remission: A Randomized Controlled Trial, The Journal of Clinical Endocrinology & Metabolism, 2022.

58

Obstructive Sleep Apnea Syndrome (OSAS) and Diabetes

- Short sleep (< 5.5 hours) triples the likelihood of T2DM in observational studies after all controls.
- Severe obstructive sleep apnea increased incident diabetes 71% over 13 years independently of adiposity.
- Both short (<5.5 hrs) and long (> 9 hrs) sleep duration are significantly associated with adiposity & insulin resistance.

Obesity – the metabolic syndrome



European Endocrinology, 2013;9(2):107–9
Diabetes Res Clin Pract. 2018 May;139:195-202

59

ESAP: Easy Slee

- 100% specificity for mild OSAS in T2DM (n = compared with PSG
- Neck circumference > 17/16 inches in males/ 100% specific
- Both more specific but less sensitive than BM STOP-BANG
- A positive ESAP was defined as a 1+ cm gap v patient encircled their hands around the nec

Table 1. Classic STOP-Bang Score

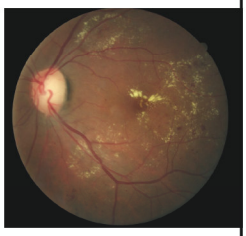
S	Snoring
T	Tiredness
O	Observed apnea
P	High blood pressure
B	Body mass index >35 kg/m²
a	Age >50 years
n	Neck circumference >40 cm
g	Gender, male

Sleep Disord. 2019; 2019: 3184382.

60

OSAS and DR/DME

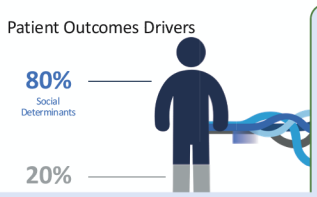
- Studies found DR rates were 2-2.5X higher in T2DM patients (n = 230) with untreated/under-treated OSA followed for 4 yrs
  - After all adjustments, OSA increased odds of progressing to severe NPDR/PDR 5-fold
- CSME patients with confirmed OSA & Tx with grid laser gained an extra line of VA if treated with CPAP > 2.5 hrs/night @ 6 months
- DME patients (n = 30 receiving Avastin), the probability of OSA symptoms was directly proportional to the # of required injections



Am J Respir Crit Care Med. 2017 Oct 1;196(7):892-900.
Retina. 2014 Dec;34(12):2423-30
Respiration. 2012;84(4):275-82

61

Social Determinants Of Health Affect the Patient Care Journey and Can Drive A Majority Of Overall Patient Outcomes



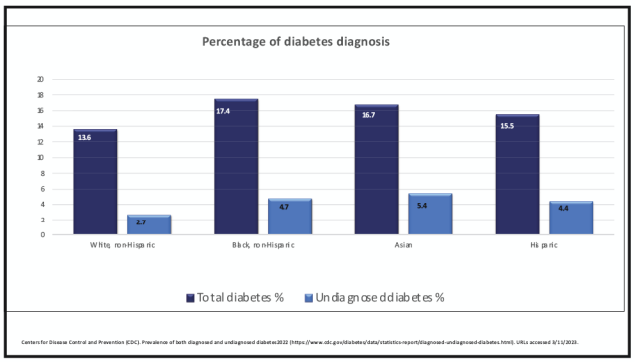
Factors that contribute to underutilization of care

- Trust
- Patient-provider communication
- Fear of medical or surgical treatment
- Transportation issues
- Lack of insurance/cost
- Other health problems
- Poor social support structure
- Cultural and language barriers
- Lower literacy level

Despite being at risk for higher visual impairment and blindness, Black and **Hispanic/Latino patients are less likely than White patients to be seen by an ophthalmologist or have a dilated exam.**

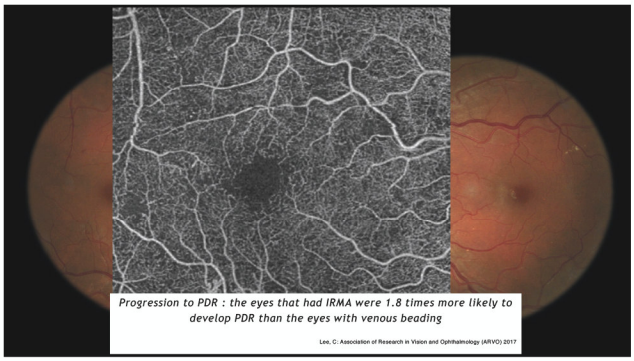
1. Hood CM et al. *Am J Prev Med*. 2016;50(2):129-135. doi:10.1016/j.amepre.2015.08.024 2. Office of Disease Prevention and Health Promotion. Accessed April 19, 2023. https://www.healthypeople.gov/2020/topics-objectives/topic/social-determinants-of-health

62



Centers for Disease Control and Prevention (CDC). Prevalence of both diagnosed and undiagnosed diabetes2022 (https://www.cdc.gov/diabetes/data/statistics-report/diagnosed-undiagnosed-diabetes.html). URLs accessed 3/13/2023.

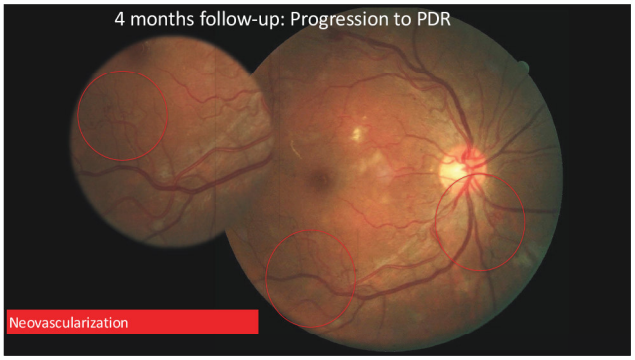
63



Progression to PDR : the eyes that had IRMA were 1.8 times more likely to develop PDR than the eyes with venous beading

Lee, C: Association of Research in Vision and Ophthalmology (ARVO) 2017

64



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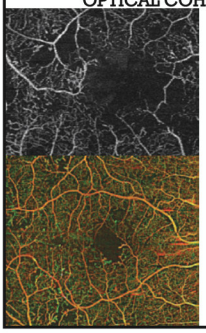
66

OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY (OCTA)

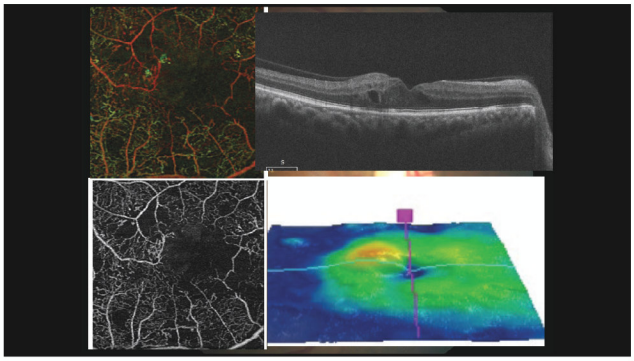


Diabetic Retinopathy

- Vascular anomalies (loops & dilations)
- Microaneurysms (MAs)
- Neovascularization
- Capillary dropout & FAZ enlargement

- Evaluation of subclinical DR may change follow-up or how the PCP manage the patient
- Color code points to area of abnormality
- Microaneurysms are green because they are in DEEP layer

67



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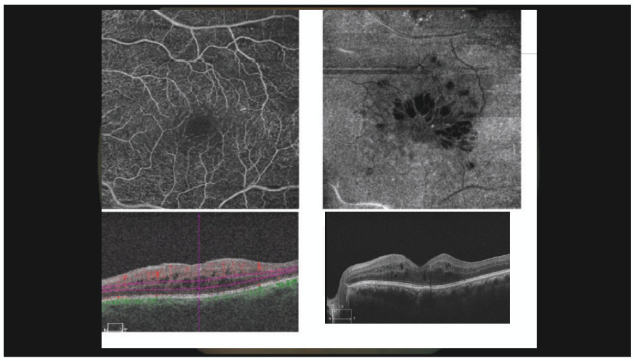

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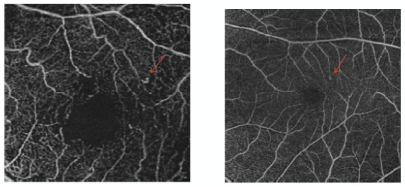
MAS DUE TO THEIR SIZE, SHOULD BE EVALUATED IN A 3X3



3X3 vs 6X6

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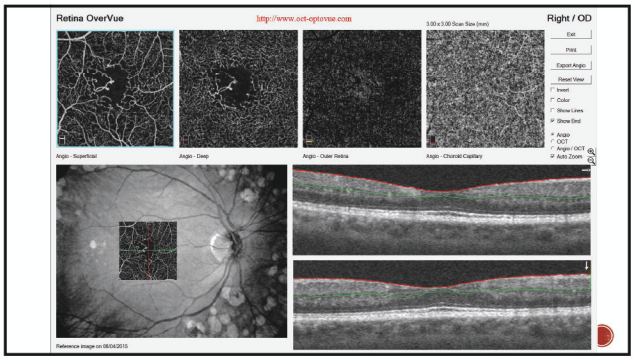

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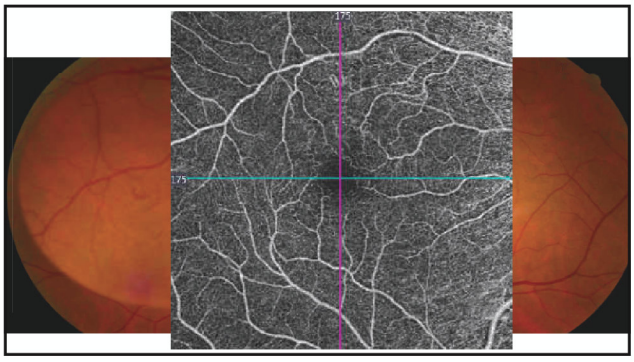


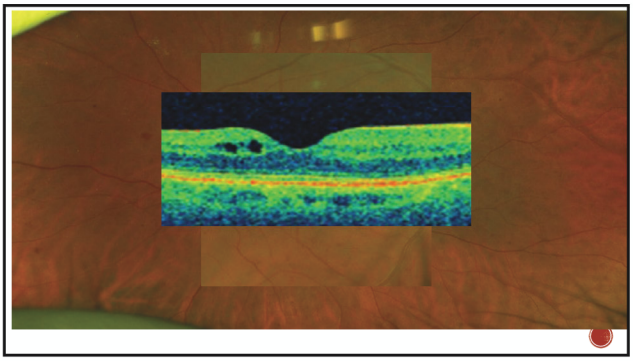
72

•Eyes with predominantly peripheral lesions- PPLs (defined as outside of ETDRS 7 standard field) had a 4.7-fold increased risk of progression to proliferative diabetic retinopathy (PDR) over 4 years.
Ophthalmology. 2015 May;122(5):949-56.

- Diabetic Retinopathy Clinical Research Retina Network (DRCR.net) Protocol AA- peripheral lesions (PPL) using ultra-widefield (UWF) color retinal imaging were not predictive of significant, 2-step worsening on the Diabetic Retinopathy Severity Scale (DRSS)
- FA-PPL but not color-image PPL have predictive value for NPDR progression and should be included in future DR studies.

JAMA Ophthalmol. 2022;140(10):946-954. Published correction in JAMA Ophthalmol. Published online November 17, 2022.

73



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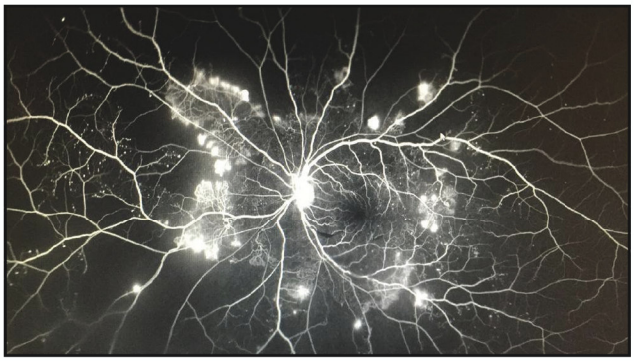

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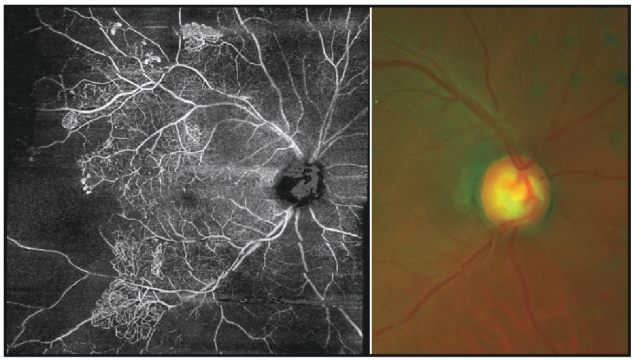

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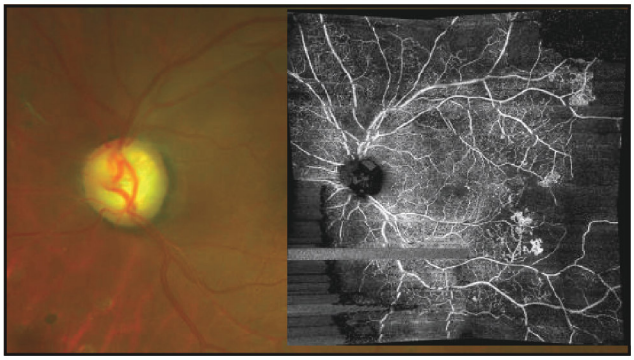

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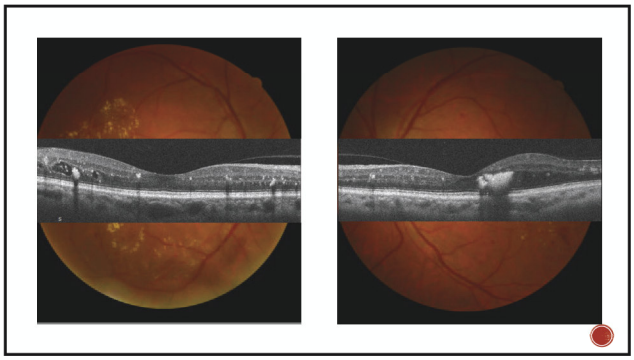

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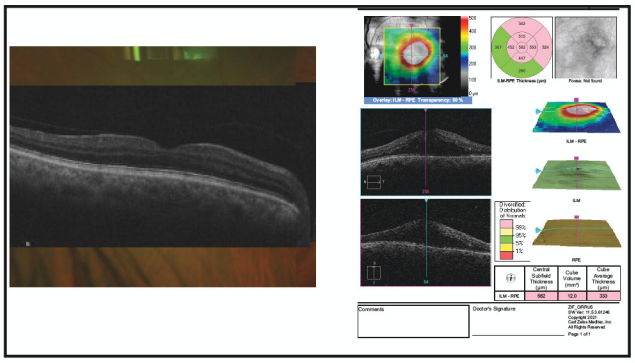

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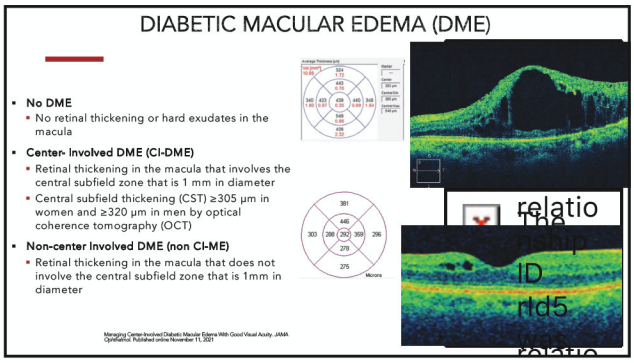

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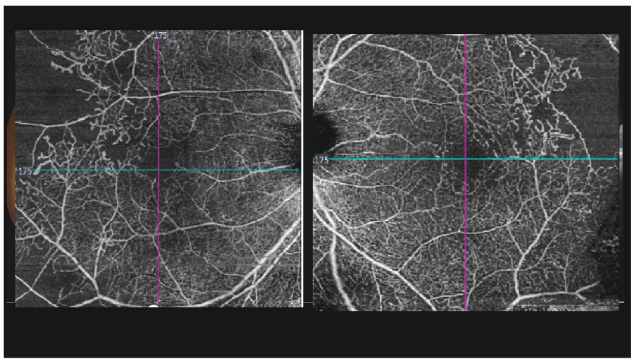

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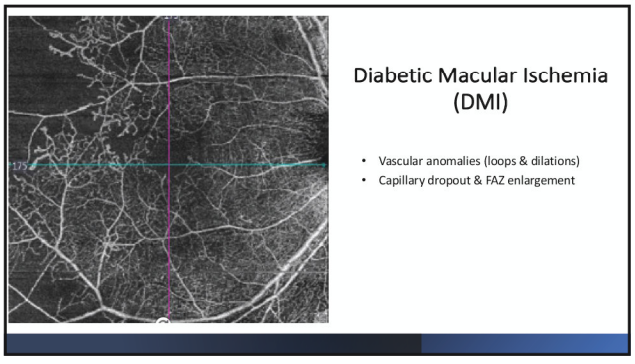

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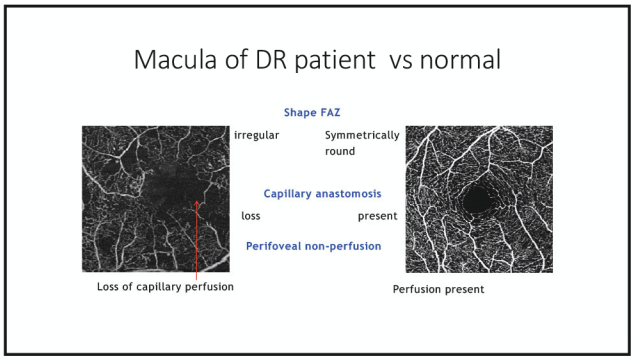

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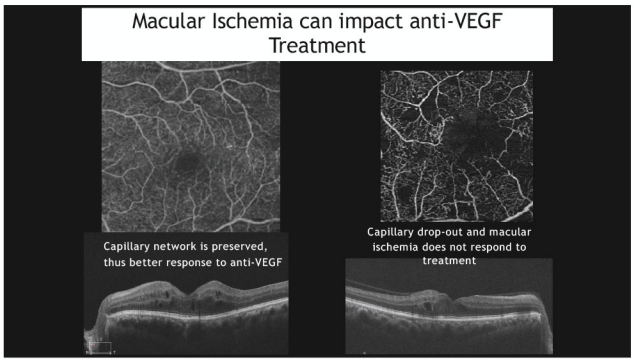

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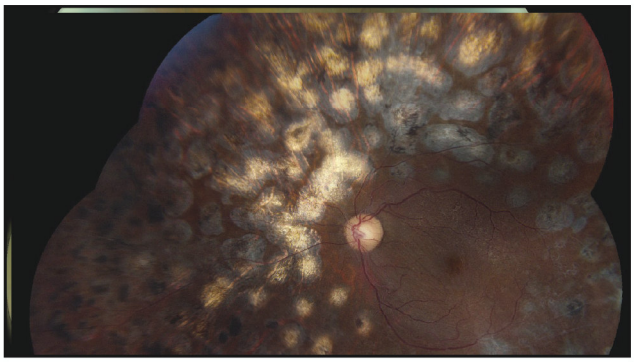

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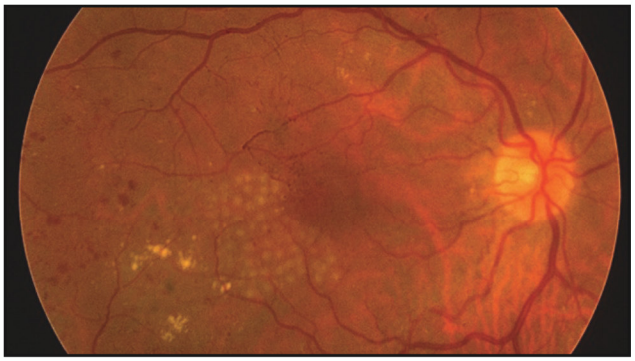
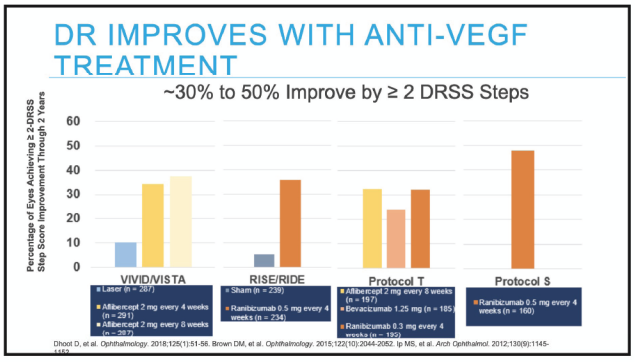


87

Seminal Diabetic Macular Edema Studies

- **Rise/Ride studies-** Lucentis 0.3mg for diabetic macular edema (DME) based on data from two-phase 3 clinical trials: 759 patients. Evaluated 0.3 mg vs. 0.5 mg (AMD dose) vs. sham/laser. FDA approved 0.3 mg dose for DME 8/2012.
- **RESTORE** - 12-month randomized trial and open label 24-month extension– 3 monthly loading doses and then PRN treatment showed efficacy in maintaining visual and anatomic benefit
- **DRCR Protocol I** – 5 years results of Lucentis for DME with prompt or deferred laser. Most eyes treated with Lucentis and either prompt or deferred laser maintain vision gains obtained in first year through 5 years with little additional treatment over last 3 years
- **VIVID and VISTA-DME** – monthly injection of Eylea for DME.

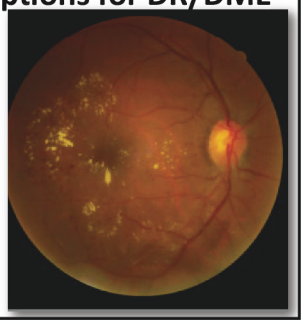
88



89

Current Treatment Options for DR/DME

- Ranibizumab (Lucentis 0.3 mg) – RIDE/RISE ($1150)
- Aflibercept (Eylea) – VIVID/VISTA ($2000)
- Bevacizumab (Avastin) – used with step therapy and for cost reasons ($70)
- Dexamaethasone implant (Ozurdex) – MEAD ($1400)- Protocol U
- Fluocinolone implant (Iluvien) – FAME($9300)
- Intravitreal Triamcinolone (Triessence) - $150
- Beovu (Brolucizumab) – used rarely



90

PALADIN Trial: FAc for DME

- The 0.19-mg fluocinolone acetonide (FAc) implant was approved by the FDA in 2014 for the treatment of DME in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in IOP.
- PALADIN was a 3-year, phase 4, open-label observation study in the US with a focus on safety outcomes in patients treated according to the FDA label for the implant.
- Data through the end of the study at 36 months (n=94 eyes) are presented here.
- Primary endpoint: Changes in IOP and interventions to manage IOP elevations
- Secondary endpoints: Changes in BCVA, changes in CST, adjunctive DME treatment frequency

Singer MA et al. *Ophthalmology*. 2022;129(6):605-613.

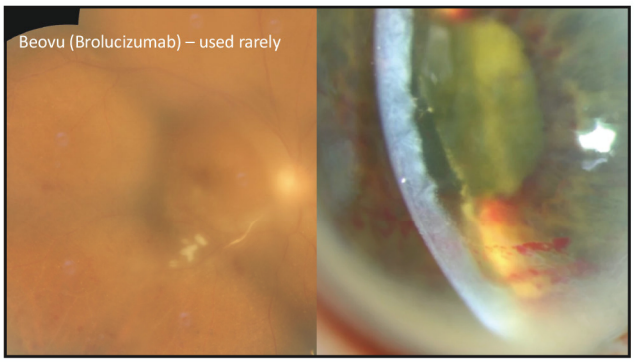
91

REINFORCE: A Prospective Multicenter Study of Dexamethasone Intravitreal Implant (DEX) in DME

- DEX has shown efficacy in patients with DME in controlled trials
- Data on real-world outcomes in DME patients receiving DEX as monotherapy or adjunctive therapy are limited
- Study objective: To assess the effectiveness, safety, and real-world use of DEX in clinical practice in patients with DME
- Prospective, multicenter, observational registry study
- Ocular history, treatment, and outcomes data were collected at the patient's first DEX injection and each subsequent visit up to 1 year
- Primary endpoints: Mean maximum BCVA change (best improvement) from baseline following each DEX injection, percentage of patients with ≥15-letter improvement in BCVA, average improvement in BCVA

Singer MA. *Ophthalmic Surg Lasers Imaging Retina*. 2018;49(6):425-435.

92

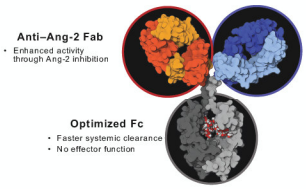


93

Vabysmo: First Bispecific Antibody Designed for Intravitreal Use

Engineered for efficacy, duration within the eye, and fast systemic clearance

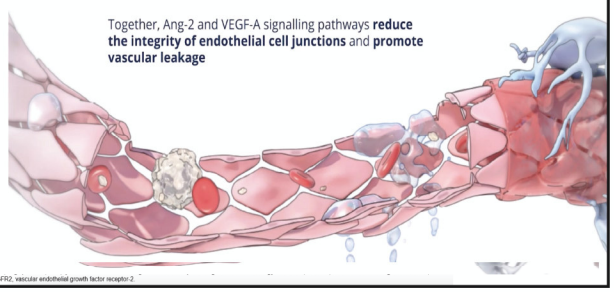
1 molecule, 2 targets



Regula JT, et al. EMBO Mol Med 2016;8:1265-1288. Regula JT et al. EMBO Mol Med. 2019;11(5):e10666.
Ang-2, angiopoietin-2; fab, fragment antigen binding; Fc, fragment crystallizable; VEGF-A, vascular endothelial growth factor-A.

94

Under Physiological Conditions, the Angiopoietin Pathway Maintains Vascular Stability and Homeostasis[1-3]



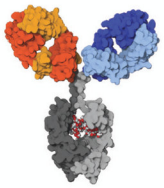
VEGFR2, vascular endothelial growth factor receptor-2

95

Faricimab: 1 Molecule Targeting 2 Signaling Pathways via Inhibition of Ang-2 and VEGF-A to Improve Vascular Stability for Durable Efficacy

Anti–Ang-2 Fab
Stabilizes vessels
Reduces vascular leakage
Reduces inflammation

Anti–VEGF-A Fab
Reduces vascular leakage
Inhibits neovascularization



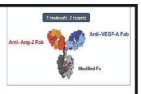
Modified Fc
Reduces systemic exposure
Reduces inflammatory potential

- YOSEMITE and RHINE were **phase 3**, randomized, double-masked, **active comparator–controlled trials**
- Designed to assess the **efficacy**, **safety**, and **durability of faricimab**
- In **treatment-naïve patients** with center-involving **DME** (CST ≥ 325 µm)[a]
- Comparable 1-year **BCVA gains** and **improved anatomic outcomes** with faricimab **up to Q16W** vs aflibercept Q8W were **maintained through year 2**[2]

YOSEMITE: NCT03622580; RHINE: NCT03622593. [a]CST was measured as the distance from the internal limiting membrane to Bruch's membrane. CrossMAb molecule representative of faricimab.
Ang-2, angiopoietin-2; BCVA, best-corrected visual acuity; CST, central subfield thickness; DME, diabetic macular edema; Fab, fragment antigen binding; Fc, fragment crystallizable; Q8W, every 8 weeks; Q16W, every 16 weeks; VEGF-A, vascular endothelial growth factor-A.
1. Regula JT et al. *EMBO Mol Med*. 2016;8:1265-1288, with erratum in Regula JT et al. *EMBO Mol Med*. 2019;11(5):e10666. 2. Wells JA. Faricimab update in DME. Presented at: Angiogenesis, Exudation, and Degeneration Symposium; February 11-12, 2022; Virtual.

96

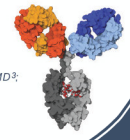
Vabysmo (faricimab)



- Roche/Genentech
  - FDA approved January 3, 2022 for AMD and DME
- First bi-specific antibody for intraocular use
  - One arm: Vegf-A inhibitor
  - Other arm: Angiopoietin-2 (Ang-2)inhibitor
    - growth factor that promotes vascular destabilization and and inflammation
  - Dual inhibition of VEGF and Ang-2 have proven more effective than inhibiting either target alone
- Multiple studies show similar results to monthly Lucentis/Eylea but able to object less frequently, many patients q 16 weeks
- October 2023- FDA approved for RVO
  - COMINO and BALATON

97

Elevatum Study Design and Rationale: Phase 4 Trial of Faricimab (Vabysmo) in Underrepresented Patients With Diabetic Macular Edema



Joseph M. Coney, MD, FACS[1]

Adrienne W. Scott, MD, FASRS[2]; Manuel Amador, MD[3]; Jennifer Chang, PharmD, MBA[3]; Ivaylo Stoilov, MD[3]; Matthew Meldorf, MD[3]; Luis Gonzalez, MD, MPH[4]; and Matthew A. Cunningham, MD[5]

[1] Retina Associates of Cleveland, Inc., Cleveland, OH; [2] Johns Hopkins University School of Medicine, Baltimore, MD; [3] Genentech, Inc., South San Francisco, CA; [4] NJRetina, Teaneck, NJ; [5] Florida Retina Institute, Clermont, FL

Presented at the American Society of Retina Specialists Annual Meeting
Seattle, WA | July 27–August 1, 2023

98

Racial and Ethnic Disparity in the Prevalence of Diabetes and Diabetic Retinopathy/Diabetic Macular Edema

Underrepresented populations are **more affected** by diabetes and **diabetic eye diseases**[1,2]

- Prevalence of diabetic retinopathy is **33.4% in Hispanic** patients and **26.5% in Black** patients **vs 18.2% in White** patients[3]
- **Hispanic and Black** patients have **worse baseline VA** and **disease severity** on starting anti-VEGF therapy for DME vs **White** patients[4]

A retrospective study showed that **VA improvements** following 1 anti-VEGF injection were **lowest** in **Black (26.7%) and Hispanic (39.4%)** patients with DME compared with **White (50.0%)** patients with DME[5]

Minority populations are **largely underrepresented in clinical trials** that have led to FDA-approved ophthalmology therapies[6]

The **aim** of **Elevatum** is to **evaluate** the treatment response and safety of **faricimab** in traditionally **underrepresented**, treatment-naïve patients with DME

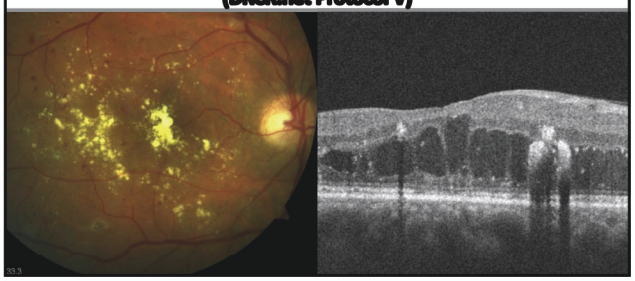
99

High Dose Aflibercept (Eylea)

- PULSAR (AMD) and PHOTON (DME) Studies
  - Looked at 8 mg vs 2 mg of Eylea
  - Demonstrated non-inferior and clinically equivalent vision gains at 48 weeks with 8 mg at 12- and 16-week dosing after 3 initial doses compared to Eylea every 8 weeks after initial dosing
- Eylea HD FDA approved 8/18/2023 for AMD, DME and DR
  - Recommended dose 1 injection every 4 weeks for first 3 mos for all indications, then every 8-16 weeks (2-4 mos) for AMD and DME and every 8-12 weeks (2-3 mos) for DR

100

When Central-involved DME in Eyes with Very Good Visual Acuity (DRCR.net Protocol V)



101

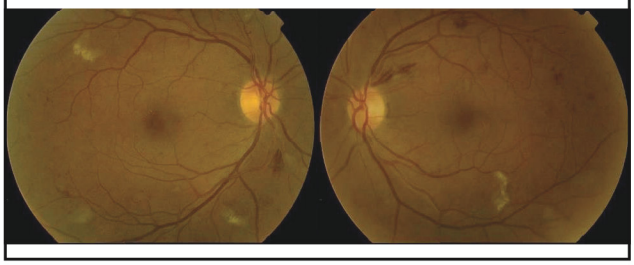
Treatment for Central-involved DME in Eyes with Very Good Visual Acuity (DRCR.net Protocol V)

- 702 randomized participants completed two-year follow-up
- What is the best *treatment strategy* for eyes with central-involved (CI) DME and good visual acuity?
  - » For eyes with center-involving DME and visual acuity of 20/25 or better, observation with close follow-up may be a reasonable initial management option and doesn't compromise visual acuity outcomes at two years.
  - » Close follow-up is important, as patients were followed every eight to 16 weeks and rescued with aflibercept if their vision declined.
- DME can be clinically sub-divided into three relevant categories
  - CI-DME with VA impairment
  - CI-DME with good VA
  - Non-CI-DME.

Baird SJ, Wolfe JD, Regillo CD, et al. Evidence-Based Guidelines for Management of Diabetic Macular Edema. Journal of VitreoRetinal Diseases. 2019.

102

Would patients with severe NPDR benefit from Anti-VEGF Treatment?



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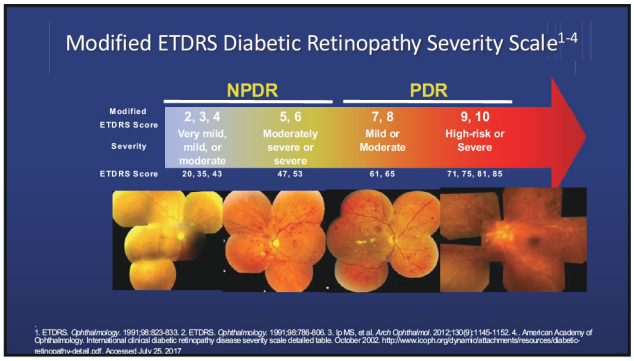
Modified ETDRS Diabetic Retinopathy Severity Scale[1-4]



1. ETDRS. *Ophthalmology*. 1991;98:823-833. 2. ETDRS. *Ophthalmology*. 1991;98:786-806. 3. Ip MS, et al. *Arch Ophthalmol*. 2012;130(8):1145-1152. 4. American Academy of Ophthalmology. International clinical diabetic retinopathy disease severity scale detailed table. October 2002. http://www.icoph.org/dynamicattachments/resources/diabetic-retinopathy-detail.pdf. Accessed July 25, 2017

104

Panorama Study

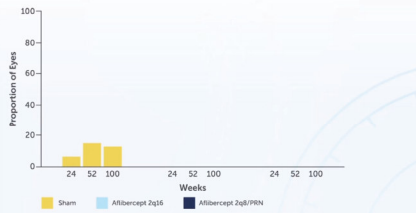
- Enrolled eyes with moderate-to-severe and severe nonproliferative diabetic retinopathy (NPDR) with or without DME
- Showed that eyes treated with aflibercept (Eylea, Regeneron) had significantly greater improvement of 2 or more steps in DR severity compared with the sham group.
- As a secondary outcome, the study demonstrated that the anti-VEGF treatment reduced the likelihood of developing vision-threatening complications such as center-involved DME (CI-DME) or PDR.

DRCR.net Protocol W

- Protocol W is a prospective multicenter study by the DRCR Retina Network that included eyes with moderate-to-severe NPDR and without baseline CI-DME
- The study was designed as a long-term evaluation of intravitreal aflibercept's ability to prevent PDR and CI-DME in eyes with advanced DR.
- Two-year result summary result - Preventive treatment with aflibercept resulted in a threefold reduction in the development of CI-DME with vision loss (14.8% in the sham group vs 4.1% in the aflibercept group).
- Treatment was also associated with a nearly twofold reduction in the development of new-onset PDR (33.2% in the sham group vs 13.5% in the aflibercept group)

105

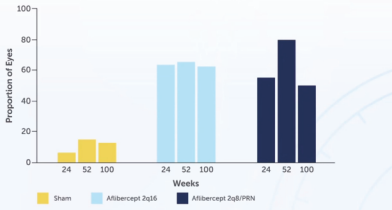
PANORAMA: Anti-VEGF Improves DRSS Level ≥2 Steps in Moderately Severe to Severe NPDR



DRSS, Diabetic Retinopathy Severity Scale; NPDR, nonproliferative diabetic retinopathy; VEGF, vascular endothelial growth factor.
Brown DM, et al. *JAMA Ophthalmol*. 2021;139(9):946-955.

106

PANORAMA: Anti-VEGF Improves DRSS Level ≥2 Steps in Moderately Severe to Severe NPDR



DRSS, Diabetic Retinopathy Severity Scale; NPDR, nonproliferative diabetic retinopathy; VEGF, vascular endothelial growth factor.
Brown DM, et al. *JAMA Ophthalmol*. 2021;139(9):946-955.

107

Anti-VEGF Reduces Risk of VTCs in Moderate to Severe NPDR

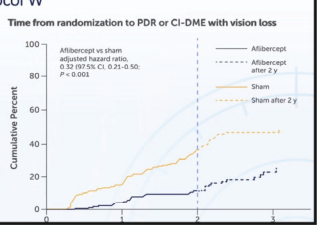
Protocol W

Cumulative Probability of Disease Development Within 2 Years

Outcome	Aflibercept n = 200	Sham n = 199
CI-DME with vision loss or PDR	16.3%	43.5%
CI-DME with vision loss	4.1%	14.8%
PDR	13.5%	33.2%

3X

Time from randomization to PDR or CI-DME with vision loss



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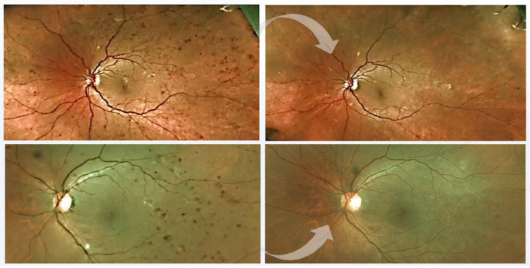
Anti-VEGF Improves NPDR

Case 1

Case 2



109

Original Investigation

February 7, 2023

Four-Year Visual Outcomes in the Protocol W Randomized Trial of Intravitreous Aflibercept for Prevention of Vision-Threatening Complications of Diabetic Retinopathy

Raj K. Maturi, MD[1,2]; Adam R. Glassman, MS[3]; Kristin Josic, PHD[3]; et al

Author Affiliations

JAMA. 2023;329(5):376-385. doi:10.1001/jama.2022.25029

110

Key Points

Question In patients with nonproliferative diabetic retinopathy (NPDR) and good vision but without center-involved diabetic macular edema (CI-DME), does early aflibercept reduce disease progression and improve long-term visual acuity compared with initial observation and treatment only if disease worsens?

Findings This study presents 4-year primary outcomes of a randomized clinical trial that included 328 patients (399 eyes), randomized to 2.0 mg aflibercept injections or sham injections. Among those receiving aflibercept, proliferative diabetic retinopathy or CI-DME developed in 33.9% vs 56.9% among those who received sham—a difference that was statistically significant. Change in visual acuity was −2.7 vs −2.4 letters, a difference that was not statistically significant.

Meaning At 4 years, treatment of NPDR with aflibercept vs sham treatment resulted in statistically significant anatomic improvement, but no improvement in visual acuity.

111

Protocol AE

A Pilot Study Evaluating Photobiomodulation (PBM) Therapy for DME

Protocol AE: whether photo-biomodulation (670 nm wavelength) has a beneficial effect in eyes with DME

23

112

WHAT IS PHOTOBIOMODULATION?

- Low-Level Light Therapy
- Use of red-infrared light to stimulate beneficial cellular activity
- Increases energy production, alters signaling modalities, activates transcription factors
- Cytoprotective properties, used in wound repair

113

A Randomized Trial of Photobiomodulation Therapy for Center-Involved Diabetic Macular Edema with Good Visual Acuity (Protocol AE)

Abstract

Purpose: To determine if treatment with a photobiomodulation (PBM) device results in greater improvement in central subfield thickness (CST) than placebo in eyes with center-involved diabetic macular edema (CI-DME) and good vision. Design: Phase 2 randomized clinical trial. Participants: Participants had CI-DME and visual acuity (VA) 20/25 or better in the study eye and were recruited from 23 clinical sites in the United States. Methods: One eye of each participant was randomly assigned 1:1 to a 670-nm light-emitting PBM eye patch or an identical device emitting broad-spectrum white light at low power. Treatment was applied for 90 seconds twice daily for 4 months. Main Outcome Measures: Change in CST on spectral-domain OCT at 4 months. Results: From April 2019 to February 2020, 135 adults were randomly assigned to either PBM (n = 69) or placebo (n = 66); median age was 62 years, 37% were women, and 82% were White. The median device compliance was 92% with PBM and 95% with placebo. OCT CST increased from baseline to 4 months by a mean (SD) of 13 (53) μm in PBM eyes and 15 (57) μm in placebo eyes, with the mean difference (95% confidence interval [CI]) being −2 (−20 to 16) μm (P = 0.84). CI-DME, based on DRCR Retina Network sex- and machine-based thresholds, was present in 61 (90%) PBM eyes and 57 (86%) placebo eyes at 4 months (adjusted odds ratio [95% CI] = 1.30 (0.44–3.83); P = 0.63). VA decreased by a mean (SD) of −0.2 (5.5) letters and −0.6 (4.6) letters in the PBM and placebo groups, respectively (difference [95% CI] = 0.4 (−1.3 to 2.0) letters; P = 0.64). There were 8 adverse events possibly related to the PBM device and 2 adverse events possibly related to the placebo device. None were serious. Conclusions: PBM as given in this study, although safe and well-tolerated, was not found to be effective for the treatment of CI-DME in eyes with good vision.

Kim JE, Glassman AR, Josic K, Melia M, Aiello LP, Baker C, Eells JT, Jampol LM, Kern TS, Marcus D, Salehi-Had H, Shah SN, Martin DF, Stockdale CR, Sun JK; DRCR Retina Network. A Randomized Trial of Photobiomodulation Therapy for Center-Involved Diabetic Macular Edema with Good Visual Acuity (Protocol AE). Ophthalmol Retina. 2022 Apr;6(4):298-307.

114

Anti-VEGFs Biosimilars

- Per the FDA:
  - "A biosimilar is a biological product that is approved based on data showing that it is highly similar to a biological product already approved by the FDA
- Concerns about biosimilar safety, efficacy, and immunogenicity
  - Byooviz (Samsung) approved Sept 2021- Wet AMD, RVO, and myopic CNV
  - Cimerli (Coherus) approved Oct 2022- DME, diabetic retinopathy (DR), wet AMD, RVO, and myopic CNV.
  - Bevacizumab- Latest 2024- Avzivi (bevacizumab-tnjn)
- Many in development
  - Ranibizumab
  - Aflibercept
  - Bevacizumab

115

116

Ocuterra

- Topical Administration of anti-VEGF agent in eye drop form (OTT-166)

BIOTECH

Phase 2 fail sends OcuTerra's eye drop dreams down the drain

By **Gabrielle Masson** · Mar 14, 2024 9:15am

- Secondary endpoints:
  - Prevention of progression to VTC
  - Delay in time to PRP or intravitreal injection

117

Ocuphire Pharma's APX3330

- A twice-daily oral tablet

Ocuphire Pharma Announces Successful End-of-Phase 2 Meeting with FDA for Oral APX3330 in Diabetic Retinopathy

November 02, 2023 Download as PDF

- Participants received either APX3330 600 mg per day or a placebo. The primary endpoint was the percentage of participants with a 2-step or greater improvement in the Diabetic Retinopathy Severity Scale (DRSS) by week 24.
- Moderately severe to severe NPDR and mild PDR

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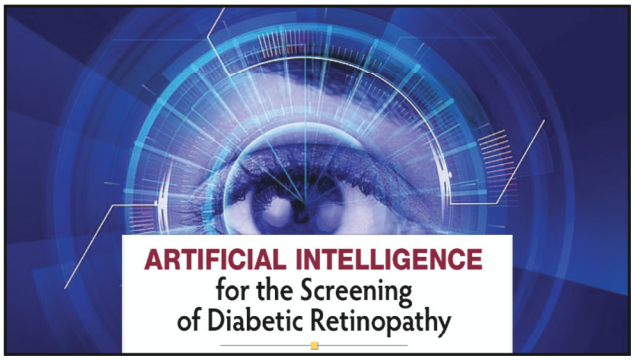

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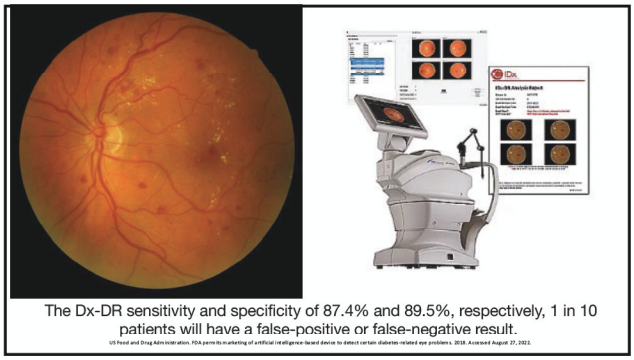

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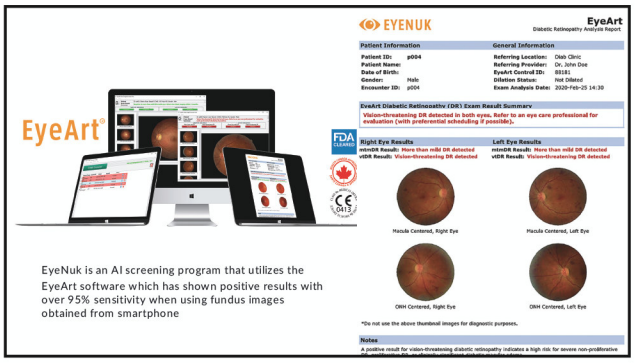

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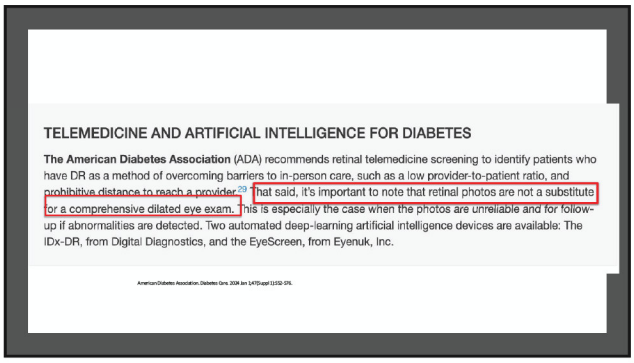

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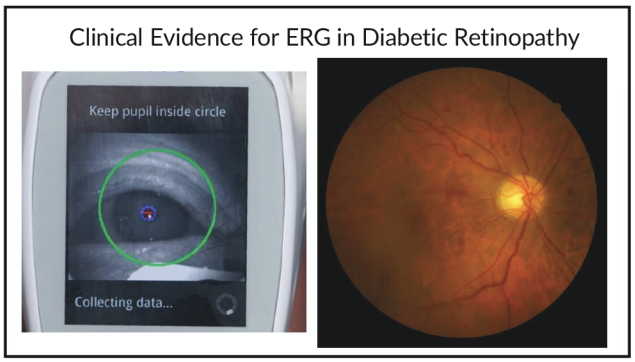

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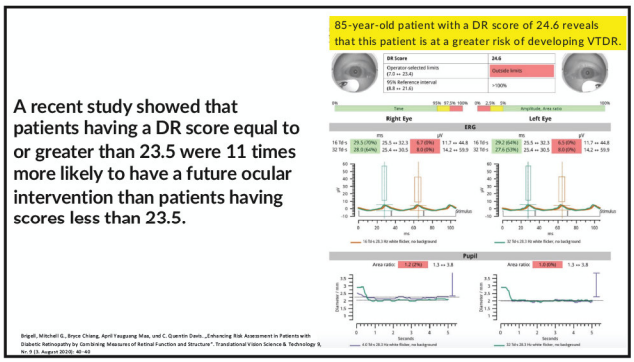

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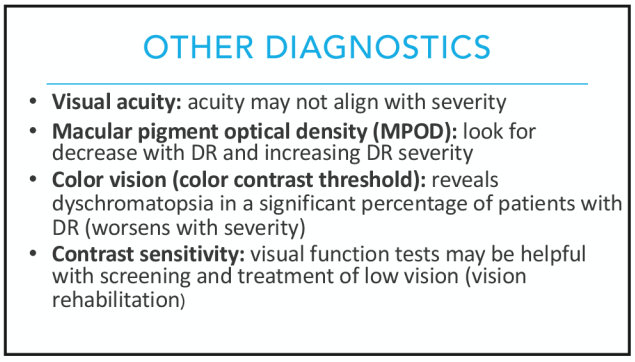

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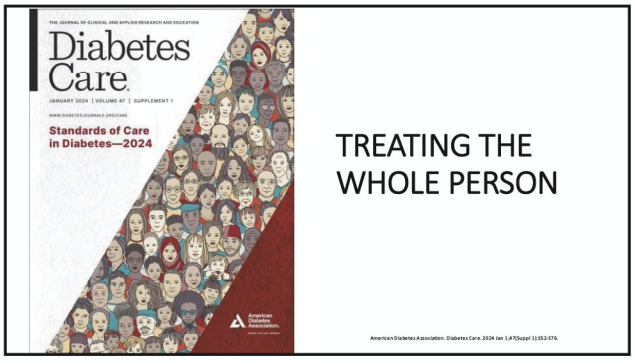


126

MULTIDISCIPLINARY DIABETES CARE TEAM

127

Interdisciplinary Communication Is Essential

- Bidirectional communication between a patient's primary care provider and eye care professional is crucial to properly coordinate care.
- All health care team members should be aware of the patient's overall medical status and individualized therapeutic targets.
- The patient's primary care provider should refer patients for annual eye examinations.
- The patient's primary care provider should be informed of the results of each eye exam, even when retinopathy is minimal or not present.

American Optometric Association. *Eye Care of the Patient with Diabetes Mellitus*, 2nd ed. St. Louis, MO: American Optometric Association, 2019

128

THE LANGUAGE OF DIABETES CARE

For people with diabetes, language has an impact on motivation, behaviors, and outcomes. When talking with people with diabetes, use language that:

- Is neutral, nonjudgmental, and based on facts, actions, or physiology/biology
- Is free from stigma
- Is strengths-based, respectful, inclusive, and imparts hope
- Fosters collaboration between patients and providers
- Is person-centered

129

DIABETES EDUCATION

The American Diabetes Association (ADA) recommends that all people with diabetes be referred for diabetes education and support at four critical times:

1. At diagnosis
2. Annually for assessment of education, nutrition, and emotional needs
3. When new complicating factors influence self-management
4. When transitions in care occur

130

Five-step approach to behavior change

Step 1: Elicit context conversation
- Talk about values, use open-ended questions

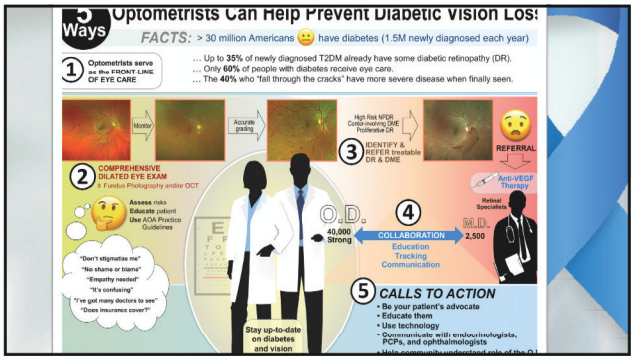
Step 2: Validate context
- Frequently, simply acknowledging a patient's situation can have a positive impact
- Use reflective listening and validating statements

Step 3: Challenge or change context
- If you've identified a modifiable contextual factor, address it!
- Ask the patient to identify which contextual factor they think they could address
- Help patient identify ways to address this contextual change

Step 4: Connect behavior to values
- If you have elicited values, try to help your patient see where self-management can connect to their values to build motivation

Step 5: Praise and encourage
- Praise anything you can, express faith in their ability to improve self-management

131



132

Bottom line

- Array of new treatment options Diabetic Retinopathy/DME
- Early diagnosis and appropriate treatment, including today's Advance approaches to both diabetes and diabetic eye disease, could prevent 95% of vision loss caused by diabetes

133

rreynold@nova.edu

134