SECO 2022
WHERE SIGHT MEETS VISION™
MARCH 9-13 | NEW ORLEANS

Modern Day Diabetes

Jeffry Gerson, OD

#506

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Disclosure statements:

Allergan (Self) : Board Member/Advisory Panel; bausch health (Self) : Board Member/Advisory Panel, Consultant, Speaker/Honoraria; Essilor (Self) : Consultant; Maculogix (Self) : Consultant, Speaker/Honoraria

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Modern Day Diabetes

Jeffry Gerson, O.D., F.A.A.O.
jgerson@Hotmail.com
Grin Eye Care

Disclosure

- I have been on advisory boards/a consultant to/received honoraria from/ or been on speakers bureau list of the following:
  - Allergan, AstaReal, Bausch & Lomb, Essilor, Genentech, Luneau Technology, Maculogix, Notal Vision, Optos, Regeneron, VSP, ZeaVision

These affiliations will have no affect on the content of this lecture

Conclusion

- Optometry is on the front line of diabetes care
  - Whether through making initial diagnosis of DM or DR or assisting in monitoring
- Optometry will likely take a more active role in diabetes care
  - Whether through treatment or education
- YOU have the opportunity to make a difference in the lives of your patients with diabetes (whether or not they have DR)

BTW: I’m not going to bore you with

- Just how much DM there is
  - 30M (90M Pre-DM) with up to 1/3 not knowing
- Rates of increase of DM
- Overall poor control
- Overall cost to economy
- The differences between T1 and T2

WARNING

- This course is as much (or more) about diabetes than it is about diabetic eye disease
  - Diabetic eye disease is more than retinopathy, but I will focus on DR as far as diabetic eye disease

Should We Delay Eye Exams During the Pandemic?

- CEBM says YES if minimal or no DR at previous exam and if “good” metabolic control

Factors Favoring Normal Eye Exam Intervals	Factors favoring reduced exam frequency
More-than-mild NPDR Evidence of rapid DR progression DME Poor glycemic control (HbA1c > 9%) Rapid improvement in glycemic control Diabetes Duration > 10 yrs	No or mild NPDR without evidence of DME No evidence of DR progression Good glycemic control (HbA1c < 7.5%) No rapid improvement in glycemia Diabetes Duration < 10 years Severe obesityknown immunocompromise

- Meticulous in-office hygiene (masks, breath shields, social distancing, minimization of talking/exam duration) is required in all cases

Centre for Evidence-Based Medicine accessed 8/19/20 at https://www.cebm.net/covid-19/rapid-review-diabetic-retinopathy-screening-during-the-covid-19-pandemic/

48yo T2DM, A1c 9.0

- Doc, be nice to her, she has been “shamed” due to her DM control

Myth or Fact

Everyone with diabetes needs to take insulin.

This is a MYTH.

People with type 1 diabetes need insulin to survive.

Type 2 diabetes may be managed with diet and exercise, pills, insulin, other injectable medicines, or a combination of these.

Diabetes only occurs in people with overweight or obesity.

This is a MYTH.

Most people with type 1 diabetes are lean.

Although being overweight is a risk factor for type 2 diabetes, the two do not always go hand in hand. For example, most Asian people with diabetes do not have obesity.

Type 2 diabetes is less serious than type 1 diabetes.

This is a MYTH.

Both type 1 and type 2 diabetes are serious diseases, and if not adequately managed, both can lead to devastating long-term complications.

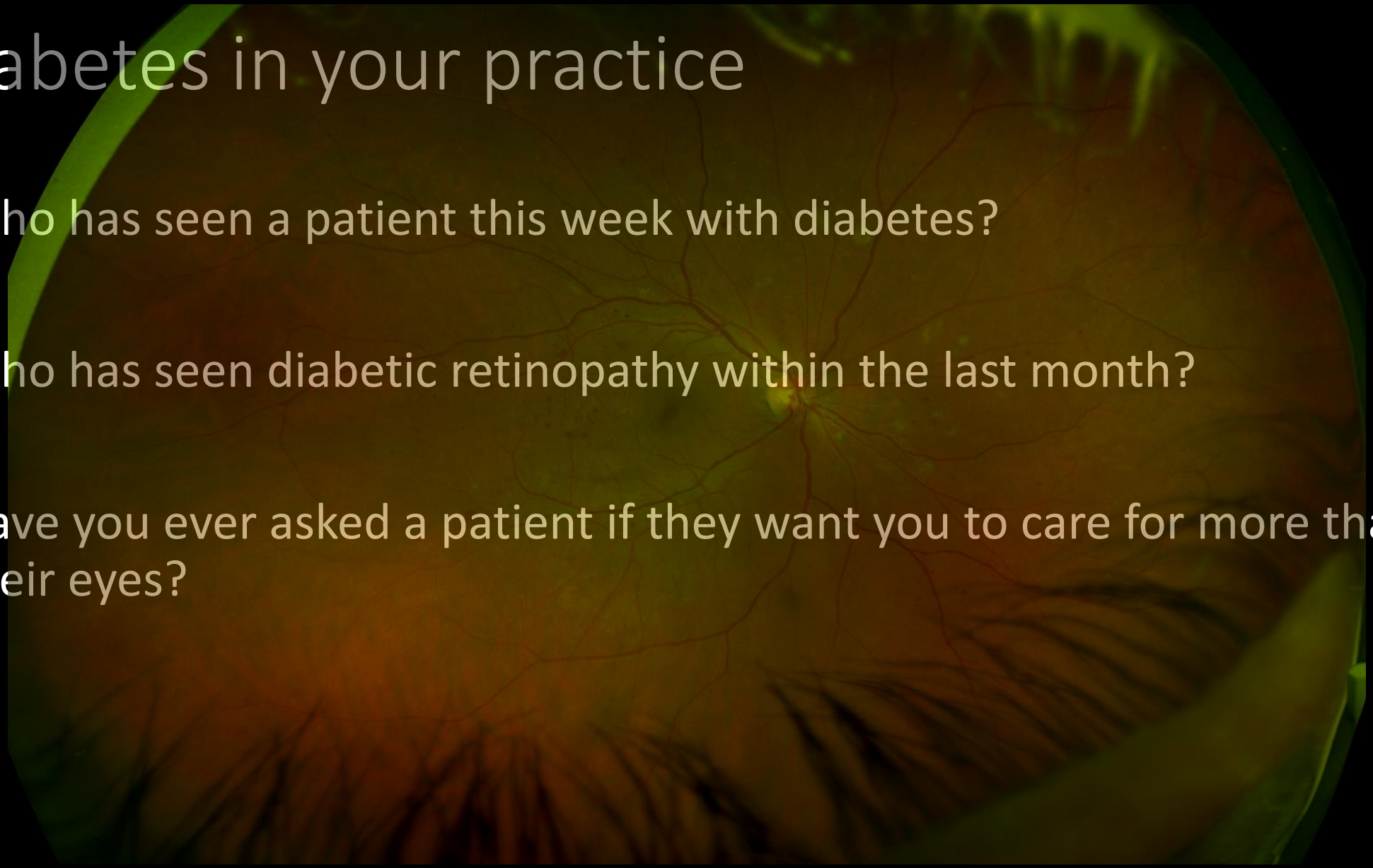
Crucial Message for Patients with Diabetes

Good vision on an eye chart or in daily life ≠ healthy eyes!

Patient with PDR and 20/20 visual acuity.
Image courtesy of Image courtesy of
Charles Wykhoff, MD, PhD

Patients must be reminded consistently by ***all*** **members of the diabetes-care team** about the importance of dilated retinal exams

Diabetes in your practice



- Who has seen a patient this week with diabetes?
- Who has seen diabetic retinopathy within the last month?
- Have you ever asked a patient if they want you to care for more than their eyes?

What are some of the things you may hear

- “I have borderline diabetes”

- “I used to have sugar but now I don’t”

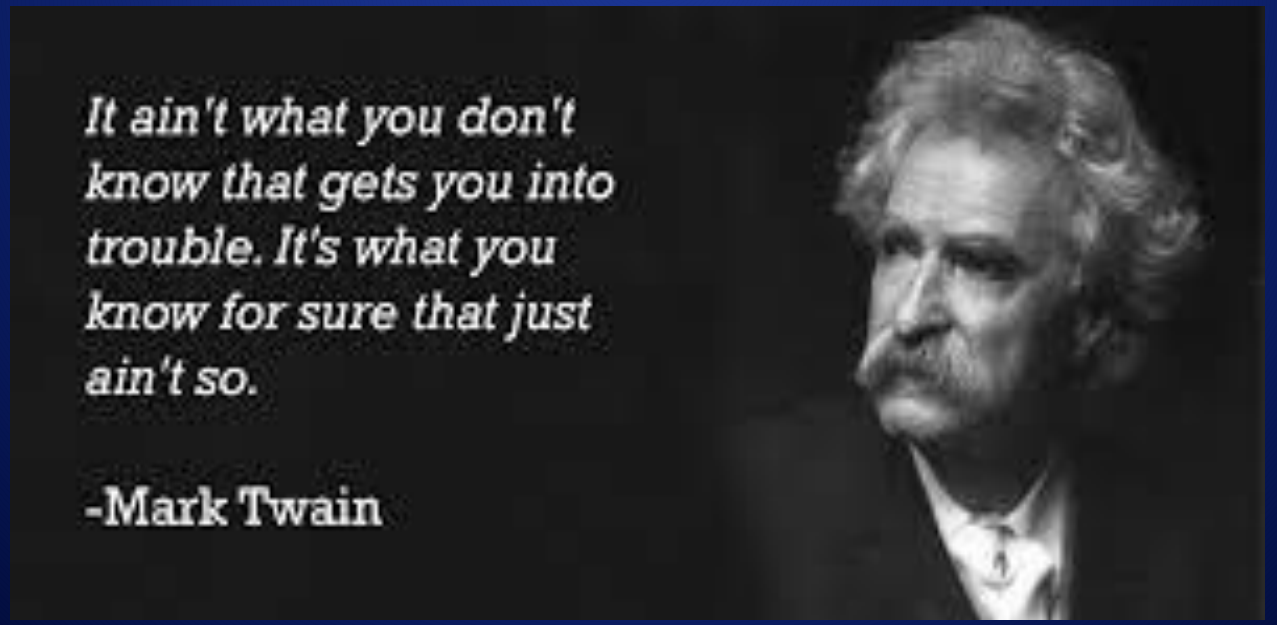
- “ My diabetes is diet controlled”

Something else you'll hear

- What 4 medicines are almost all people with T2Dm on?

Why bother with some of the facts?

- We assume that the PCP or Endo (or their staff) has enough time and DOES discuss enough of the facts with their patients
- That assumption may not be correct….



The world of PCP's

- 145 of 155 PCPs attending retreat for academic affiliated multispecialty practices
- 6% identified all the risk factors to prompt preDM screening
- 17% identified lab parameters for DX PreDM
- 11% recommended referral for behavioral wt loss program w PreDM

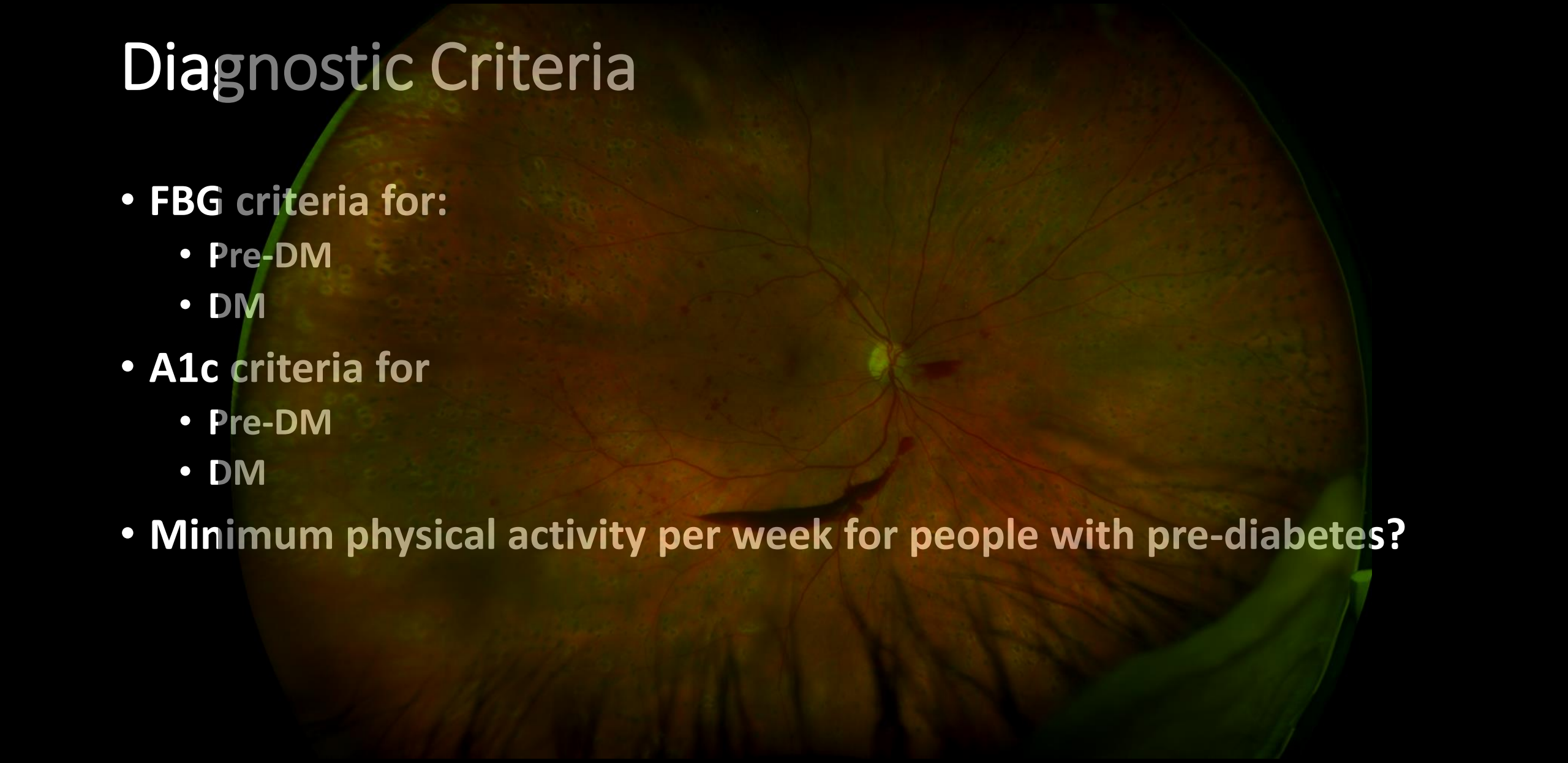
J General Intern Med. 7/17

Lets quiz ourselves

- **Which of the following is a risk factor to screen for DM:**
  - **Age at least 45**
  - **BMI at least 25kg/m**
  - **HTN**
  - **Dyslipidemia**
  - **Heart Dz**
  - **Fam h/o DM in 1st degree relative**
  - **Sedentary lifestyle**
  - **AA race**
  - **Asian race**
  - **Hispanic**
  - **h/o Gest DM**
  - **Smoking**

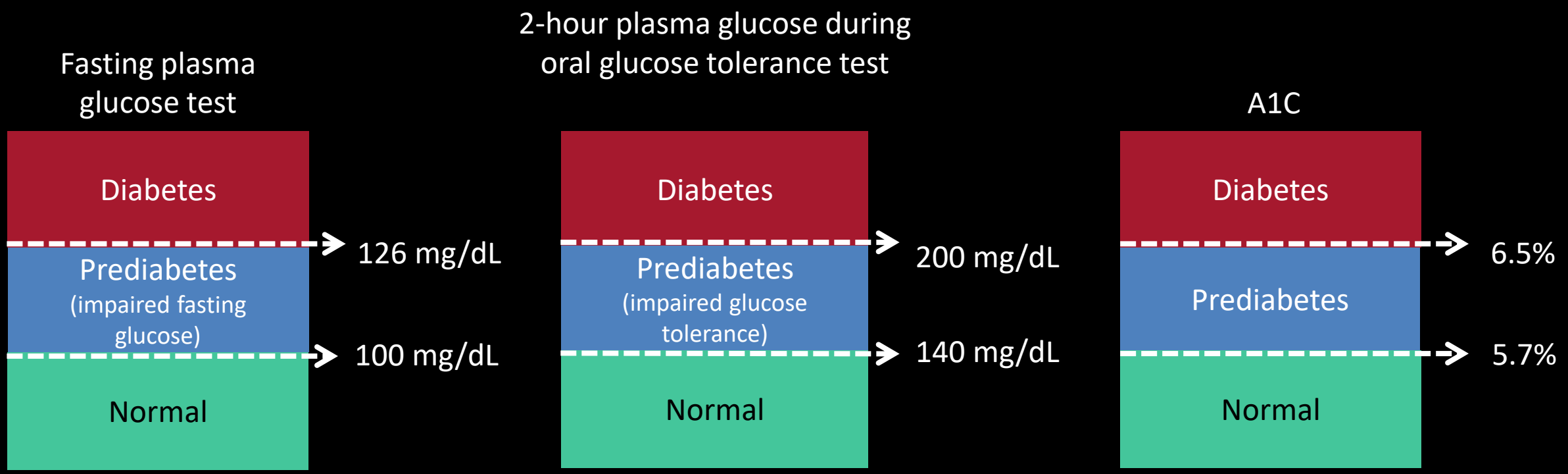
How many out of 12??

Diagnostic Criteria



- **FBG criteria for:**
  - **Pre-DM**
  - **DM**
- **A1c criteria for**
  - **Pre-DM**
  - **DM**
- **Minimum physical activity per week for people with pre-diabetes?**

Three Blood Tests to Diagnose Diabetes



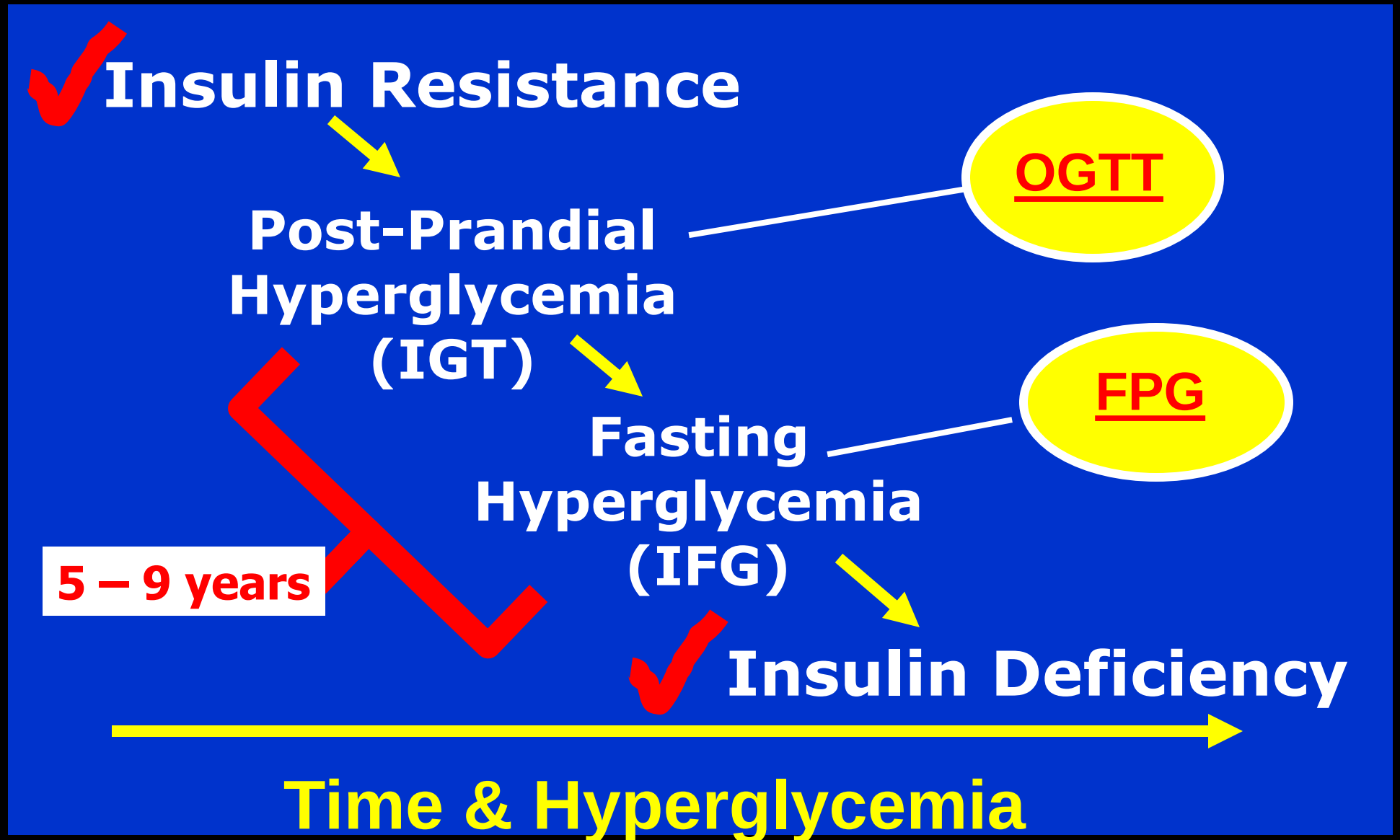
In the absence of clear-cut high blood glucose, diagnosis requires two abnormal test results.

American Diabetes Association. Diabetes Care 2020;43(Suppl. 1):S14–S31

Are people always told they have diabetes

- What if somebody has A1c of 7.0 and they don’t know they have diabetes
  - Were they not told or are they minimizing?
  - What is our job here?

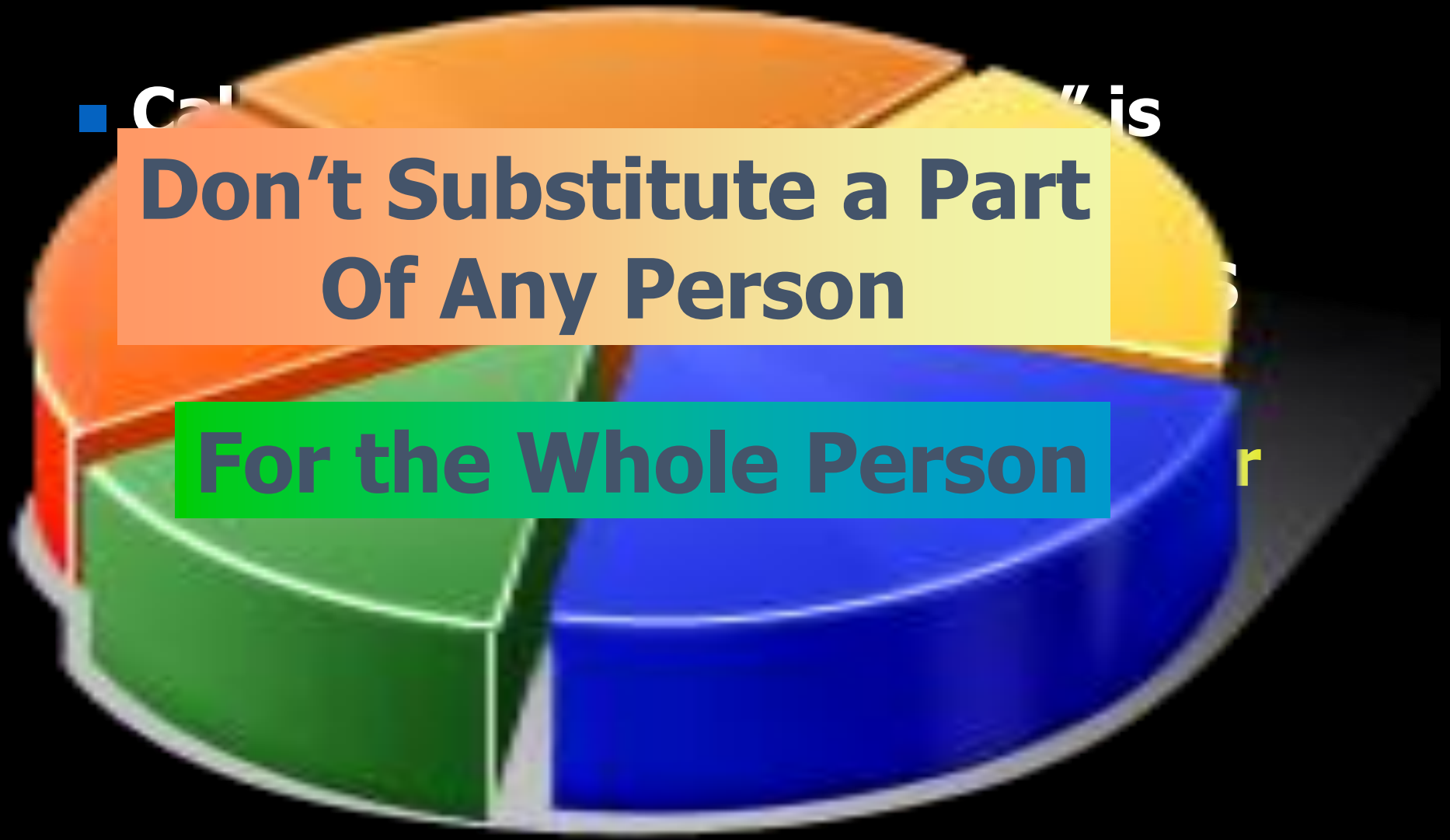
Natural History of T2DM



The Challenge for OD's in Diabetes Care….

Those Who Aren't What We Call Them

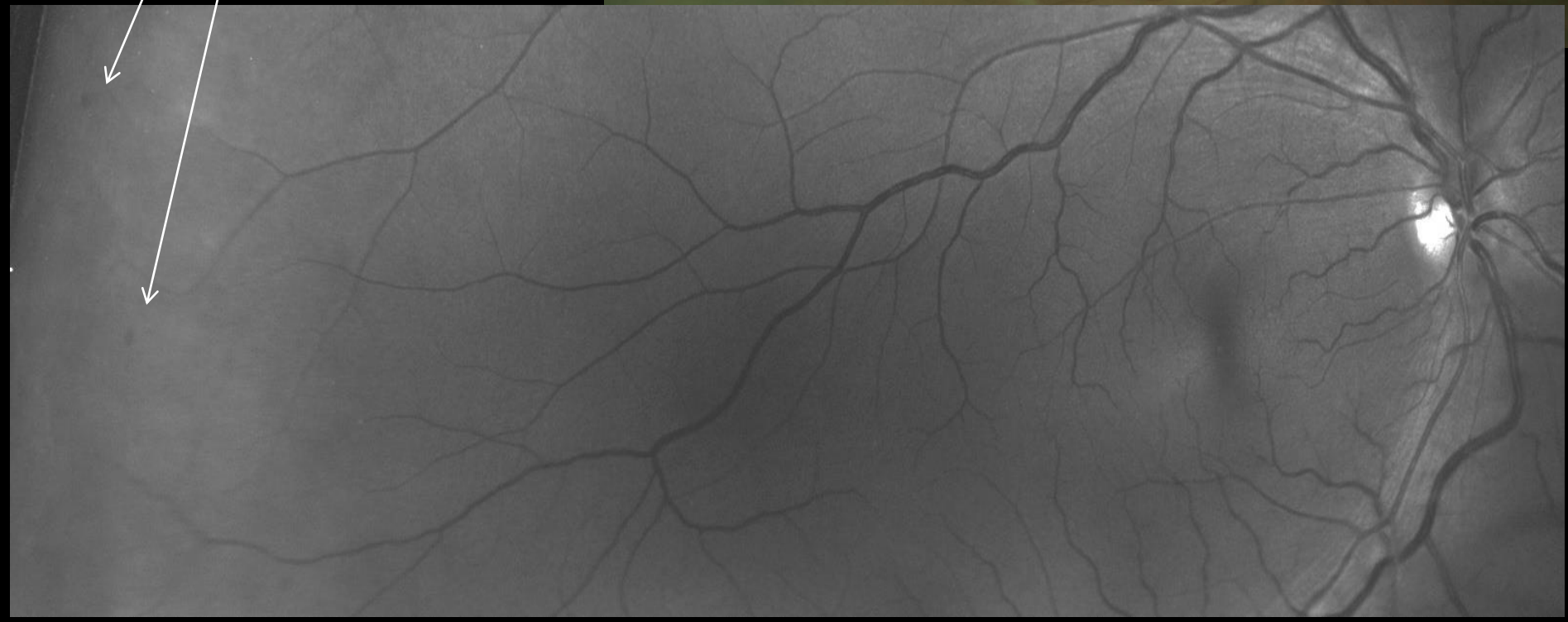
- Cal… …" is



Don't Substitute a Part Of Any Person

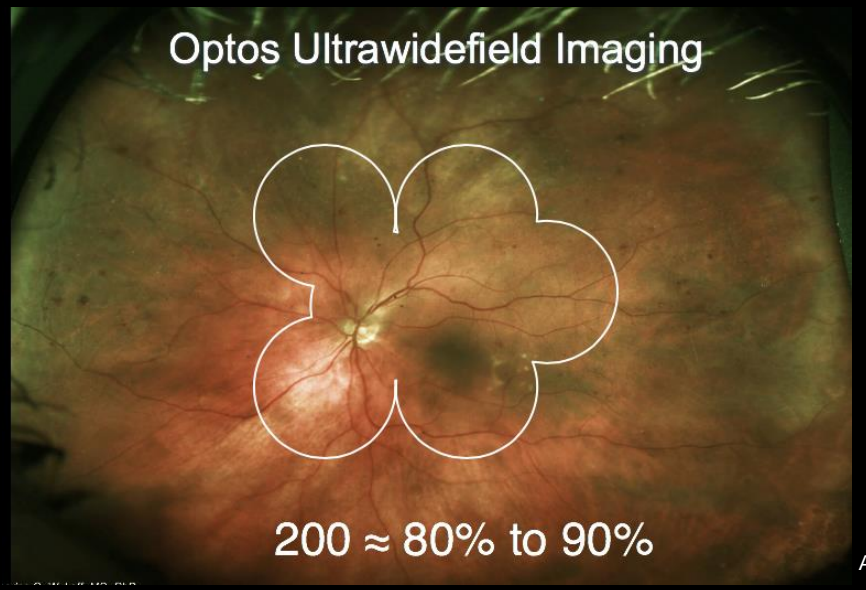
For the Whole Person

- What does this mean to you?



Do Peripheral Findings Predict Disease Progression?

- At 4 years, patients with predominantly peripheral lesions had:
  - A 3.2-fold increased risk of ≥ 2-step DRSS worsening: 11% → 34%
  - **A 4.7-fold increased risk of PDR: 6% → 25%**



>10% of eyes classified as more severe when peripheral lesions were considered

Silva PS, et al. *Ophthalmology*. 2015;122(5):949-956.

Abbreviation: PPL, predominantly peripheral lesion.

DM Treatment by ODs?

- Insufficient numbers of and economic incentives for becoming primary care medical providers will require delivery of common primary care services by all knowledgeable and capable health care personnel
- Optometrists see and will detect a significant percentage of new diabetes and DR cases in the US (320,000 in 2016 per AOA estimates)
- **PREDICTION: Optometrists will increasingly treat patients with type 2 diabetes using lifestyle recommendations & safe/effective oral mono-therapy**

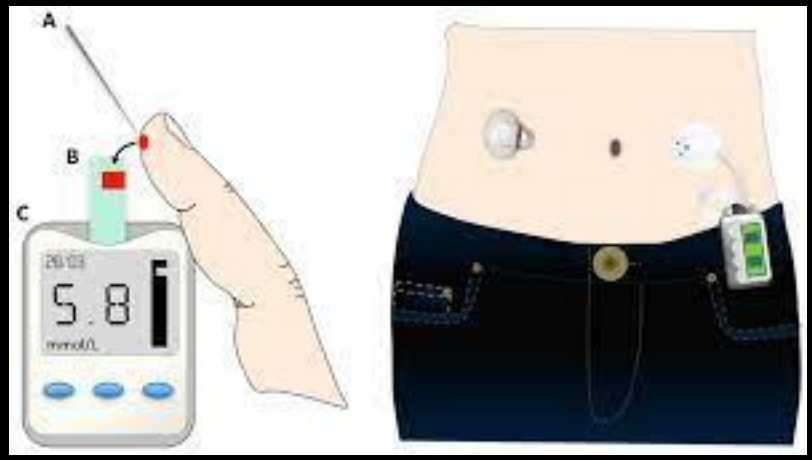
Public Perception

- ~40% of people with diabetes feel that a comprehensive eye exam is not needed.[1]
- 79% of Americans don't know that diabetic eye diseases can have no noticeable symptoms.[2]
- >50% of Americans don't know that a comprehensive eye exam can detect diabetes.
  - In 2014, eye doctors found manifestations of diabetes in 240,000 people who did not know they had the disease.
- It is likely that fewer than one-third of all diabetic retinopathy (DR) cases are ever diagnosed.[3]

[1]Chou C, Sherrod CE, Zhang X, et al. Diabetes Care 2014;37:180–188; [2]American Optometric Association. Available from https://www.aoa.org/about-the-aoa/press-room/press-releases/aoas-annual-survey-reveals-misconceptions-about-diagnosing-diabetes-and-its-related-eye-diseases?sso=y. Accessed 22 September 2020; [3]Bressler NM, Varma R, Doan QV, et al. JAMA Ophthalmol 2014;132:168–173

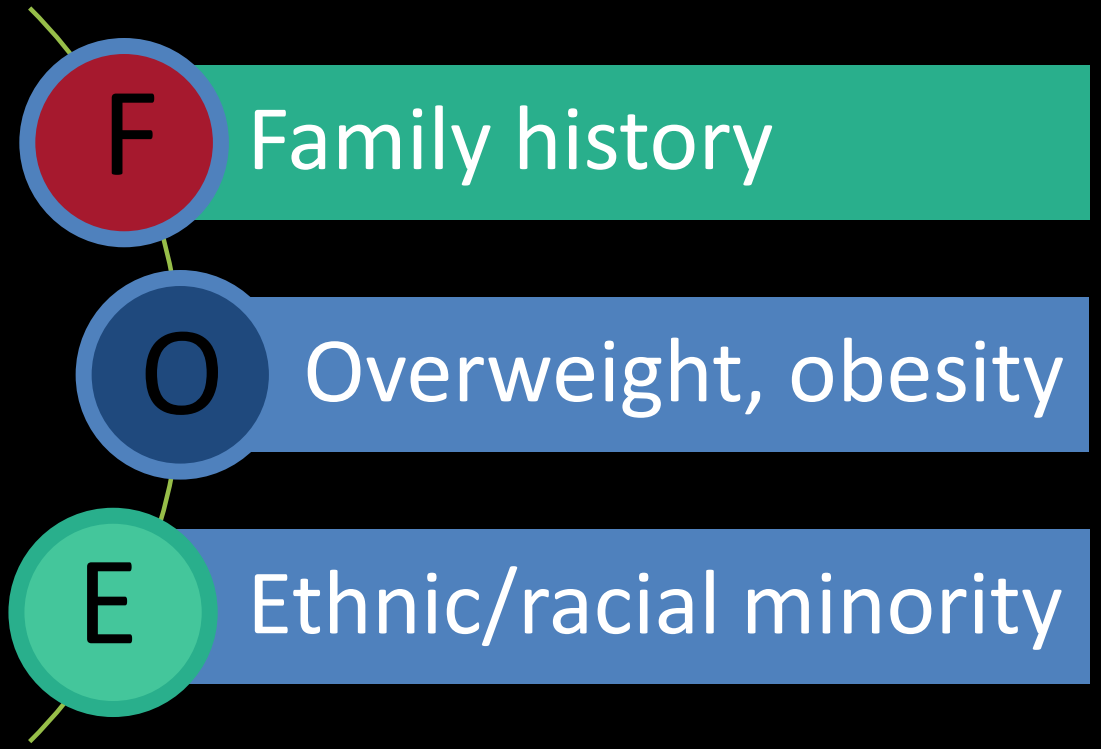
Let me introduce 2 terms to start to think about

- Continuous glucose monitor
- Time in range



Risks for Type 2 Diabetes

Primary Risks



Other Risks

- Prediabetes
- Ge (≥45 years)
- Heart disease
- Physical inactivity
- High blood pressure
- Low HDL cholesterol and/or high triglycerides
- Gestational diabetes
- Polycystic ovary syndrome

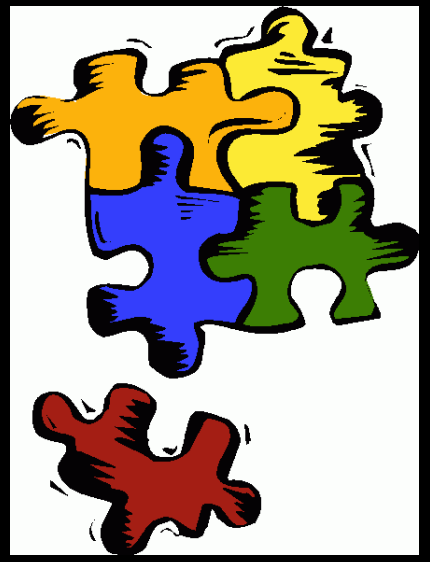
American Diabetes Association. Diabetes Care 2020;43(Suppl. 1):S14–S31

ADA Diabetes Risk Test

- Available online at diabetes.org/risktest
- Also available for downloading free in 10 different languages at professional.diabetes.org/patented
- Takes into account:
  - Age, sex, height, weight
  - Race/ethnicity, family history
  - Physical activity
  - Gestational diabetes, high blood pressure
- Find out your risk in 1 minute

Who Develops Diabetes

- Genetics with Type 2
  - If 1 parent with T2DM, then 50% likelyhood
  - If 2 parents with T2Dm, then 80%
- Genetics with Type 1
  - If 1 parent with T1DM, then 10% likelyhood
  - If 2 parents with T1DM, then 20%



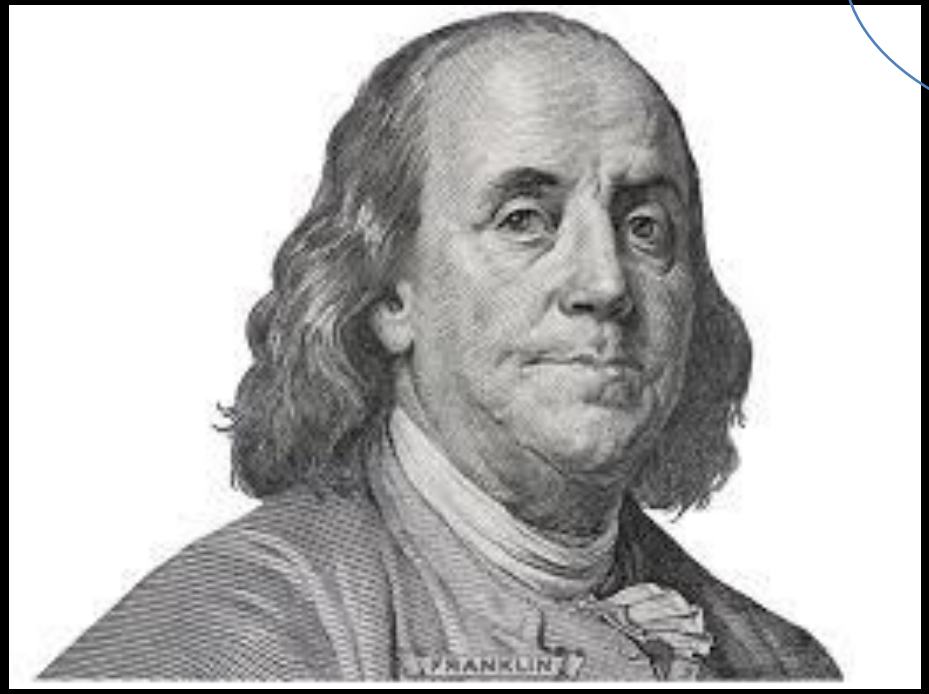
What Is Prediabetes?

- Blood glucose that is higher than normal but not high enough to be type 2 diabetes.

- High risk for type 2 diabetes and CVD
- Affects 1in 3 American adults and 85% don’t know they have it
- No hallmark signs or symptoms
- Estimated economic burden of prediabetes: $43.4 billion

Kumar R, Nandhini LP, Kamalanathan S, Sahoo J, Vivekanadan M. World J Diabetes 2016;7:396–405;
Dall TM, Yang W, Gillespie K, et al. Diabetes Care 2019;42:1661–1668

Benjamin Franklin Said It Best



#1 Path Diabetes Prevention?

Making lifestyle changes!

- Healthy eating
- Physical activity
- Smoking cessation
- More sleep; less stress

HEALTHY LIFESTYLE

Other paths to prevention include:

- Medication (usually metformin)
- Bariatric surgery (in certain cases)
- But lifestyle change is still #1, and everyone can do it!

What Is the National DPP?

- A partnership of public, private, and government groups working to prevent or delay type 2 diabetes
- Run by the CDC

- Making lifestyle change programs based on the DPP research study available nationwide

To find a local or online program: nccd.cdc.gov/DDT_DPRP/Registry.aspx

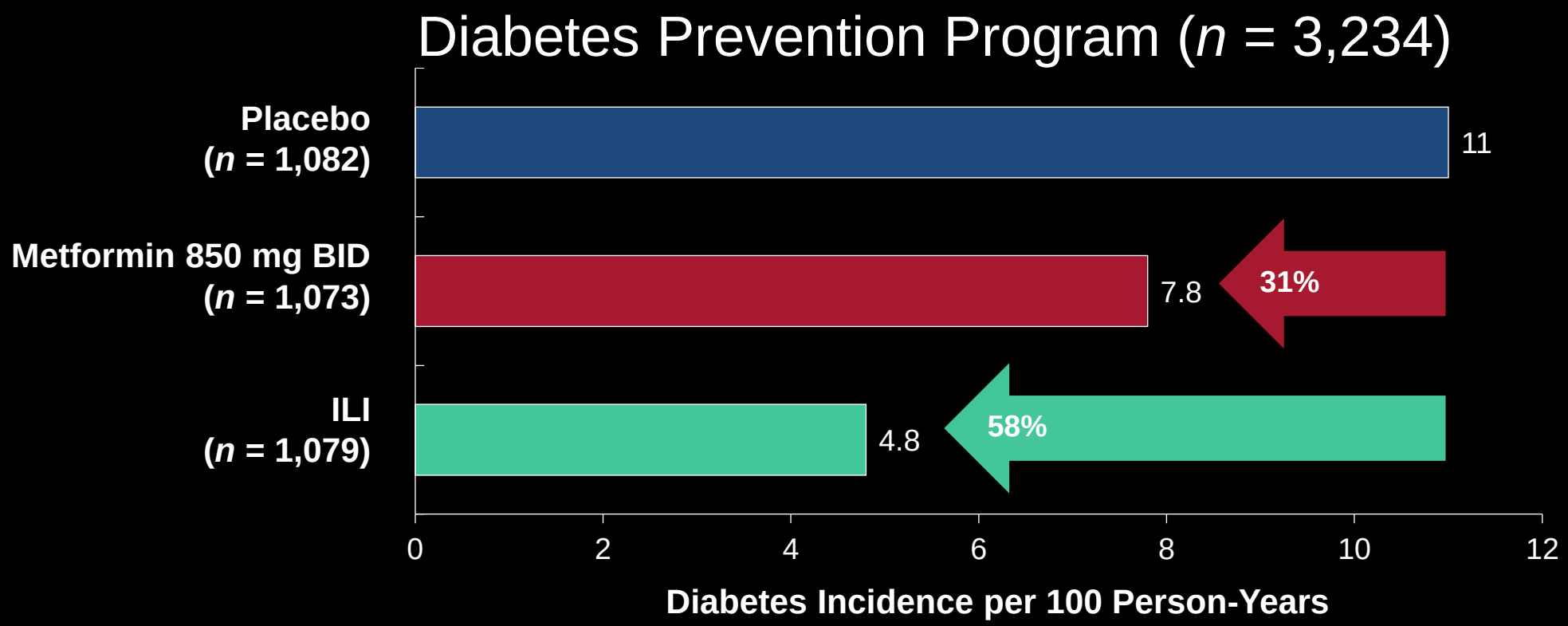
Centers for Disease Control and Prevention. Information available from www.cdc.gov/diabetes/prevention/index.html. Accessed 11 May 2020

Diabetes Prevention Program (DPP) Study

- People at high risk (prediabetes or previous gestational diabetes)
- Representative of the U.S. population
- Three groups:
  - Intensive lifestyle intervention (ILI)
  - Metformin
  - Routine care
- ILI included lifestyle coaches, personal trainers, dietitians
- ILI goal: 7% weight loss through low-cal, low-fat diet and at least 150 minutes of moderate exercise per week

Knowler WC, Barrett-Connor E, Fowler SE, et al.; Diabetes Prevention Program Research Group.
N Engl J Med 2002;346:393–403

ILI Prevented Type 2 Diabetes the Best



Knowler WC, Barrett-Connor E, Fowler SE, et al.; Diabetes Prevention Program Research Group.
N Engl J Med 2002;346:393–403

Why are Many Pre-DM Patients Started on Metformin?

- DPP showed metformin was most effective for patients < age 60 and with BMI > 35 kg/M^2 and women with a history of gestational DM
  - Lifestyle intervention still had equivalent efficacy in these groups
  - Taking a pill may promote compliance > ongoing lifestyle modification

N Engl J Med. 2002 Feb 7;346(6):393-403

Diabetologia. 2017 Sep;60(9):1601-1611

26-Year Data from the DPPOS

- Diabetes Prevention Program Outcomes Study
- Prediabetes subjects: Usual care v. metformin v. lifestyle intervention with 150 min moderate exercise/week (mean age = 72 yrs)
- 25% risk reduction with exercise vs 18% metformin vs usual care
  - No significant difference in DKD/DR/CV disease between metformin & exercise in those who developed T2DM
  - 12% reduction in cancer; not statistically significant)

Diabetes Prevention Recommendations

- Weight loss of 5–7% through healthier eating and exercise
  - For someone who weighs 200 lb: aim for losing 10–14 lb
- Smoking cessation
- Regular health care, with diabetes screening at least annually

Centers for Disease Control and Prevention. Available from https://coveragetoolkit.org/about-national-dpp/ndpp-overview/. Accessed 27 July 2020

Why Should ODs Care About Diabetes Prevention?

- **Every day, 55 Americans with diabetes go blind**

- **You won't go blind from diabetes if you don't develop diabetes**

Dietary Recommendations

- Healthy eating:
  - Choose nutritious nonstarchy vegetables, lean proteins, high-fiber whole grains, healthy fats, with some fruit and low-fat dairy.
  - Avoid saturated fat.
  - Moderate salt intake.
  - Limit refined and added sugars.

Evert AB, Dennison M, Gardner CD, et al. Diabetes Care 2019;42:731–754

Michael Pollan's Adage

What We Do

Eat Food-like Products, Far Too Much, Mostly Refined Carbs with Low Nutrient Density, Trans Fats & Devoid of Fiber

Food for thought

- Chocolate: Meta-analysis of 336k+ patients
  - More chocolate (>3.5x/month) decreased risk of CAD vs no or less than 1/wk[1]
- FAST FOOD
  - 36.3% of children and adolescents eat fast food daily and 13.8% of calories from fast food[2]

1. Krittanawong et al. Euro J of Prevent Cardiol. 7/2020 2. Fryar et al. NCHS Data Brief No. 375, August 2020

Exercise Recommendations

- Exercise
  - Build up to at least 150 minutes per week of moderate aerobic exercise, such as walking.
  - Get regular strength and balance exercise, too.
  - When sedentary, try to stop every half hour for a few minutes of walking or other active movement.

American Diabetes Association. Diabetes Care 2020;43(Suppl. 1):S48–S65

Centers for Disease Control and Prevention. Available from https://coveragetoolkit.org/about-national-dpp/ndpp-overview/. Accessed 27 July 2020

Good Control Does NOT Eliminate Risk of Severe DR

- **10 year risk of PDR and/or CSME in a newly Dx patient with A1c = 6.5% and BP = 120/80 is 8%**
- **With mild NPDR the 10 yr risk is 12%**

Diabetologia. 2011 Oct;54(10):2525-32

Benefits of Exercise for People with Diabetes

- Promotes overall health
- Improves blood glucose control and insulin sensitivity
  - Can help lower glucose levels
- Reduces cardiovascular risk
- Facilitates weight loss (and weight maintenance)
- Enhances well-being
- Can help prevent or delay type 2 diabetes

Colberg SR, Sigal RJ, Yardley JE, et al. Diabetes Care 2016;39:2065–2079

Depression and DR

- Depression is more common in patients with DR.
  - 3.8 times more depression with DR than without[1]
  - Up to 90% of those with DR may have some mood disturbance.[2]
  - Severity of DR, DME, and vision loss is significantly associated with poor psychosocial outcomes.[3]
    - Could be avoided with DR prevention and timely treatment
  - Often resulting from fear of loss of function and quality of life
- Depression can lead to worsening DR.
- Combined psychiatric therapy recommended[4]

[1]Sharif S, Raza MT, Mushtaq S, Afreen B, Hashmi BA, Ali MH. Cereus 2019;11:e5145; [2]Ameerh MAA, Hamad GI. Eur J Ophthalmol Epub ahead of print on 22 March 2020 (doi: 10.1177/1120672120912691); [3]Khoo K, Man REK, Rees G, Gupta P, Lamoureux EL, Fenwick EK. Qual Life Res 2019;28:2017–2039; [4]Chen X, Lu L. Psychosomatics 2016;57:465–471

Mental health and DR

- 95.5k subjects: 4,315 (4.5%) had DR, 18.8% had anxiety, and 21% had depression
- Prevalence of depression and anxiety higher in pts w DR
  - Stat signif for depression
  - Higher depression in all DR but lowest for PDR
    - More depression in men vs women
  - Anxiety only increased in mild NPDR
- Less anxiety in >65yo vs younger

Daniel Olson, MD. ARVO 2020.

Diabetes and Eye Health

Recap: Why Diabetes Matters for Eye Health

- Risks for diabetes-related complications such as eye, kidney, nerve, and heart diseases are increased even in prediabetes.
- About 20% of people with newly diagnosed type 2 diabetes already have eye disease.
- Diabetes is the leading cause of blindness in people less than 74 years of age.
- Diabetes-related eye diseases can be prevented or delayed with early identification and treatment.

Fong DS, Aiello L, Gardner TW, et al. Diabetes Care 2004;27(Suppl. 1):S84–S87

American Diabetes Association. Diabetes Care 2020;43(Suppl. 1):S135–151

Hypoglycemia in the Eye Care Clinic

Hypoglycemia (low blood glucose) is common and requires immediate treatment.

- Symptoms: shaking, sweating, irritability, confusion
- Where allowed, clinics should keep a glucose meter and supplies, as well as fast-acting carbohydrates, on hand.
- Follow the “15-15 Rule” to treat:
  - Give 15 g of fast-acting carbohydrate (for example, glucose tablets, fruit juice, sugar-sweetened soda, or hard candies).
  - Check blood glucose after 15 minutes; if it is still <70 mg/dL, repeat treatment.

American Diabetes Association. Available from mhttps://www.diabetes.org/diabetes/medication-management/blood-glucose-testing-and-control/hypoglycemia. Accessed 13 May 2020

Communication and Support Are Essential

Eye care patients with diabetes need:

- Clear explanations about their eye conditions
- Information about the links between diabetes and eye disease
- Support—not scare tactics
- Key messages:
  - Being able to read an eye chart and see OK in daily life ≠ healthy eyes.
  - Having regular dilated eye exams is the way to protect your vision from diabetes complications.

Back to Time in Range..

The Vast Majority of T2DM Patients Don't Achieve Metabolic Targets within 5 YEARS of DX!

DISCOVER Trial of 16K T2DM Subjects Worldwide: 38 Nations

- After 5 years Dx with T2DM:
  - Mean A1c = 8.3% (Europe = 8.1%; US = 8.6%)
  - Mean Age at Dx = 51.6 years (EU = 61.9; US = 58.3)
  - Only 17.6% with HbA1c $\leq$ 7% (18.7% EU; US = 17.1%)
  - Only 49.2% with HbA1c $\leq$ 8% (53.9% EU; 47.1% US)
  - Microvasccular Dz = 18.9% CAD/Stroke = 12.9%
  - Metformin alone = 55.6% met + SFU = 20.9%
  - Metformin + DPP4 inhibitor (Januvia) = 23.5%

Diabetes Res Clin Pract. 2019;151:20-32.

Is HbA1c the Best Predictor of DR Risk?

- **Disease duration and HbA1c thought to be most predictive YET….**
- **Analysis of DCCT/EDIC data shows that mean A1c during the studies accounted for a mere 6-11% of DR risk!**

Glacco et al. Diabetes. 2015 Sep;64(9):3273-84

- **Moreover, the Joslin "Gold Medlist" study showed little correlation between development of sight-threatening DR and A1c in patients with T1DM > 50 years…….**

Diabetes Care. 2011 Apr; 34(4): 968–974

Continuous Glucose Monitoring (CGM)

- Continuous glucose monitoring systems (CGM) render fingerstick glucose testing irrelevant except for purposes of calibration
- These systems are becoming increasingly popular amongst all DM patients (especially on insulin Tx)
  - 40% of T1DM
  - ≈9% of T2DM
- Allow real-time alerts for high and low blood glucose and calculation of glucose time-in-range
  - Predict DR & DKD independently of A1c
- Helps correct deficiencies of A1c

Sensors (Basel). 2019 Feb; 19(4): 800.

1:22

May 1, 2020 - Jul 29, 2020

2 | 7 | 14 | 30 | **90**

Glucose

Average Glucose

126 mg/dL

Standard Deviation

35 mg/dL

GMI

6.3 %

Time in Range

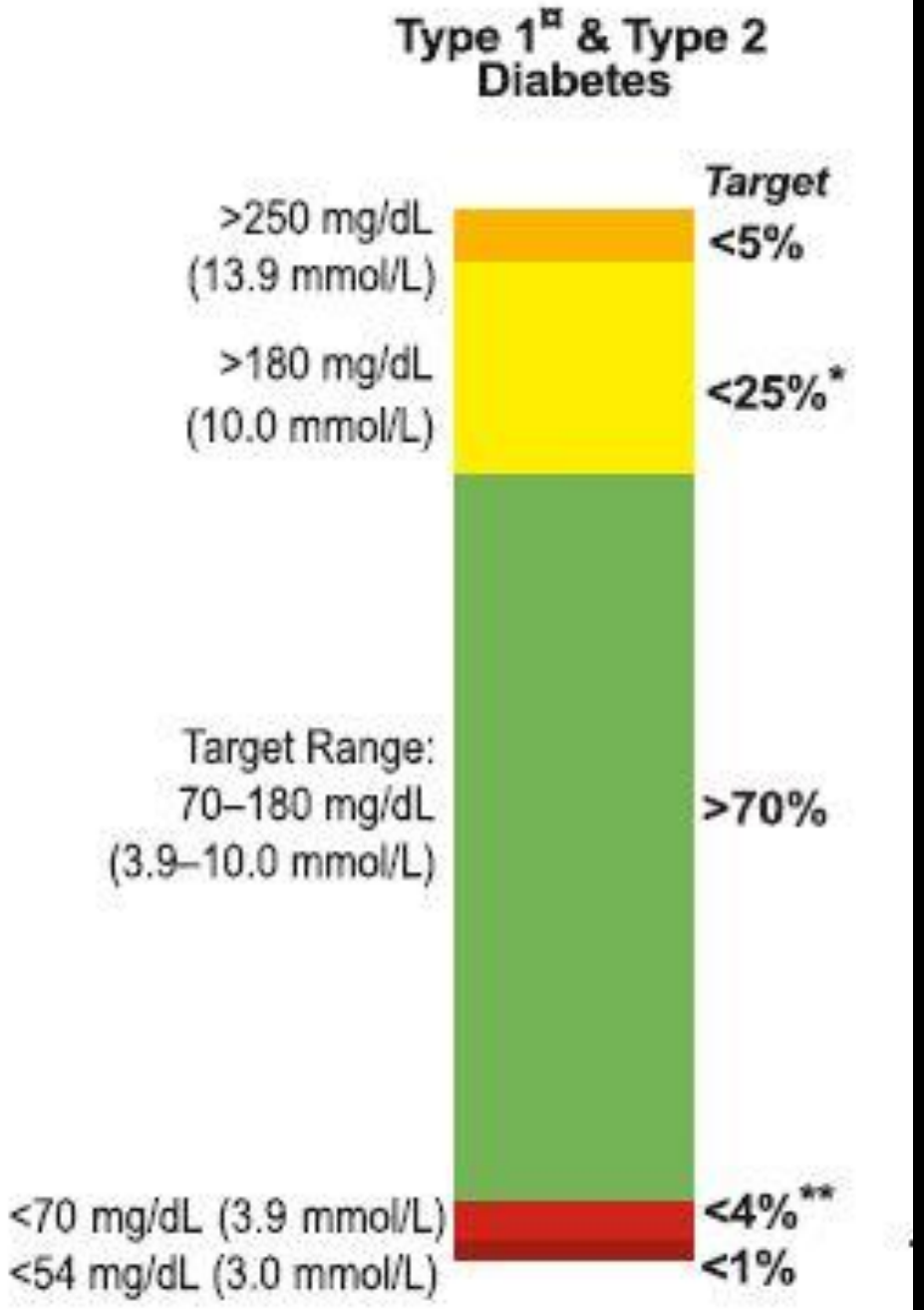
<1% Very High
6% High
90% In Range
3% Low
<1% Very Low

+1% change since prior 90 day period

Target Range: 70-180 mg/dL

Patterns

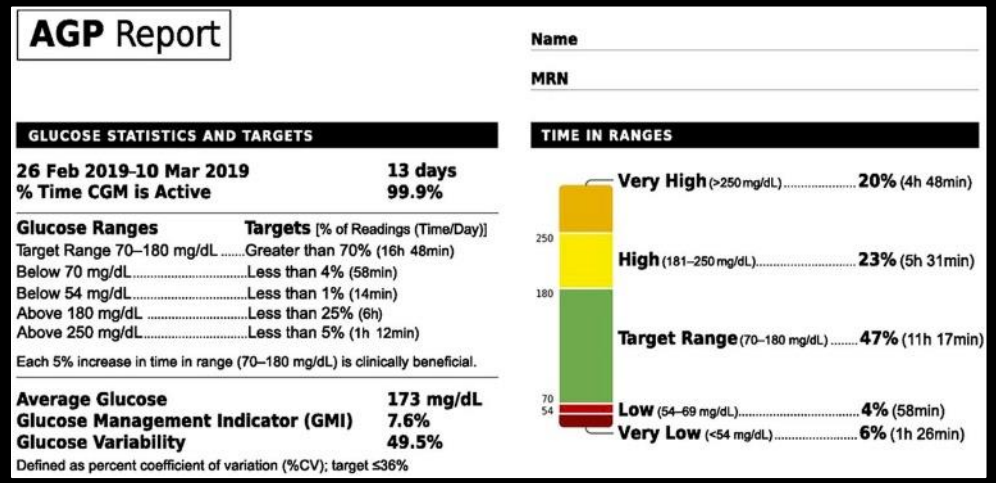
No patterns detected



New Metrics for Assessing Glycemic Control

For patients with access to continuous glucose monitoring (CGM), additional metrics are emerging to guide treatment. Among these are:

- Glycemic variability: degree to which glucose readings vary from the mean or median glucose level
- Time above range: % time spent with glucose 181–250 mg/dL (level 1) or >250 mg/dL (level 2)
- Time in range: % time spent with glucose 70–180 mg/dL
- Time below range: % time spent with glucose 54–69 and <54 mg/dL



Sample Ambulatory Glucose Profile report

American Diabetes Association. Diabetes Care 2020;43(Suppl. 1):S66–S76

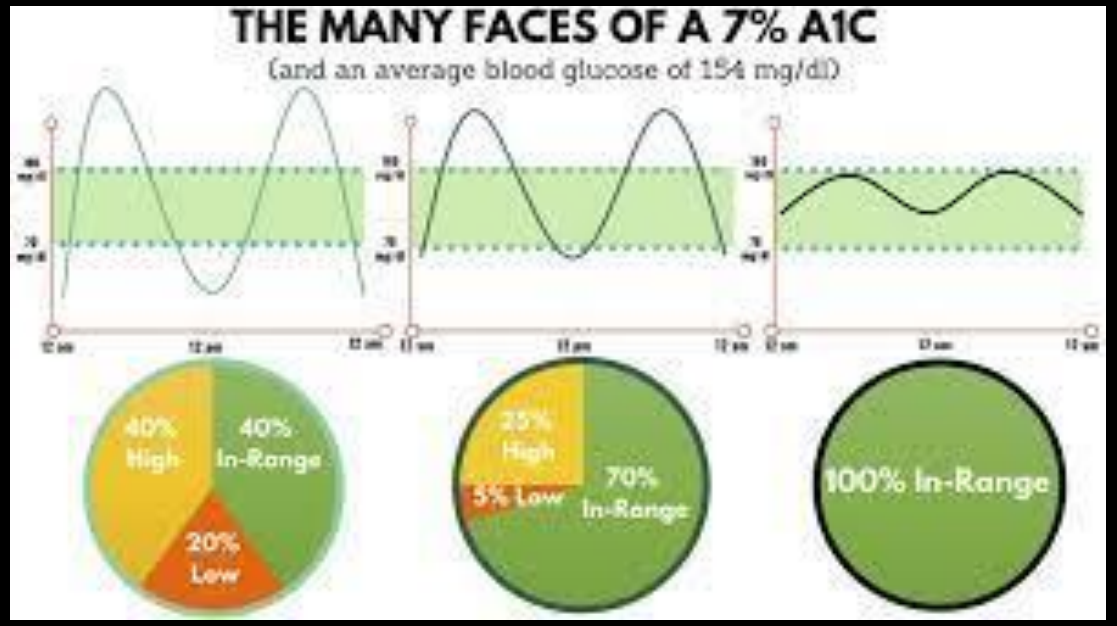
Improved HbA1c 1-1.5% in non-insulin users
ADA Scientific Abstract 84-LB June 13, 2020
Equivalent to adding insulin

CGM and TIR

- Simple math:
  What is the average of:
  - 50+250+50+250+50+250 =?

  What is the average of :

  150+150+150+150+150=?



Does it matter?

Benefits of Glucose Time-In-Range

- TIR refers to the percentage of the day a patient's blood glucose is 70-180 mg/dl
- For any given TIR, there is WIDE variability in HbA1c (e.g. TIR = 60%, HbA1c range = 7-12%)
  - 1441 participants from the DCCT
  - 3262 T2DM patients in China
- **A 10% decrease in TIR increases DR risk 64% and risk of microalbuminuria 40%** ($p < 0.001$)
- → **INDEPENDENT of HbA1c**

Diabetes Care. 2019 Mar;42(3):400-405 Diabetes Care 2018 Nov; 41(11): 2370-2376
J Diabetes Sci Technol. 2019 Jul;13(4):614-626

CGM in Poorly Controlled T2DM

- 8-month RCT of 175 pts on basal insulin and mean HbA1c $\geq$ 9%
- CGM vs. conventional SMBG lowered HbA1c a mere 0.4% ($p = 0.02$)
- CGM increased TIR 15% (3.6 hrs/d) and decreased time-above-range ($TAR_{>250}$) by 16% ($p<0.001$)
- Equivalent to a 60% risk reduction for the development of DR

JAMA. 2021;325(22):2262-2272.

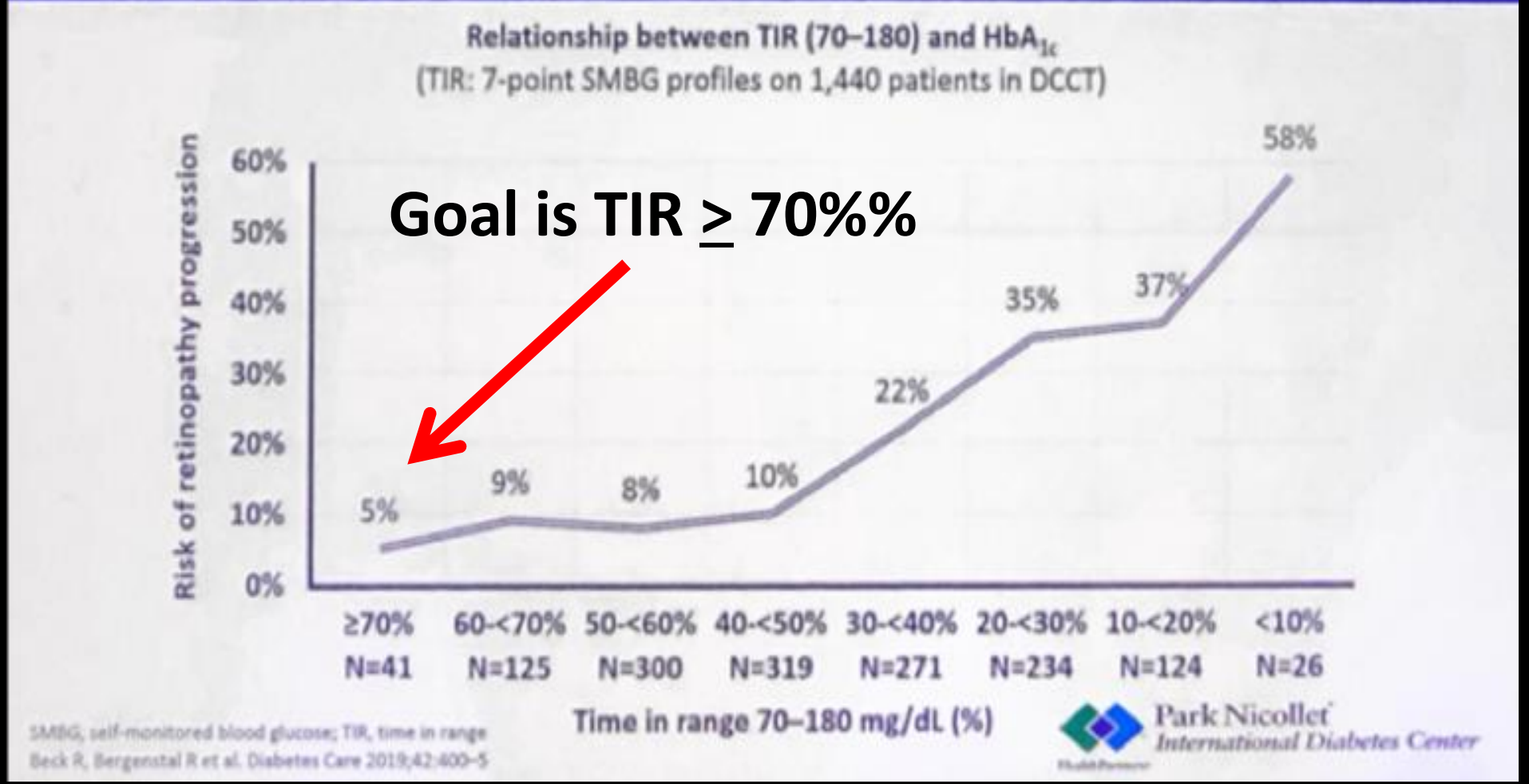
How Can Patients Improve TIR?

- Get a CGM or Flash Glucose Sensor
  - Dexcom or Metronic CGM / Freestyle Libre
- Reduce carbohydrate content to 30 grams maximum per meal
- Eat lower glycemic index foods/meals
- Exercise (aerobic > resistance) immediately after a meal
- Use a semi-closed-loop insulin pump
  - Tandem, Medtronic, Omnipod Horizon
- Use an ultrafast-acting insulin analog (
  - FIASP (Novolog) or Lyumjev (Humalog) → 15 m onset
- Try intermittent fasting

Chous AP, Optometry Times, May 13, 2020

Validation of time in range as an outcome measure for diabetes clinical trials

Hazard Ratio for DR Progression



In DCCT, the TIR difference in those with and without DR was 2.5 hours

Optimizing Diabetes Treatment Is *Essential*

- Individualized management of glycemia, blood pressure, and lipids
- Both A1C and glucose time in range (TIR) are independently predictive of DR incidence/progression in both type 1 and type 2 diabetes.

TIR ↓ 10%	DR risk ↑ 64%	Microalbuminuria risk ↑ 40%

- A 1.0% decrease in A1C results in a 50% decreased risk in significant DR (two-step) progression.
- Analysis: DCCT subjects without DR had a mean 2.5 hours/day more TIR.

Beck RW, Bergenstal RM, Riddlesworth TD, et al. Diabetes Care 2019;42:400–405; Lu J, Ma X, Zhou J, et al. Diabetes Care 2018;41:2370–2376;
U.K. Prospective Diabetes Study Group. Lancet 1998;352:837–853; Skyler JS. Endocrinol Metab Clin North Am. 1996;25:243–254

BTW: Who are my best two MD referral sources?

- 1. A PCP that you will hear a little about later
  - Helped identify a patient with DM based on refractive shift
- 2. An Endocrinologist that is a patient of mine
  - When he was in I started talking to him about CGM and TIR
    - He was SHOCKED that I knew what they were and knew data
    - Now sends his patients to me and not the MDs in my practice!

What Has Been the Standard Treatment of NPDR?

- **Counsel on improving metabolic control if sub-optimal**
- **Counsel on importance of follow-up examination to detect progression to PDR/DME**

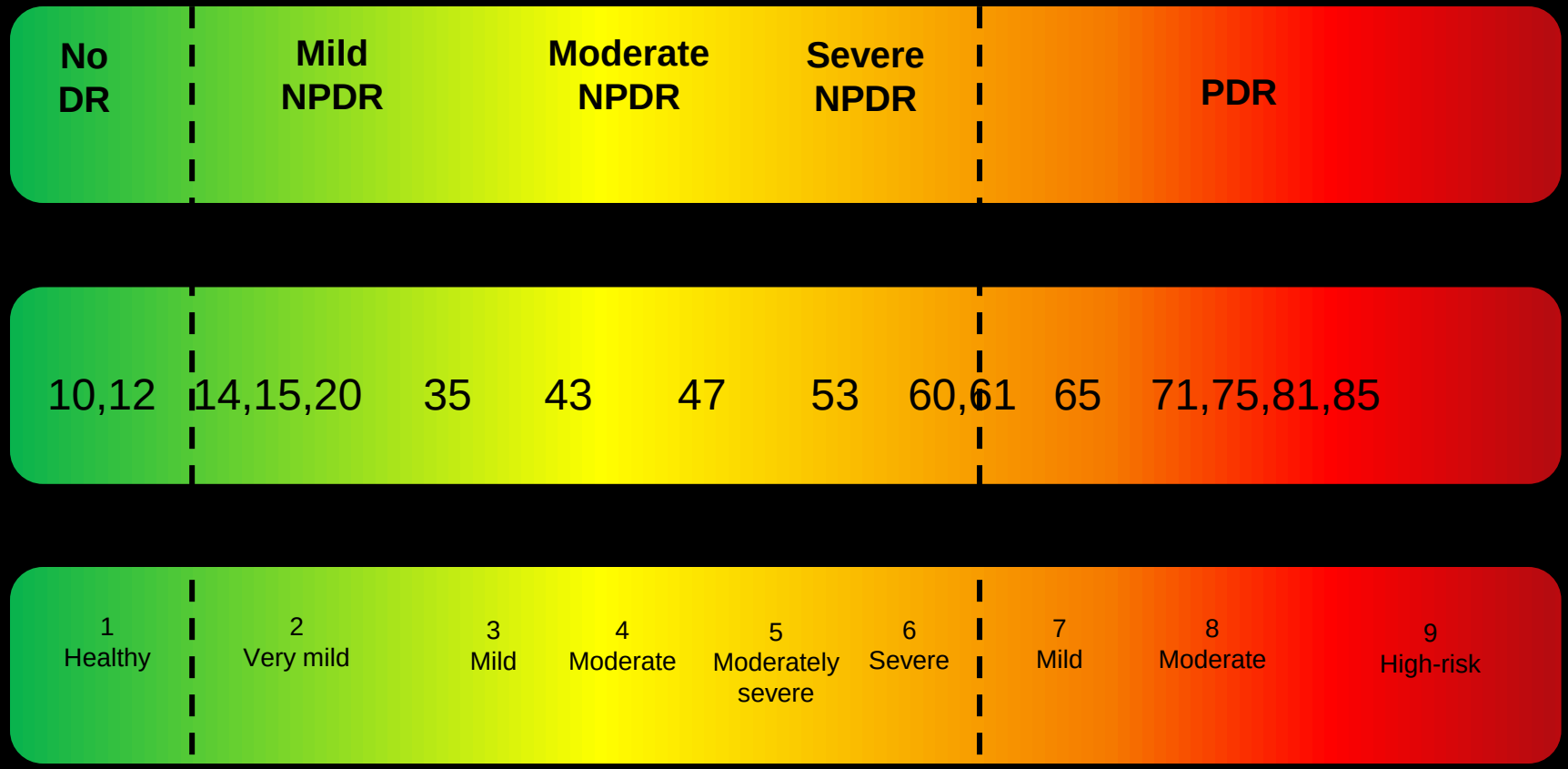
Management of NPDR

- Can we do better than ‘watchful waiting’ for some patients?

Are you surprised to know that this is not the only DR grading scale?

- Why would this be??

Setting the stage: Diabetic Retinopathy Severity Scales

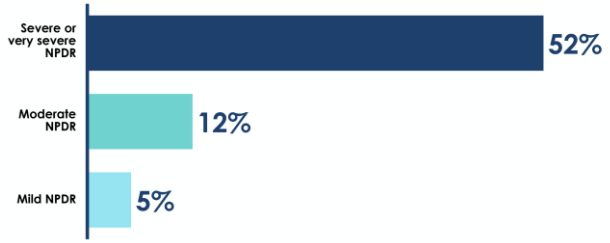


1. Scott I et al. *Diabetes and Ocular Disease: Past, Present and Future Therapies*. New York, NY: Oxford University Press; 2010. 2. ETDRS Research Group. *Ophthalmology*. 1991;98(5 Suppl):823-833.
3. Ip MS et al. *Arch Ophthalmol*. 2012;130(9):1145-1152.

DR, diabetic retinopathy; ETDRS, Early Treatment Diabetic Retinopathy Study; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

DR Severity Can Progress Quickly to PDR From Any Stage of Disease

Natural rate of progression to PDR in 1 year[1]



Reference: 1. American Optometric Association. http://aoa.uberflip.com/i/1183026-evidence-based-clinical-practice-guideline-eye-care-of-the-patient-with-diabetes-mellitus-second-edition/0?m4=. Accessed December 11, 2020.

15

Untreated DR Is at Serious Risk for Progression to Vision-Threatening Complications

Progressed to PDR within 4 years[1]

AOA guidelines advise HCPs to refer patients with severe NPDR and/or PDR to retina specialists within 2 to 4 weeks[2]

Moderate NPDR; n=39,116; severe NPDR; n=10,692.[1]

References: 1. Moshfeghi AA. Data presented at: Macula Society 2020 Meeting; February 19-22, 2020; San Diego, CA. **2.** American Optometric Association. http://aoa.uberflip.com/i/1183026-evidence-based-clinical-practice-guideline-eye-care-of-the-patient-with-diabetes-mellitus-second-edition. Accessed November 18, 2020.

Patients With Severe Disease Were More Likely to Have Sustained Blindness Without Treatment[1]

In a large retrospective analysis, just 2 years after diagnosis of DR

AAO IRIS® (Intelligent Research in Sight) registry records from January 1, 2013, through December 31, 2017; N=53,535 patients newly diagnosed with DR (n=678 evaluated for risk of sustained blindness). Risk of sustained blindness increased with development of glaucoma, AMD, RVO, DME, vitreous hemorrhage, or retinal detachment. Sustained blindness defined as ≥2 visual acuity readings of 20/200 or worse ≥3 months apart; no improvement beyond 20/100 after first 20/200 reading

AAO, American Academy of Ophthalmology; AMD, Age-related Macular Degeneration; RVO, retinal vein occlusion.

Reference: 1. Wykoff CC et al. Presented at: American Academy of Ophthalmology Annual Meeting; October 27-30, 2018; Chicago, IL.

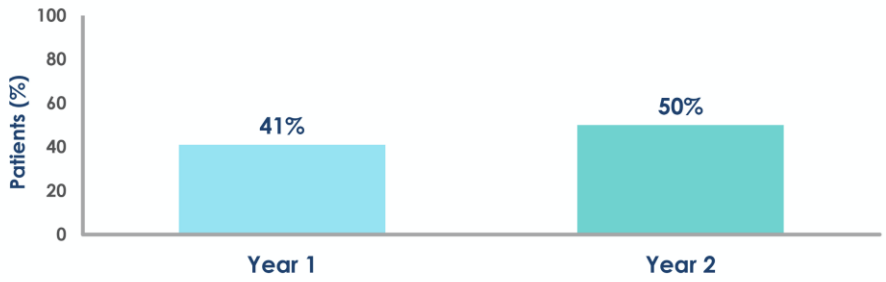
DR Severity at Baseline Is a Significant Predictor of Disease Progression[1]

Real-world VESTRUM data:
Incidence of progression to PDR and DME in 4 years by baseline NPDR severity

*P<0.001 compared to moderate NPDR.
†P<0.001 compared to moderate NPDR.
Moderate NPDR, n=39,116; severe NPDR, n=10,692.
Reference: 1. Moshfeghi AA. Data presented at: Macula Society 2020 Meeting; February 19-22, 2020; San Diego, CA.

Patients Are at Risk for Developing Vision-Threatening Complications That Can Lead to Blindness[1]

Patients with moderately severe to severe NPDR who progressed to PDR, ASNV, or CI-DME

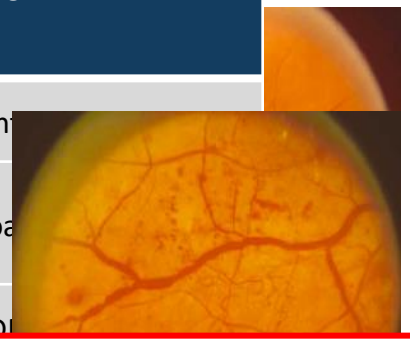


Treatment has been shown to reduce the risk of progression. Join us for parts 2 and 3 of this series, where we further discuss

Reference: 1. Wykoff CC. Data presented at: Angiogenesis, Exudation, and Degeneration Annual Meeting; February 8, 2020; Miami, FL.

Diabetic Retinopathy Severity Score (DRSS)

Level	ETDRS DRSS Severity	Description
1	10 and 12	DR absent
2	14, 15, 20	DR questionable, microa
3	35	Mild NPDR
4	43	Mo
5	47	Moderat
6	53	Se
7	60, 61	Mild PDR
8	65	Moderate PDR
9	71	High-risk PDR
10	75	High-risk PDR



2-step improvement in DRSS
From DRSS 53, Severe NPDR (level 6)
To DRSS Level 43, Moderate NPDR (level 4)

2-step improvement in DRSS
From DRSS level 53, Severe NPDR (level 6)

7
5

* Used to determine step change in the diabetic retinopathy severity score
DR: diabetic retinopathy; ETDRS: Early Treatment Diabetic Retinopathy Study; NPDR: nonproliferative diabetic retinopathy; PDR: proliferative diabetic retinopathy
The Diabetes Control and Complications Trial. *Arch Ophthalmol.* 1995, Aiello. *Am J Ophthalmol.* 2003, Jonas. ETDRS report number 10. *Ophthalmology*. 1991

PANORAMA Trial

- Only eyes with moderately severe or severe NPDR and no DME (DRSS Level 47 or 53)
- Aflibercept versus sham injection Q8 or Q16 weeks in year 1 (after 5/3 monthly loading dose injections) and PRN/Q16 weeks only in year 2
- Primary Outcome: percentage of eyes with a ≥ 2-step improvement in DRSS
- Secondary Outcome: percentage of eyes developing a vision threatening complication, defined as PDR/anterior segment neo and/or CI-DME

Study of the Efficacy and Safety of Intravitreal (IVT) Aflibercept for the Improvement of Moderately Severe to Severe Nonproliferative Diabetic Retinopathy (NPDR) (PANORAMA). Accessed 5/10/2020 at https://clinicaltrials.gov/ct2/show/NCT02718326

PANORAMA Phase 3
52 & 100 Week Data

- Aflibercept (Eylea) Q8 ▶PRN or Q16 weeks for moderately severe to severe NPDR sans DME
- 80%/65% achieved ≥ 2-step DRSS improvement at 52 weeks and 50%/62% at 100 weeks (p< 0.0001)

**That's correct, the Q8 week to PRN Arm did less well

- VTC (PDR/ASneo) reduced 82-85% at 52 wks & 77-83% at 100 weeks (p < 0.0001)
- CI-DME reduced 68-74% at 52 weeks & 68-76% at 100 weeks

Results From PANORAMA. Presented at: 2019 AAO Annual Meeting, San Francisco, CA, October 12-15, 2019.

NNT for Level 47/53 NPDR

Only 3 patients with moderately severe or worse NPDR need to be treated to prevent 1 vision-threatening Complication (PDR/ASNV or CI-DME)

Is this a favorable NNT?

- NNT to prevent one CV death with 5 years of statin therapy in a patient with known heart disease = 83
  - NNT to prevent one non-fatal MI is 39 (NNT = 104 if no Hx of CVD)
- NNT = 333 to prevent a first, non-fatal MI with aspirin therapy
- NNT = 17 to prevent one case of PDR and/or CSME with oral fenofibrate therapy in T2DM with mild NPDR

Data from thennt.com, accessed September 14, 2019
Lancet 2007;370(9600):1687-97

Key Takeaways from the PANORAMA Study

- Even retina specialists under-grade DR severity on clinical exam
  - without FA, referral of moderate NPDR (DRSS Level 43) or worse makes pragmatic sense
- Anti-VEGF therapy can ‘turn back the clock’ on NPDR severity and significantly reduce the risk of bad outcomes, but serial Tx is required AND defined-interval treatment may be better than PRN treatment

DRCR.net Protocol V

- **Is there benefit to ‘preventive’ anti-VEGF or focal laser therapy in patients with center-involved DME and very good visual acuity?**

- **20/25 or better at enrollment**
- **Main outcome is % with loss of ≥ 5 ETDRS letters at 2 years**

Results

- % of patients losing ≥ 5 ETDRS letters at 2 years
  - 16% aflibercept Q 4 wks PRN
  - 17% grid/focal laser
  - 19% observation

NO Stat Significant Difference

  - No significant difference in subjects losing ≥ 2 lines

  - Mean VA at baseline and 2 years wa 20/20 in all 3 groups
  - 3/4 of laser group and 2/3 of observation group **did not** require AVT @ 2 years

PRP vs Ranibizumab

- Protocol S by DRCR.net
- Ranibizumab non inferior to PRP

Real life implications?

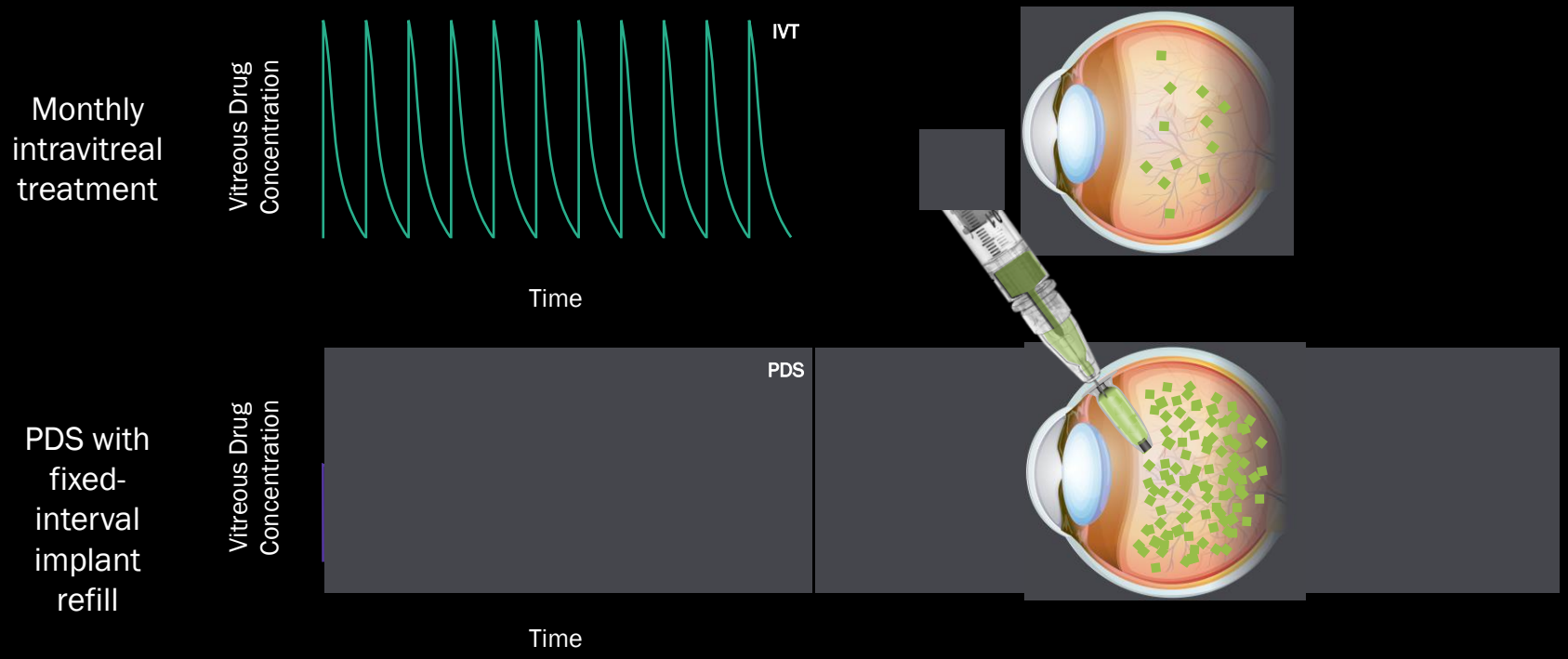
- About 1/3 of patients referred to retina never make it to their first appointment
- Frequent loss to follow-up which leads to sub-optimal outcomes

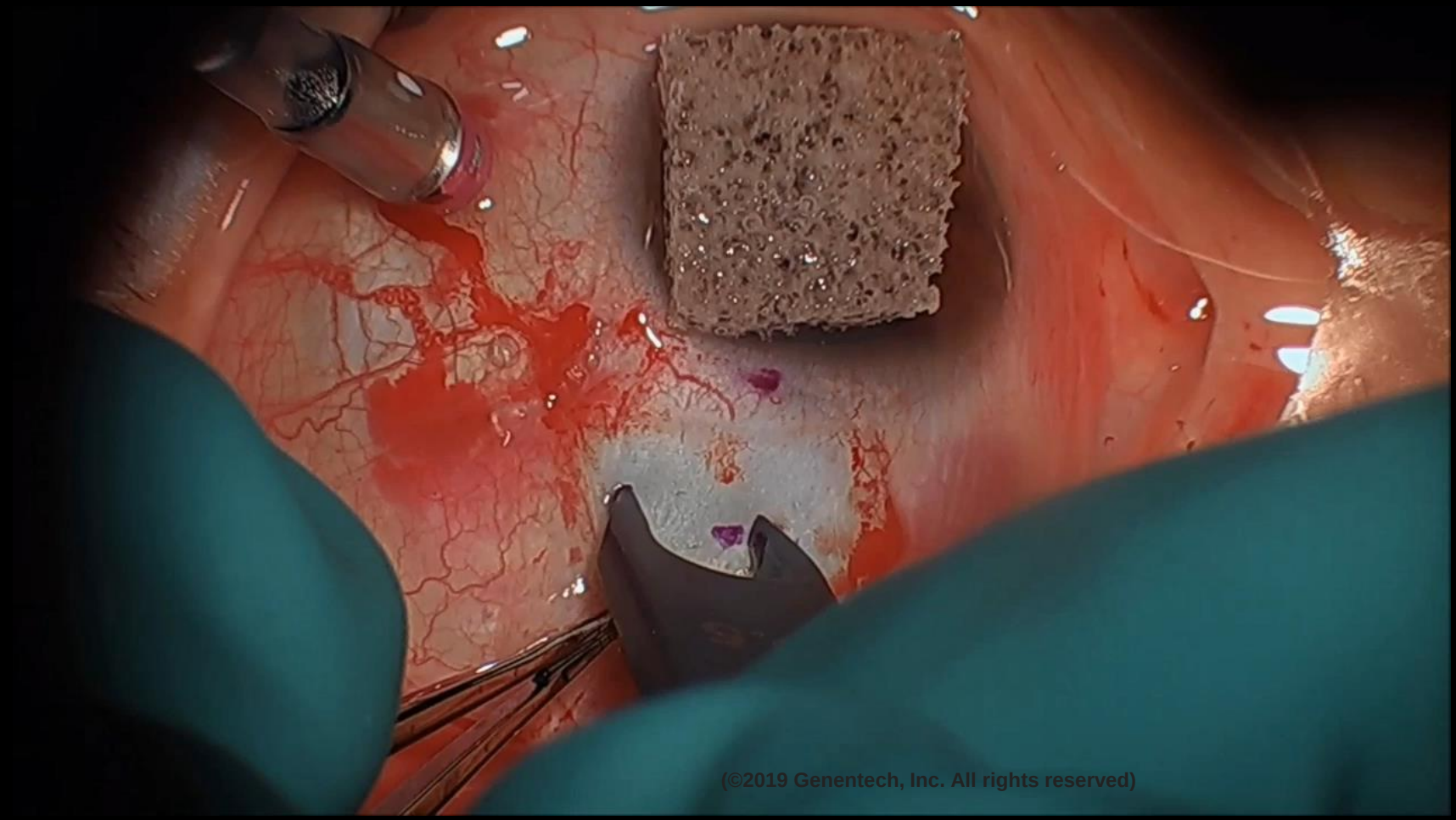
New terminology and ideas in DME

- CSME???
- CI vs non-CI DME
- What about good vision and CI-DME
  - Protocol V showed no difference from prompt antiVegf vs laser vs observation in VA outcomes at 5 yrs!

Could injections become a thing of the past??

PDS vs Monthly Intravitreal Ranibizumab Therapy

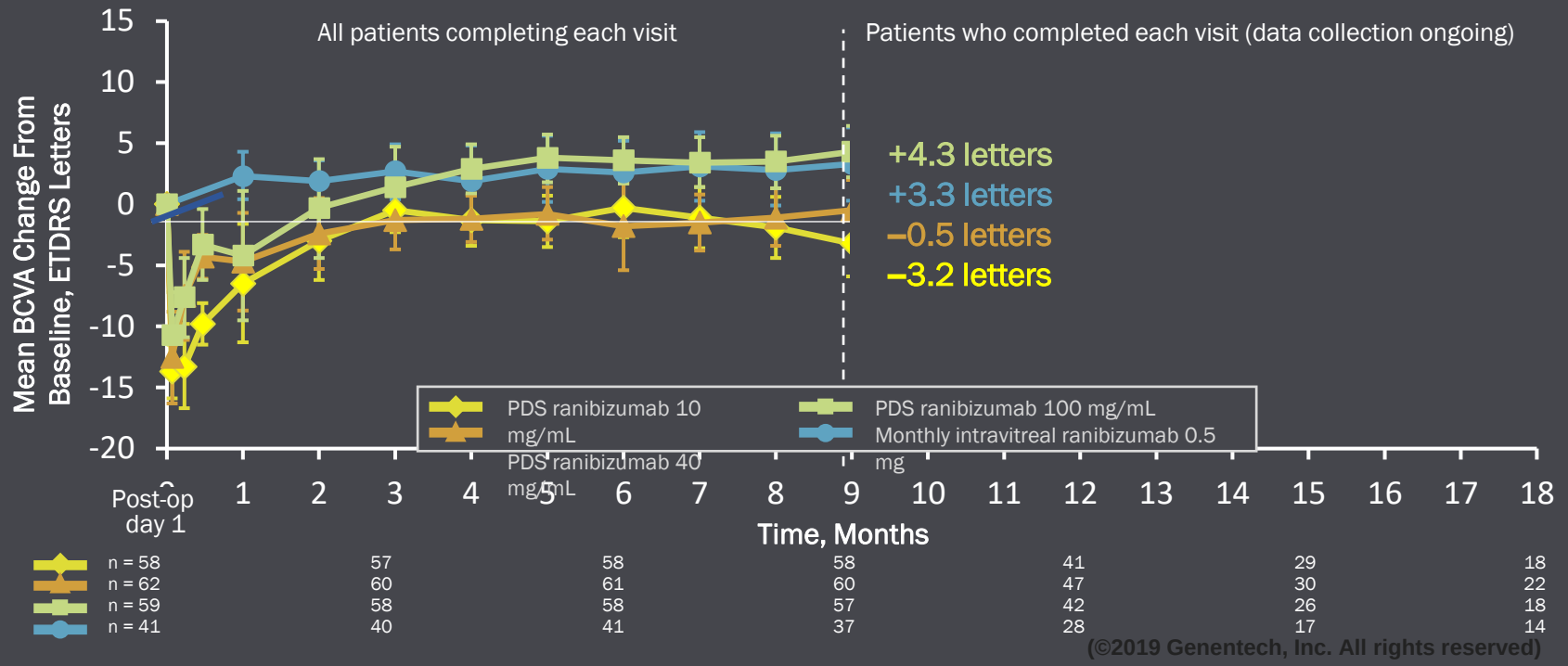




PDS, Port Delivery System with ranibizumab.

Vision Outcomes at 9 Months: PDS 100 mg/mL Comparable to Monthly Intravitreal Ranibizumab Injections

Mean BCVA Change From Baseline, Patients Previously Treated With Any Anti-VEGF[a]



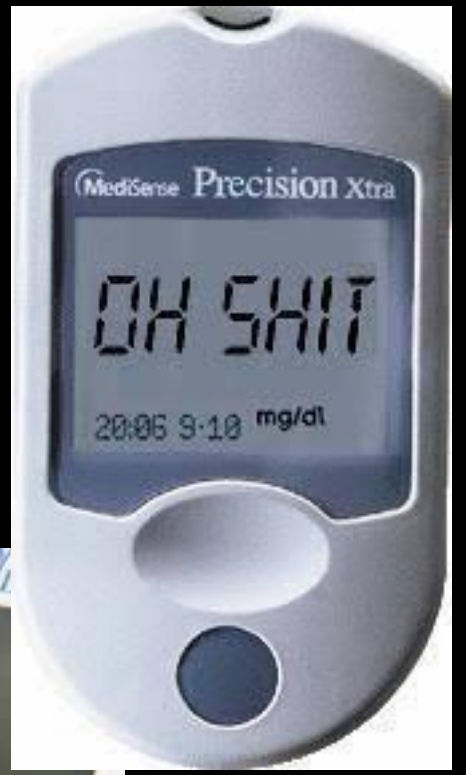
[a] Patients received ≥ 2 and ≤ 9 anti-VEGF injections before baseline. Observed data, modified intent-to-treat population (N = 220). All PDS patients completed each visit through month 9; from month 9 on, data for patients who completed each visit (data collection ongoing). Vertical bars represent 95% CI of the mean.
BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; PDS, Port Delivery System with ranibizumab; post-op, post operation; VEGF, vascular endothelial growth factor.

“Dr. Gerson, your ‘friend’ wants to be worked in”

- 46 yo male cc: “Recent changes in vision”
- Enters office w HUMUNGI Starbucks in 1 hand and water bottle in other
- Recently not feeling well
- Hx: h/o Pituitary adenoma
- Weight: 375 height: 5’11”
  - BMI: 52.3

What do we want to know

- Vision is 20/20 w +1.00 shift OU
- Normal eye exam
  - Note; pt worried about VF due to h/o pituitary adenoma
- Decided to check BG:



- I called the PCP
- Told pack a bag, and meet head to PCP's office

What happened next

- Went to PCP
  - Rechecked BG and agreed way too high
  - Sent to hospital
  - Pt called me from the hospital
    - “You’ll never believe what my doctor was saying in the hallway about you”
    - NOTE: Now the PCP is a patient of mine!!!

Jake’s diet likely needs to be changed, but…

- Can there be more to nutrition than sugar and the right foods?

Can you potentially use a supplement to improve outcomes in diabetes/diabetic retinopathy?

BJO Online First, published on June 18, 2015 as 10.1136/bjophthalmol-2014-306534

OPEN ACCESS

The Diabetes Visual Function Supplement Study (*DiVFuSS*)

A Paul Chous,[1] Stuart P Richer,[2] Jeffry D Gerson,[3] Renu A Kowluru[4]

[1]Private Practice, Tacoma, Washington, USA
[2]Captain James A Lovell Federal Heath Care Center, North Chicago, Illinois, USA
[3]Private Practice, Olathe, Kansas, USA
[4]Kresge Eye Institute, Wayne State University, Detroit, Michigan, USA

Correspondence to
Dr A Paul Chous, FAAO, 6720 Regents Blvd, Tacoma, WA 98466, USA; dr.chous@diabeticeyes.com

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Accepted 26 May 2015

ABSTRACT

Background Diabetes is known to affect visual function before onset of retinopathy (diabetic retinopathy (DR)). Protection of visual function may signal disruption of mechanisms underlying DR.

Methods This was a 6-month randomised, controlled clinical trial of patients with type 1 and type 2 diabetes with no retinopathy or mild to moderate non-proliferative retinopathy assigned to twice daily consumption of placebo or a novel, multi-component formula containing xanthophyll pigments, antioxidants and selected botanical extracts. Measurement of contrast sensitivity, macular pigment optical density, colour discrimination, 5-2 macular threshold perimetry, Diabetic Peripheral Neuropathy Symptoms, foveal and retinal nerve fibre layer thickness, glycohaemoglobin (HbA1c), serum lipids,

the risk of DR and its progression, evidence shows that there is no level of average blood glucose (as reflected by glycosylated haemoglobin) that is totally protective against DR. The current clinical algorithm for delaying DR and preventing STR is earlier diagnosis of diabetes, tighter metabolic control, routine dilated retinal examinations and treatment (laser photocoagulation, intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents and corticosteroids) if/when DR progresses to a level that threatens vision.

The *Age-Related Eye Disease Study* (AREDS) demonstrated that a nutritional supplement could positively influence progression of a vision-threatening eye disease, age-related macular degeneration.[3] This begs the question as to whether

Mean Change/SD in visual function measures, serum lipids, hsCRP, glycohemoglobin, foveal thickness and symptoms of diabetic peripheral neuropathy with 95% p-Values

Δ from baseline	Suppl	v.	Plac	p-Value
Contrast Sens (%)	+19.1±8.9		-6.2±5.1	<0.0001
Color Error Score	-20.55±24.37		+7.5±22.01	<0.0002
5-2 MD (db)	+2.78±9.83		-0.75±0.98	<0.0001
MPOD (du)	+0.09±0.05		-0.01±0.03	< 0.0001
LDL-C (mg/dl)	-7.61±16.08		+0.82±10.15	0.01
HDL-C (mg/dl)	+3.82±6.24		-1.61±5.31	0.0004
TGs (mg/dl)	-10.46±28.48		+2.39 ±11.56	0.01
hsCRP (mg/L)	-2.14±3		-0.28±1.83	0.01
HbA1c (%)	-0.1±0.4		+0.1±0.4	0.06
Foveal Thickness	2.66±11.25μm		0.34±3.48 μm	0.35
DPNSS	-30.7%		+10.7%	0.0024

Fisher's Exact Test

No time to discuss but…

Intermittent fasting

Photobiomodulation

New systemic and retina drugs

Summary Points

- Most patients do not achieve “good” metabolic control soon after Dx → harmful metabolic memory
- Glucose control is still important for prevention of DR – but HbA1c isn’t he whole story
- Anti-VEGF therapy is proven to reverse DR severity and lower incidence of sight-threatening events in higher-risk patients
- Better diet & targeted nutritional interventions are additive, preventive strategies against DR

THANK YOU

Jeffry Gerson, O.D., F.A.A.O.

jgerson@Hotmail.com