

Diabetes Case Studies With an Eye to the Future

Julie Rodman OD, MSc, FAAO A. Paul Chous, MA, OD, FAAO

1

3

Disclosures

- Dr. Rodman is a consultant or speaker for: Visionix (Optovue), iCare, Iveric Bio, Apellis, LKC Technologies, and OcuTerra
- Dr. Chous is a consultant or speaker for: Al Optics, American Diabetes Association, EyeNUK, EyePromise, LKC Technologies, Macular Degeneration Association, OcuTerra, Regeneron, VSP, and Zeiss

What is Diabetes? (CDC)

• A chronic condition that affects how your body turns food into energy

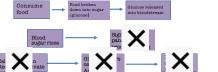


4

2

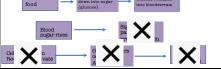
What is Diabetes? (CDC)

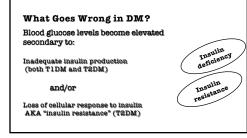
Type 1: Damage to the pancreatic beta cells
 inadequate production of insulin (typically autoimmune)



What is Diabetes? (CDC)

• Type 2: loss of cellular insulin receptors & response with progressive beta cell failure over time





7

Common Misunderstandings

- Use of insulin means a person with type 2 DM now has type 1 DM.
- Only overweight/obese people get type 2 diabetes.
- Type 2 diabetes is the "good kind" of diabete

Diagnosis of DM

FFG \( \) 126 mg/dl on two occasions

RPG \( \) 200 mg/dl with polyuria, polydipsia & weight loss

OGTT \( \) 200 mg/dl at 2 hours

HbAlc \( \) 6.5% (2009)

Pre-diabetes (IFG and/or IGT) now defined as FFG > 100mg/dl or OGTT \( \) 140mg/dl or HbAlc \( \) 5.7%

9

10

8

**Diabetes Complications** 

- Only occur in tissues containing:
- Blood vessels
- Nerves
- Proteins

11



A Constellation of Complications

Erectile dysfunction Renal disease
Peripheral neuropathy
Vascular disease

Gastropathy

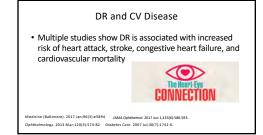
Dyslipidemia

Cardiovascular disease

Retinopathy/
macular edema

Autonomic neuropathy
Hypertension

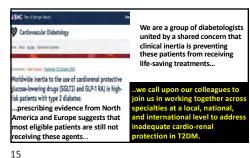
12



**Key Point**  Lowering the patient's blood sugar level and preventing vision loss are far less useful if the patient dies! 2/3 of T2DM patients on metformin monotherapy for glucose control remain at HIGH CV risk

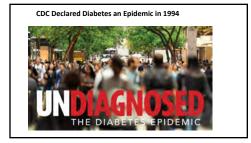
Diabetes Care. 2020;43:2034-41.

13 14



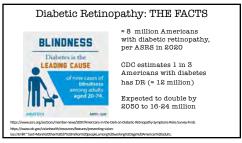
Increasing Prevalence of DM 37.3 million Americans have diabetes 96 million Americans 2018 incidence rate was have prediabetes 1.5 million NHANES analysis (2012) suggested ≥50% of American adults had diabetes or prediabetes Up to 100 million have NAFLD (largely associated with insulin resistance) You won't lose vision to DR if you don't develop diabetes

16



Mean Estimate: 100 million Americans by 2050 Significant increase in prevalence of total diagnosed and undiagnosed diabetes in adults over the next 30 years

17 18



Diabetic Retinopathy

About one in three google with diabetes here publicates factoring active to the property of patients with DR will develop DME<sup>1</sup>

DME is a complication of DR that can occur at any time<sup>4,5</sup>

19

Risk Factors for DR/DME

Disease duration

### — PREVENTION

ALL except

subtype are

MODIFIABLE

- Diabetes subtype
- Degree and duration of hyperglycemia
- Severe hypoglycemia (new findings)
- Hypertension
- Dyslipidemia
- Sleep-disordered breathing
- Other vascular diabetes complications
- Food insecurity

Contraction Oper or Indicated that the

23

• Smoking, vitamin D deficiency

Preventing Diabetes in High-Risk Patients

- The Diabetes Prevention Program (DPP) conducted at 13 US centers showed that "lifestyle modification" (walking 30 minutes each day, five days each week) lowered the risk of developing T2DM in those with prediabetes or previous GDM by 58% over a three-year period (38% @ 10 yrs).
- TWICE as effective as metformin

20

Metformin worked best if patients were heavy (BMI > 35), younger (< 60 yo) or had a Hx of GDM.</p>

21 22

For Patients with Early NPDR

- AVOID SEVERE Hypoglycemia!!!
- → Kills retinal cells in animal models PLOS One. 2011;6(6):e21586.
- → Fremantle Diabetes Study (Western Australia) showed that risk of 2+ lines of vision loss in T2DM was significantly & independently linked to hospitalization for severe hypoglycemia and cigarette smoking (n = 1551 over 4 years)
- Smoking HR = 3.17

Severe Hypoglycemia HR = 5.59 p < 0.0001

Diabetes Care. 2020 Sep;43(9):2113-2120.

24

# Hypoglycemia WORSENS DR!

- Episodic or chronic hypoglycemia ↑ GLUT1 & HIF-1 in Müller Cells leading to massive ↑ VEGF
- Chronic hyperglycemia → Early DR & hypoxia
- Hypoxia + hypoglycemia → severe DR

Patients with Early DR Should Be Advised to Minimize Hypoglycemia!

Cell Rep. 2023 Jan 31;42(1):111976.

J Diabetes Complications. 2020 Jun;34(6):107560.

25

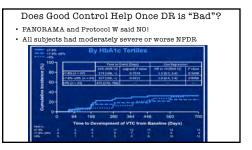
27

Julie - What is your advice to patients with established diabetes for preventing or minimizing severity of diabetic retinopathy?

- When you go to the supermarket, spend your time on the outside aisles!! Try to avoid processed, high-sugar foods.
- Limit fast food and going out to eat (if possible) . Get outside and exercise! Find an activity that
- you love, so you stick with it. Grab a friend © Get off the couch!

26

blood sugar



Strategies to Minimize Severe Hypoglycemia

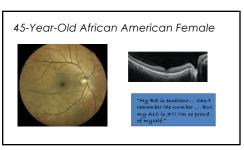
Use of a continuous glucose monitor (CGM)

Nutrients. 2022 Feb 8;14(3):706.

• Low glycemic index Mediterranean diet -Reduces insulin requirements and risk of low

28

How About Some Cases?

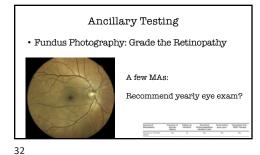


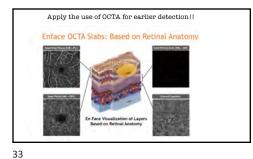
29 30

# Evaluation of Diabetes

- Three main components:
- $-{\rm History: Type}$  2 DM x 10 years; HbA1C 7.0%, FBS 120, Metformin; no other co-morbidities
- -Ocular exam: No NVI, normal IOP
- -Ancillary testing

31





Would This Change Your Follow-up?

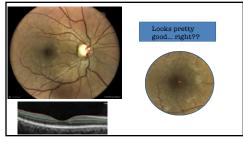
34

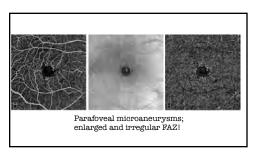


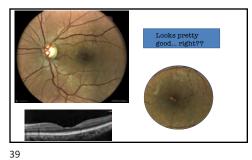
# **Evaluation of Diabetes**

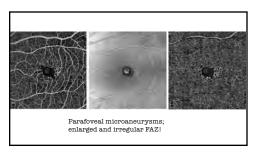
- Three main components:
- -History: Type 2 DM x 10 years; HbA1C 5.9%, FBS unknown; Jardiance
   Hypertension, hypercholesterolemia
- -Ocular exam: No NVI, normal IOP
- -Ancillary testing

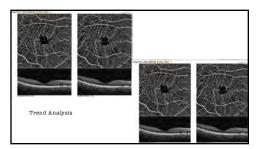
35 36



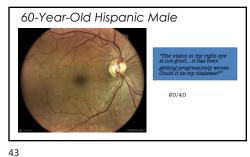








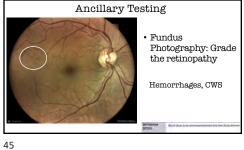




**Evaluation of Diabetes** 

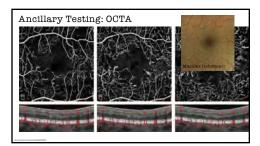
- Three main components:
- -History: Type 2 DM x 20 years; HbA1C 9.2%, FBS 200, Metformin and insulin
   HTN, Hypercholesterolemia
- -Ocular exam: No NVI, normal IOP
- -Ancillary testing

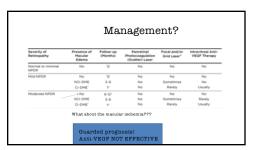
44



Ancillary Testing • OCT: Is there macular edema? No!! So, why the reduced vision?

46





48 47

# Patient RC: Short & Sweet

- 21-year-old male with T1DM x 12 years
- Recent HbA1c = 7% but pt reports it had been as high as 13% for "many years"
- Saw OMD 14 months earlier and was told he had "some early changes" but could be seen Q2 years if he kept his A1c in range
- · Complaining of reduced vision in the right eye for a few days
- 20/400 and 20/20 NI with pinhole



49

51

53

# Patient RC

- · Referred to retinal specialty
- Consult letter reports PRP and ranibizumab (Lucentis) delivered at 1<sup>st</sup>/2<sup>nd</sup> visits
- -REMEMBER, Good A1c doesn't protect from VTC once NPDR is > moderate (>DRSS Level 43)
- This patient represents a strong argument AGAINST less frequent eye examination intervals for higher-risk patients: Young males, T1DM, Hx of initial chronic, poor control, diabetes duration > 10 years

Patient KS - 2018

- 62-year-old female with T2DM x 7 years A1c = 8%
- BCVA 20/50 OD IOP = 18 mm Metformin
- CST = 426  $\mu$  uses CPAP Lantus

52



DME: Center Involving (CI-DME) or Non-Center Involving (NCI-DME)



ETDRS grid map with numerical data for central subfield retinal thickness within innermost circle (1 mm diameter)

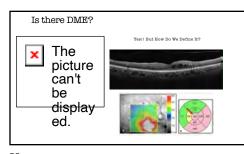
<u>CI-DME</u>: OCT demonstrating foveal involvement of intraretinal or subretinal fluid with concurrent thickening affecting the 1mm diameter **central** subfield thickness

Why Does It Matter? (ETDRS)

Eyes with CI-DME have a 10-fold greater risk of moderate vision loss compared to eyes without center involvement!

MVL = doubling of the visual angle

54



Patient Referred & Treated – RTO in 2019

• Avastin x 4 → Lucentis x 4 → Eylea x 4

• Vision 20/100 → IV Ozurdex placed

• A1c = 7.2%

• BCVA = 20/40 CST = 334μ \* IOP = 47 mm

55

KS 2021 Follow-up

• IVT aflibercept Q 4-8 weeks x 24 mos
• A1c = 6.8% \*sleep report shows 6+ hrs nightly use
• ECCE → BCVA 20/80 \*CST = 465 μ
• IOP = 24 on Cosopt

**KS Key Points** 

- Not everyone responds well to anti-VEGF.
- Add-on IV steroids are often helpful, but can result in significant ocular HTN/glaucoma.
- topical dexamethasone pro-drugs that reach the retina
   OCS-01 gave mean 7.1 letter improvement when added to
   anti-VEGF with a minimal IOP increase (DIAMOND Phase III)
- There is a Need for Complementary Therapies for DME in Some Patients

57

59

58

60

56

(Current/Future) Possibilities for KS

- Faricimab (Vabysmo): dual action by blocking VEGF-A and Angiopoietin-2 to stabilize leaky vessels
- Integrin inhibitors: work both upstream & downstream from VEGF production (a topical, OTT166 is in Phase II trial)
- Oral therapies: RZ402 is a plasma-kallikrein inhibitor shown to reduce vascular leakage/inflammation in Phase II; APX-3330 is a redox effector factor-1 (Ref-1) inhibitor that blocks HIF-1a, VEGF and NF-kB, awaiting Phase III trials
- Photobiomodulation: increases ATP and ROS scavenging in stressed retinal cells (limited success in human trials to date)



# Simple Stuff - Last Friday

- 62-year-old female with T2DM x 15 years on insulin, Ozempic (semaglutide), metformin – no DR
- "I'm doing everything my doctor says, but my A1c is bad all the time (last HbA1c = 8.5%) and my PCP wants me to take more insulin to get it down."
- · Wears a FreeStyle Libre CGM
- Chous: "What's your mean glucose on the Libre?"
- · Patient: "Huh? What do you you mean?"

90-Day Mean Glucose = 142 mg/dL
Equivalent to a 7.0% HbA1c

Let's look at your labs on MyChart
Hb = 8.4 g/dL (normal 12.3-15.3 g/dL)

This Patient Has ANEMIA, so
HbA1c Results Are Falsely High!

61

63

65

62

### So....Is HbA1c STILL the Cat's Meow?

- HbA1c has been widely regarded for nearly 30 years as reflecting mean blood glucose over the previous 60 days-90 days.
- HbA1c has been regarded as the best predictor of microvascular complications.
- Is this still the case?

Well...sort of



### Some Deficiencies of HbA1c

- Some analyses show that HbA1c compared to OGTT has a sensitivity of < 50% for diabetes Dx.
- HbA1c is NOT an average, but a weighted average (50% of value determined in the preceding 3-5 wks).
- Patients with identical HbA1c values may have widely divergent mean glucose, as determined by professional-CGM devices.

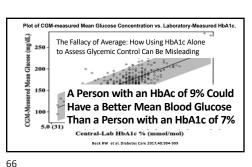
Gen Intern Med. 2014 Feb;29(2):388-94.

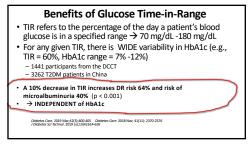
64

Adv Med Sci. 2012;57(2):296-301.

# More deficiencies of A1c

- Iron deficiency renders values inaccurate.
- Hemoglobin variants render values inaccurate.
- Ethnicity/race affect diagnostic sensitivity.
- HbA1c does not reveal glucose variability that has predictive power for DR and other diabetes complications.





67

69

Management Goals for Adults: A1C and TIR

Individualized A1C

Time in Range\*

Most foreign and foreign

An International consensus panel has just recommended that CGM metrics like time-in-range (TIR), time-above-range (TAR), time-below-range (TBR), and glucose coefficient of variation be included in all future diabetes clinical trials.

KW - What Went Wrong?

- 36-year-old with T1DM x 25 years
- Basal-Bolus MDDI therapy (Humalog + Lantus)
- Mild NPDR (a few microaneurysms)
- Excellent glycemic control x 15 years (HbA1c ranging 6.5%-7%)
- A1c has increased x 1 year from 7.2% to 8.5%
- Last HbA1c = 9.1%

70

68

# KW - What Happened?

- Total daily insulin dose has increased from 50 units to 190 units but patient says, "I'm always high."
- Patient swears no change in diet, exercise or adherence to insulin; glucose log shows no pre- or post-prandial patterns.
- (Excellent & famous) endocrinologist is unhappy.
- What Happened?

Questions

"Where do you inject?"

"The left side of my stomach because I'm right-handed and always driving"

"May I take a look at where you inject?"

Injection Site
Lipohypertrophy

71 72

# With Rotation of Injection Sites:

- A1c dropped to 6.4% within 3 months
- Insulin dosage dropped from 190 units/day to 50 units/day

"The patient's optometrist noted injection site lipohypertrophy, recommended site rotation and the glucoses have improved appreciably."



# Patient DG

- 61-year-old with excessive thirst & +3.00 diopter refractive shift
- BMI = 25
- In-office glucose = 515 mg/dl
- How do we know whether this patient has type 1 or type 2 diabetes? Why is that important?

C-peptide: co-secreted with endogenous insulin

73

74

# DG's C-peptide

- 1.0 ng/ml
- Normal range = 0.5 to 2.0
- T1DM mean C-peptide = 0.6 at Dx - Mean at 5 years is < 0.2
- T2DM mean C-peptide = 5.0 at Dx
- Mean C-peptide in LADA = 1.1
- How do we confirm latent auto-immune diabetes of adulthood (late onset T1DM)?

Diabet Med. 2013 Jul:30(7):803-17

**GADA** 

GLUTAMIC ACID DECARBOXYLASE ANTIBODIES

Hallmark Auto-antibody Associated with Auto-immune Diabetes

75

77

76

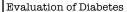
# DG Outcome

- Antibody testing was positive
- 1750 U/ml (normal is < 5.0)
- This patient has autoimmune diabetes (LADA) and has been placed on basal/bolus insulin therapy
- -HbA1c 3 months after initiation = 7.2%

PEARL: 4% - 12% of diagnosed T2DM is T1DM/LADA, and 42% of T1DM is Dx AFTER Age 30.

Characteristics and Prevalence of Latent Autoimmune Diabetes in Adults (LADA). ISRN Pharmacol. 2012;2012:580202 Lancet Diabetes Endocrinol. 2018;6(2):122-129.





Three main components:

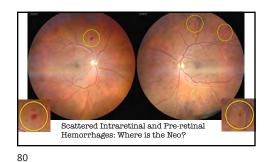
 $\underline{\underline{History}}\!\!: \texttt{Type 2 DM}$  of unknown duration; HTN and left-sided hemiparesis due to stroke

<u>Ocular exam</u>: BCVA 20/25 OD, OS; no NVI/NVA, normal IOP

Ancillary testing

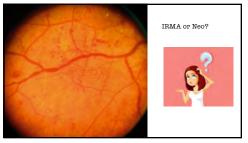
79

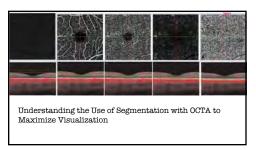
81



OCTA Indicating Neovascular Fronds Beneath the Preretinal Hemorrhages and Adjacent Capillary Non-perfusion

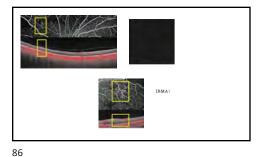
82





83



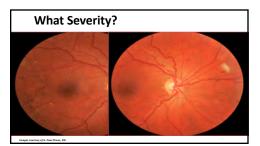


RL - Why Do I Need Treatment?

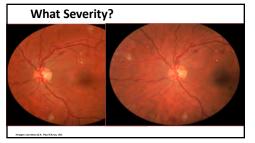
- 33-year-old male with T1DM x 19 years
- Referred by endocrinology

87

- Last eye exam was 5 years ago; BCVA 20/20 in each eye
- Last HbA1C: 7.1%; only tests glucose when he feels bad
- A1c had been > 8.5% "for years" after Dx
- -Basal/bolus insulin (Novolog/Levemir): 150 units/day
- -In-office glucose: 55 mg/dl (OJ given in exam room)
- -Patient has **hypoglycemia unawareness**



88



Severe NPDR OU AI confirms VTDR • Pt declines referral, as he has no symptoms. Reviewed photos and AI Reviewed ETDRS stats Showed example of improvement with anti-VEGF Pt still intransigent

90 89



91

93

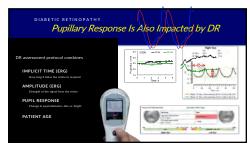
Abnormal ERG in Long-term Diabetes Shows
Delayed Implicit Time & ♥Amplitude

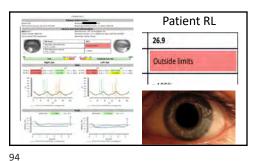
0.00005
0.00005
0.00005
0.00005
0.00005
Time (ms)

Abnormal Flicker ERG ♠Risk of Intervention in DR



92





# Progression From Any Stage of NPDR to PDR and/or DME Over 8 Weeks RetEval DR Score > 26.9 Single-Best Predictor RR = 7.2 vs a DR score < 26.9 for all NPDR stages Relative 75 Risk (Rs) of 75 Risk (Rs) of

# Patient Education You have a very high risk of severe, irreversible vision loss within the next year, based on both the appearance of your retinas and the function of your retinas. Earlier treatment may help prevent this. Let's get a retina consult. Keep your blood glucose levels stable, get a continuous glucose monitoring system to help avoid severe hypoglycemia, and follow-up with me after the retina appointment – are you on board with me?





98

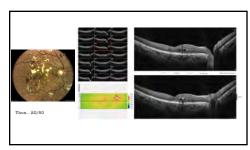




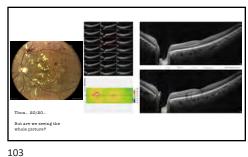
100

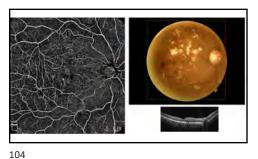
# Evaluation of Diabetes

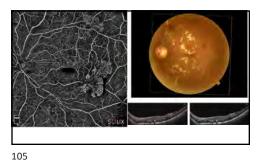
- Three main components:
- History: Type 2 DM x 10 years; HbA1C unknown; FBS 273, Glipizide, Metformin H/O DME OD (S/P laser 3 times) HTN, Hypercholesterolemia (treated)
- -Ocular exam: No NVI, normal IOP
- -Ancillary testing



101 102









# Patient GM – At Risk

- 58-year-old male with recently Dx pre-diabetes
- A1c = 6.3%; fasting glucose = 118 mg/l
- "My PCP recommended more exercise and weight loss."
- Meds include atenolol, HCTZ, d/c lisinopril ("made me cough"), ranitidine, rosuvistatin
- BMI = 36 kg/m<sup>2</sup>; waist circumference = 42"
- Smokes 1 pack/day; low macular pigment
- Eats 1 serving of fruits/vegetables/day
- Mom developed T2DM in her 70s



107 108

# 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.



110

◆Has prediabetes ◆Abdominally obese ◆Smoker

◆Male > 50-years-old ◆Thiazide diuretic◆ Potent statin

◆Little plant food ◆1st order relative had T2DM ◆ Low MPOD

WHAT ARE GM'S RISK FACTORS FOR T2DM?

**Prevention Beats Cure** 

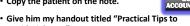
# My Plan For GM

Send a note to his PCP.

109

111

· Copy the patient on the note.



- Avoid Diabetes."

  Give him a card for a local smoking-cessation program.
- Have GM write down my recommendations, and pick 1 or 2 things he wants to fix before his next eye exam – circle those and enter in record.

Why Fast?

- T2DM is a PROGRESSIVE Disease
- Medical-Nutrition Therapy (MNT), including drugs/dieting/exercise RARELY results in disease remission.
- Remission DOES occur after bariatric surgery or with fasting + reduced carbohydrate diet.

Diabetes Care. 2016 Jun;39(6):893-901

Indian J Endocrinol Metab. 2012 Jul;16(4):552-7.

112

# **GM Outcome**

- 55 lb weight loss using alternate daily fasting
- Walking 10K steps each day
- Last A1c = 5.0%
- Taken off HCTZ and now using low dose ARB (valsartan)
- Discontinued smoking
- MPOD increased from 0.28 to 0.60 on DVS
- GM says "this was the best thing I've ever done."



 "Why didn't any of my other doctors ever recommend this before?"

113 114

# My Favorite Elliott Joslin Quote

 "Diabetologic Education is not a part of the treatment of diabetes, it is the treatment"

Joslin EP (1998) Diabetic Manual for the Doctor and patient 1918. Joslin Diabetes Cente

### The OD as Diabetes Educator

- We have the opportunity to help fill this gap.
- Multidisciplinary diabetes education provided by an optometrist, psychologist, and endocrinologist resulted in significantly better patient knowledge and satisfaction compared to usual care.

Wagner H, Pizzimenti JJ, Daniel K, Pandya N, Hardigan PC. Eye on Diabetes. *The Diabetes Educator*. 2008;34(1):84-89

115

116

**Chous Predictions** 



Predictions for Diabetes Care by Optometrists

- Optometrists will routinely DIAGNOSE diabetes and prediabetes based on ocular findings in tandem with blood glucose metrics that can be cheaply and efficiently delivered in optometric practice.
- Optometrists in the near future will be viewed as crucially important in diabetes and DR <u>prevention</u> as diabetes educators par excellence.
- Optometrists will routinely treat DR with highly effective topical, oral, and light-based therapies.

117

118

**Rodman Predictions** 



Predictions for Diabetes Care by Optometrists

- Optometrists are frontline health care providers and, thus, play a critical role in the management of patients with diabetes.
- It is no longer solely the responsibility of the PCP or dietician to discuss the importance of lifestyle intervention.
- We must stay current on the use of multimodal imaging in the diagnosis and management of diabetic retinopathy as these modalities may highlight abnormalities before they manifest clinically, thus modifying the course of the disease.

# THANK YOU!

Dr. Julie Rodman rjulie@nova.edu Dr Paul Chous

dr\_chous@diabeticeyes.com