

# **Intravitreal Targeted Treatment of Diabetic Retinal Disease: Diabetic Macular Edema**

*Trexler Topping, M.D., Chair*

*American Academy of Ophthalmology Health Policy Committee*

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*Wilmer Institute Johns Hopkins University*

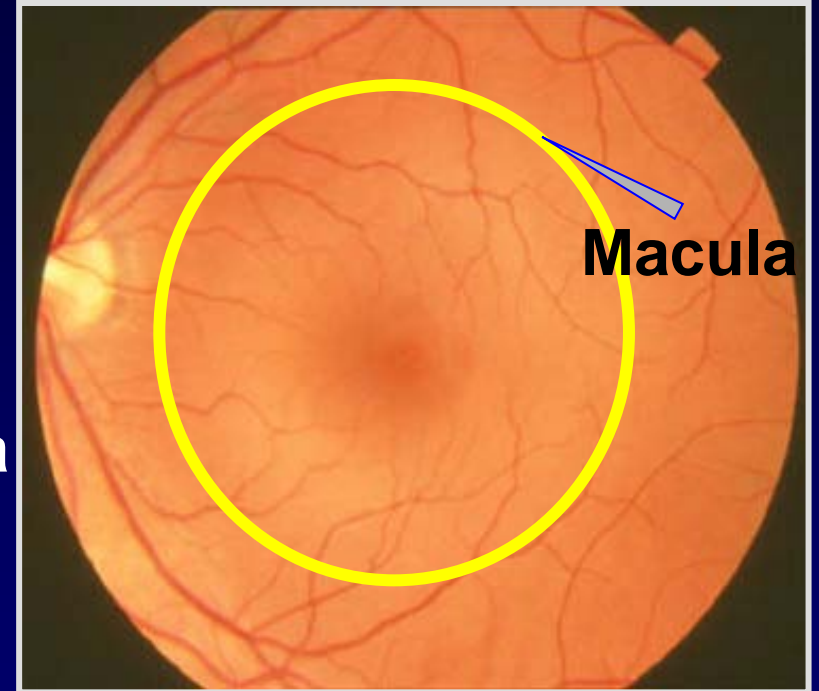
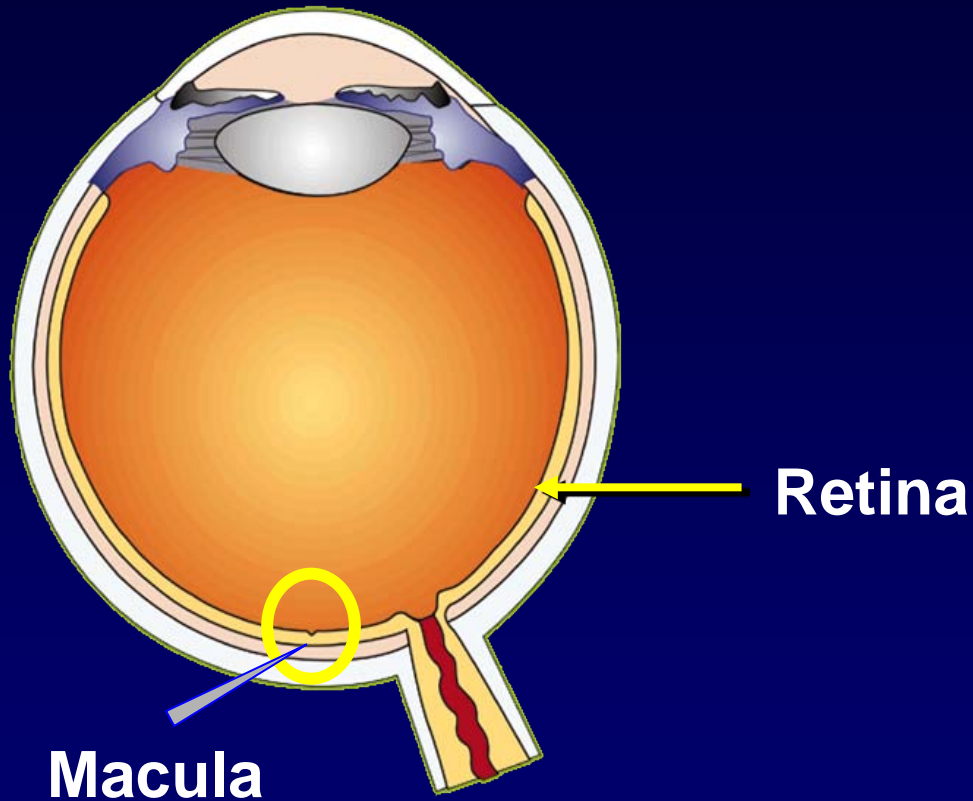
*John Thompson, M.D., President*

*American Society of Retina Specialists*

# **Leading Causes of Blindness in People Over 65 in U.S.**

- **Choroidal neovascularization  
("wet" form) of age-related macular  
degeneration**
- **Cataract**
- **Diabetic retinopathy**
- **Glaucoma**

# Macula: Center of the Retina



# A Healthy Macula Is Critical to Maintaining Normal Vision

- Vision function is mainly assessed by measuring visual acuity

Legally Blind

N C V K D

20/200

C Z S H N

O N V S R

K D N R O

15 letter loss from  
20/40, CANNOT  
Drive or Read

Z K C S V

20/80

D V O H C

O H V C K

H Z C K O

20/40

N C K H D

S Z R D N

20/20

15 letter loss =  
3 line loss, CAN  
Drive + Read

N C V K D  
 C Z S H N  
 O N V S R  
 K D N R O  
 Z K C S V  
 D V O H C  
 O H V C K  
 H Z C K O  
 N C K H D  
 Z H C S R  
 S Z R D N  
 H C D R O  
 R D O S N

=

or



Any loss of 2 or more lines when starting at 20/80 or greater, or 3 or more lines when starting at 20/100 or worse, equates to substantial impact on quality of life.

Marley was dead: to begin with. There is no doubt whatever about that. The register of his burial was signed by the clergyman, the clerk, the undertaker, and the parish council. It is all there, and Scrooge signed it. And Scrooge's name was good upon 'Change, for it was a man of business.

Old Marley was as dead as a door-nail.

Mind! I don't mean to say that I know, of my own knowledge, what it is particularly dead about a door-nail. I might have been inclined, myself, to regard a coffin-nail as the deadest piece of iron mongery in the trade. But the wisdom of our country is in the simile; and my unhallowed hands shall not disturb it, or the Country's done for. You will therefore permit me to repeat emphatically, that Marley was as dead as a door-nail.

# Near Activities



Reading ordinary print in newspapers



Work or hobbies that require seeing things up close, eg, sewing, cooking



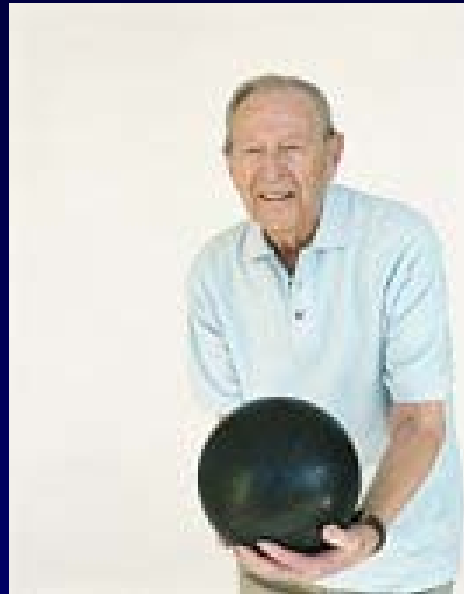
Finding things on a crowded shelf



# Distance Activities



**Going down steps, stairs,  
or curbs in dim light or at  
night**

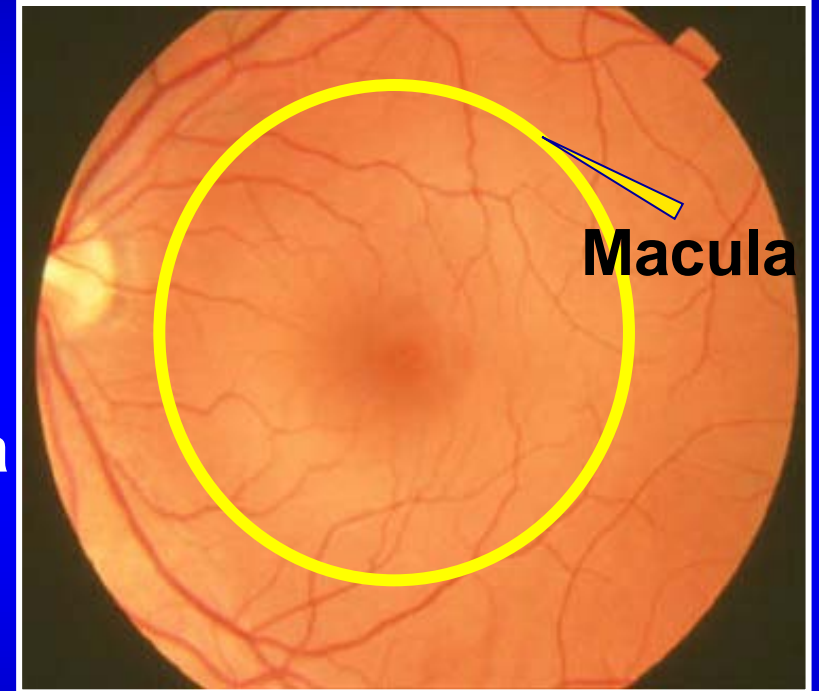
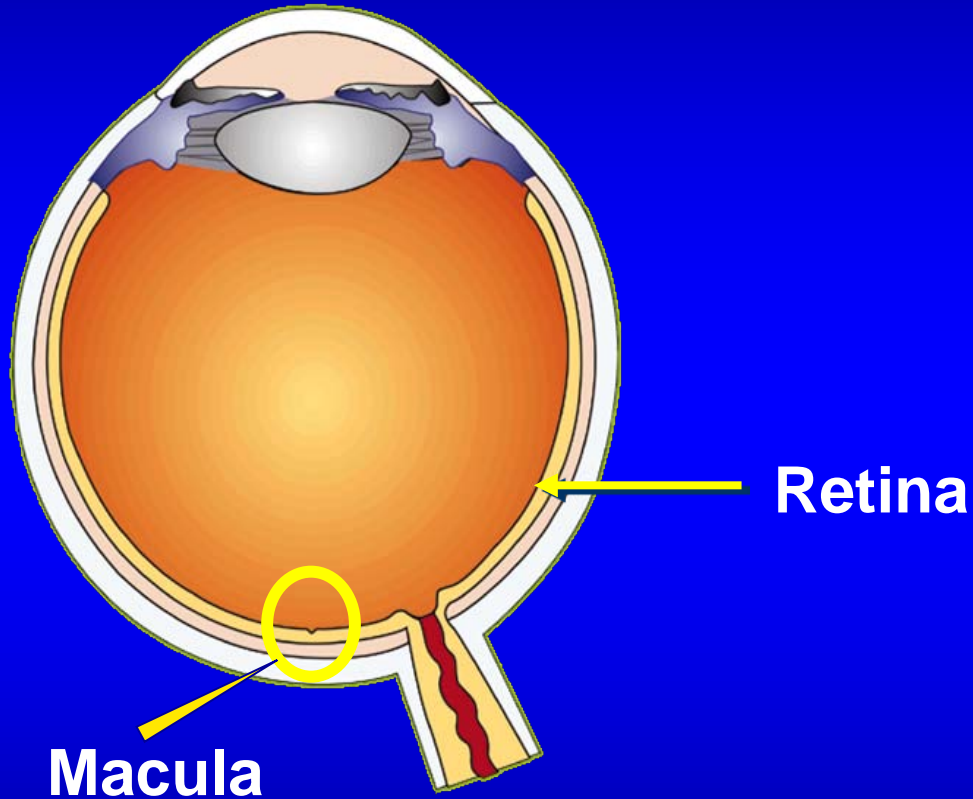


**Going out to  
movies, plays,  
sports events**



**Seeing and enjoying  
programs on TV**

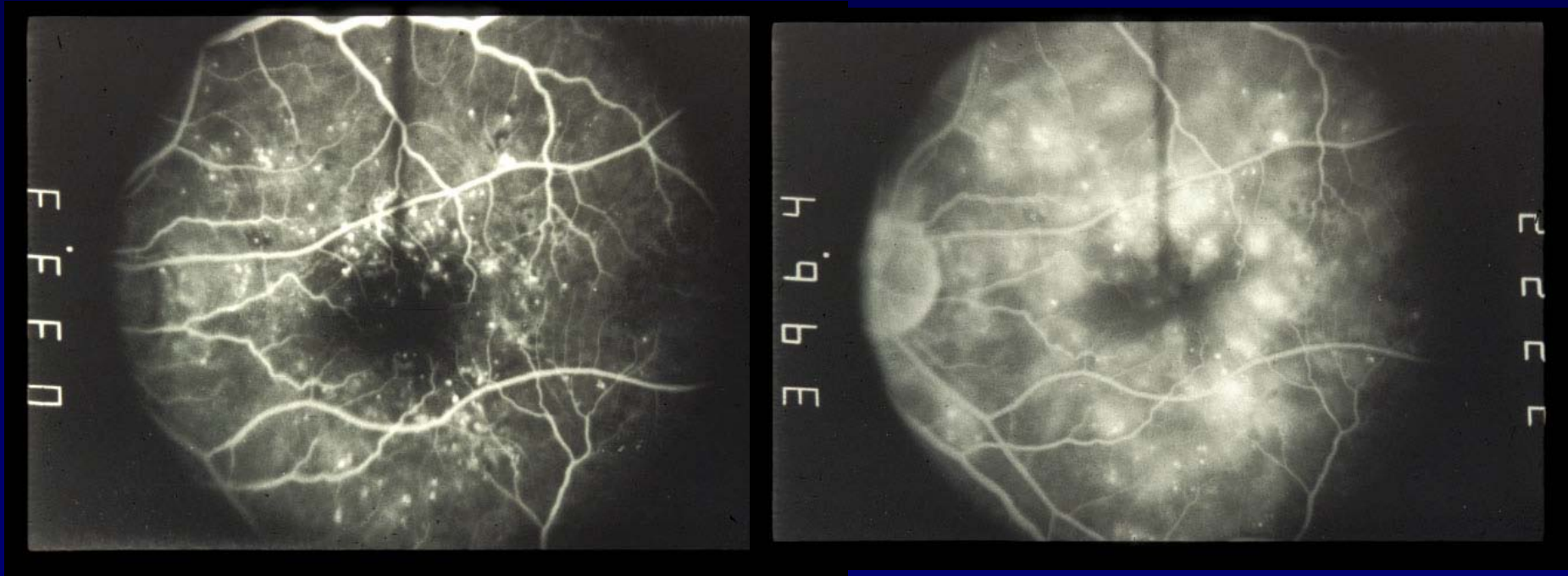
# Macula: Center of the Retina





# Consequences of Diabetes on Retina Capillaries: Leakage Leading to Macular Edema

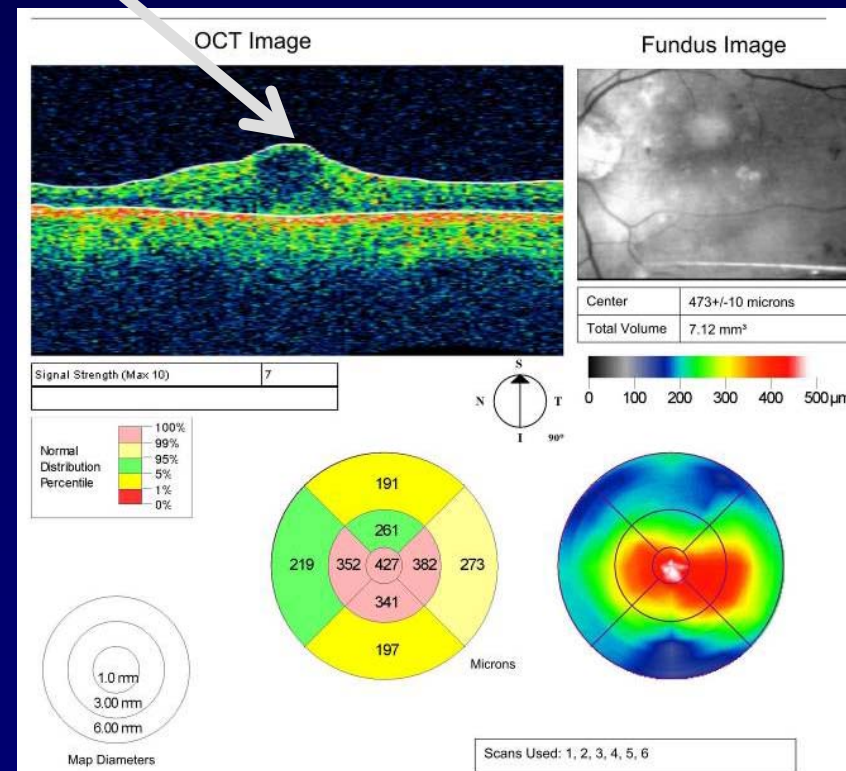
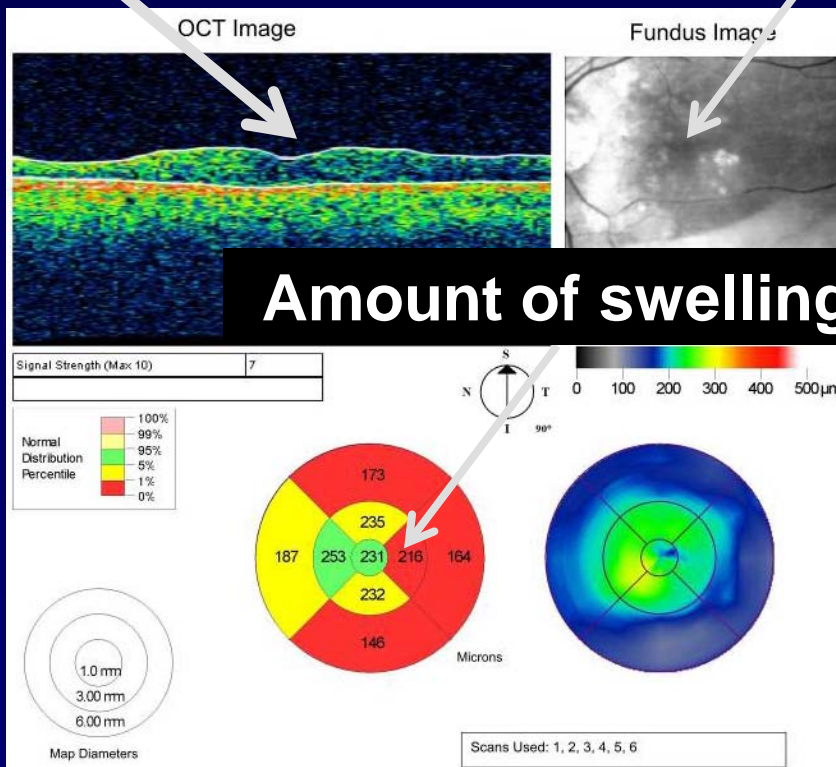
*Hyperpermeability easily visualized with fluorescein angiography*



# Consequences of Leakage of Capillaries: Swelling of Retina = Macular Edema

*Retinal Thickening Readily Imaged  
And Quantified by Ocular Coherence Tomography (OCT)*

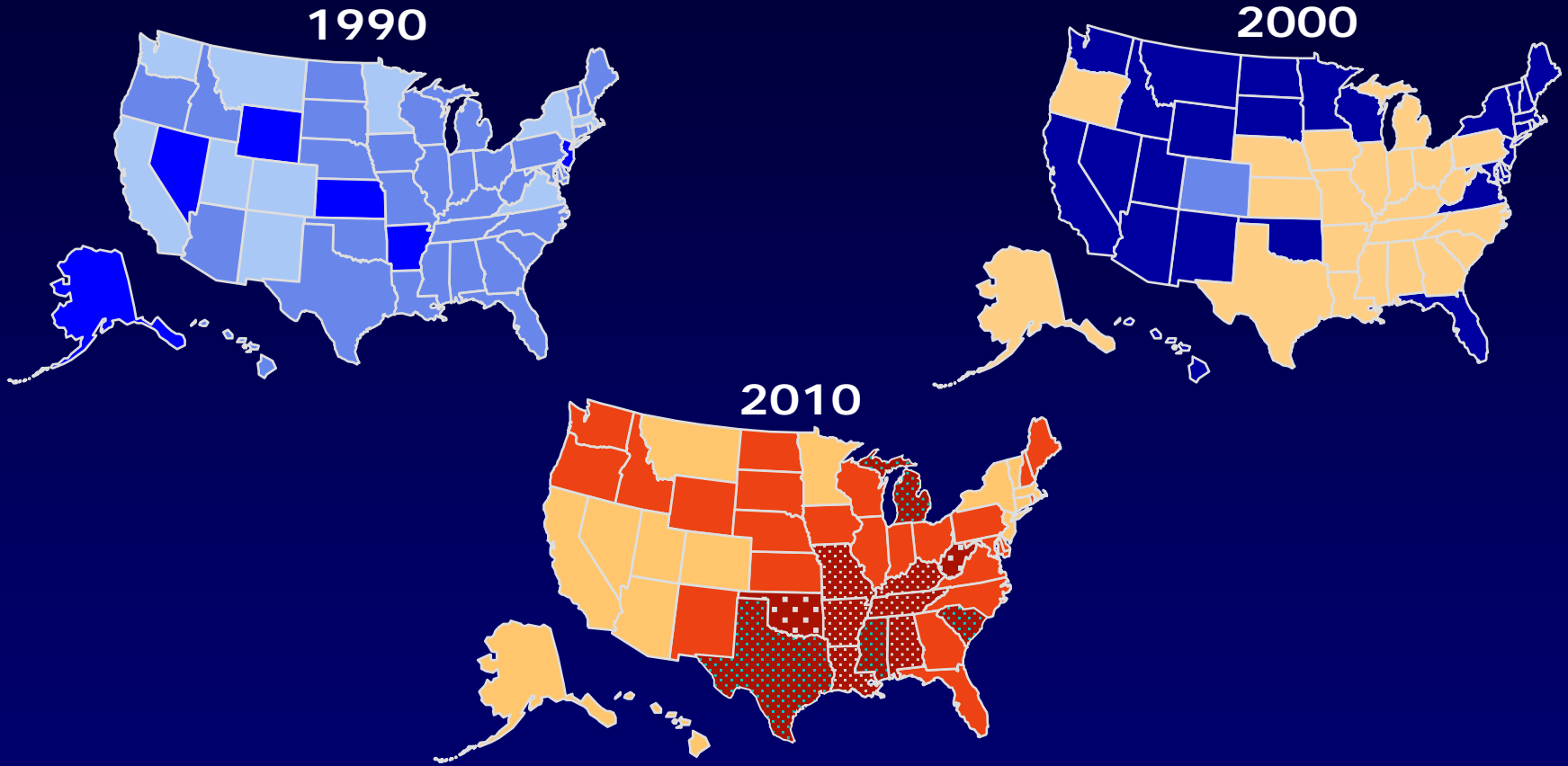
No retina swelling      Retina image      Retina swelling










# Obesity Trends\* Among U.S. Adults

## BRFSS, 1990, 2000, 2010

(\*BMI  $\geq 30$ , or about 30 lbs. overweight for 5'4" person)

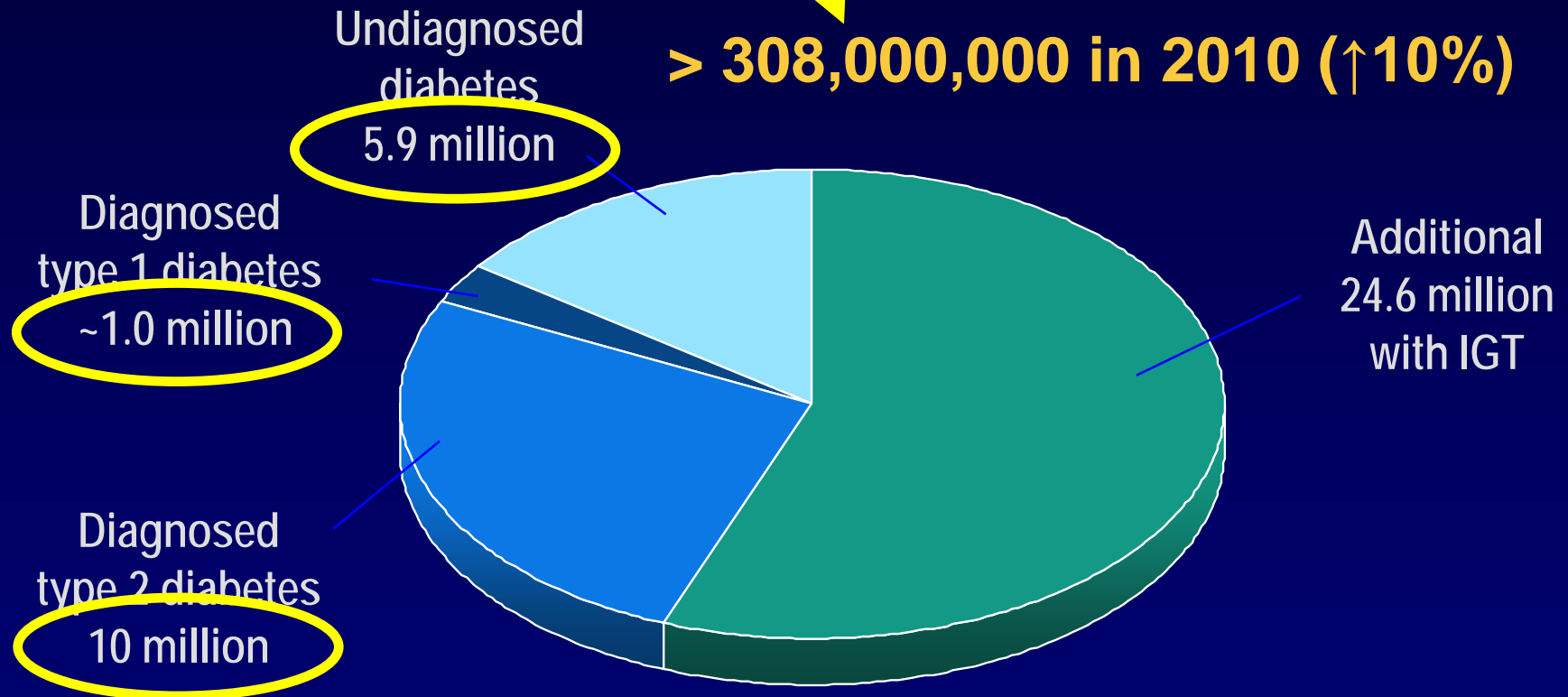


 No Data
  <10%
  10%–14%
  15%–19%
  20%–24%
  25%–29%
  ≥30%

# Prevalence of Impaired Sugar Tolerance in the United States

US Population: 275 Million in 2000

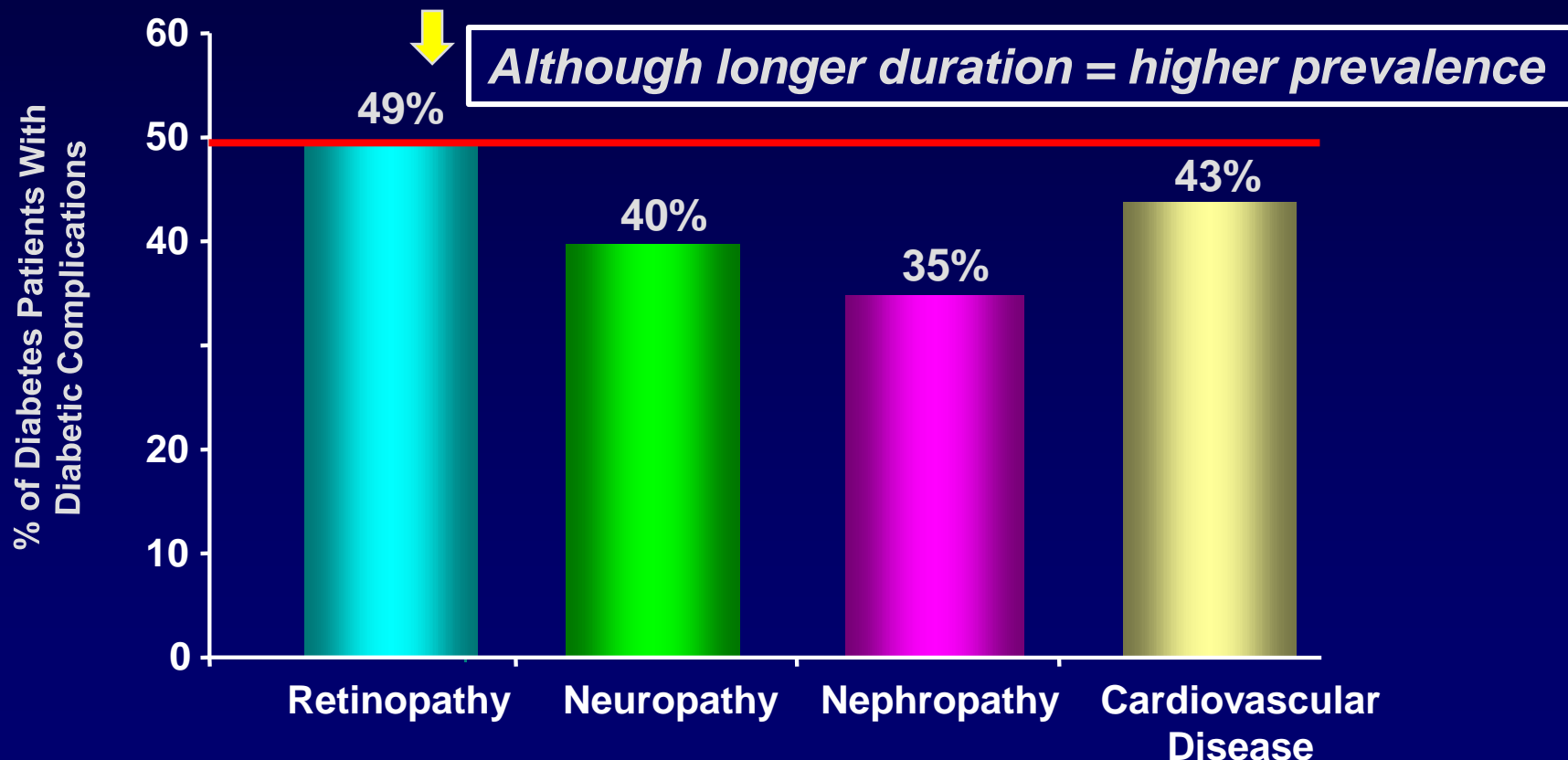
> 308,000,000 in 2010 (↑10%)



# Prevalence of Diabetic Complications

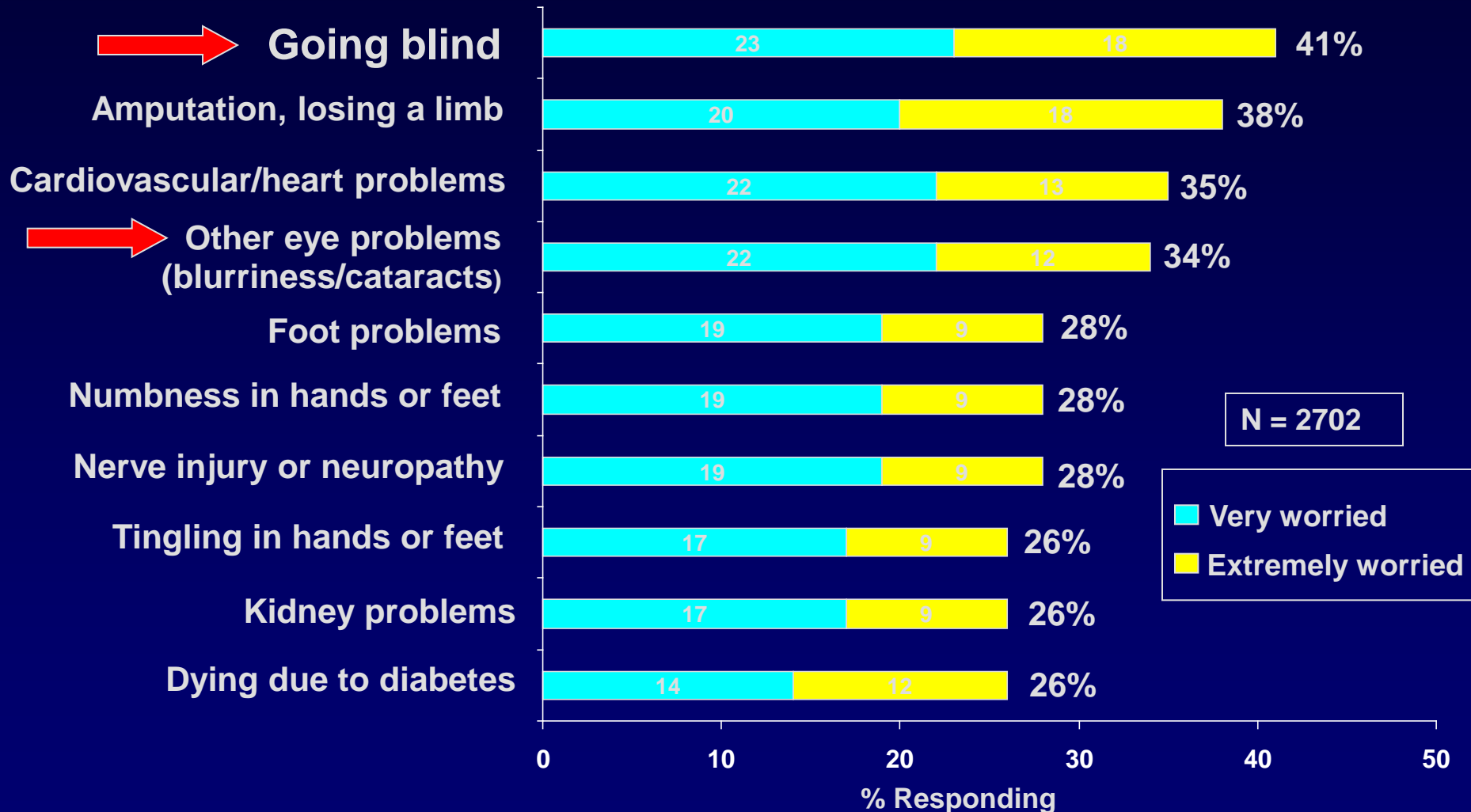
8,538,906 Persons in the US with Diabetic Retinopathy

2.9% of Entire US Population has Diabetic Retinopathy



# Two of Top 4 Concerns of Patients With Diabetes Are Vision-Related

## Top 10 concerns of patients with diabetes

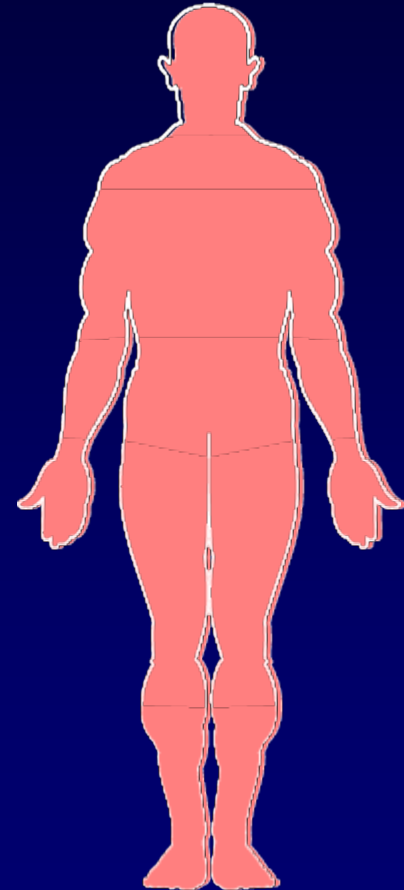


\*An international survey based on experiences with diabetic microvascular complications, (2,702 patients with both type 1 and 2 diabetes), by Consumer Health Sciences and IPSOS for the Lions Club International Foundation, in association with and with the support of Eli Lilly and Company, 2002.



# Visually-Impaired Patients Willing to Trade Years of Remaining Life to Regain Perfect Vision

Visual Acuity Range	Remaining Life Willing to Trade for Perfect Vision (%)
● 20/20-20/25 <sup>1</sup> N = 15	15
● 20/30-100 <sup>1</sup> N = 69	22
● 20/200-400 (legally blind) <sup>1</sup> N = 7	36
● Counting fingers-LP <sup>2</sup> N = 17	53
● No LP <sup>2</sup> N = 15	74



LP = light perception.

1. Adapted from Brown MM, et al. *Am J Ophthalmol*. 1999;128:324-330.

2. Adapted from Brown MM, et al. *Br J Ophthalmol*. 2001;85:327-331.

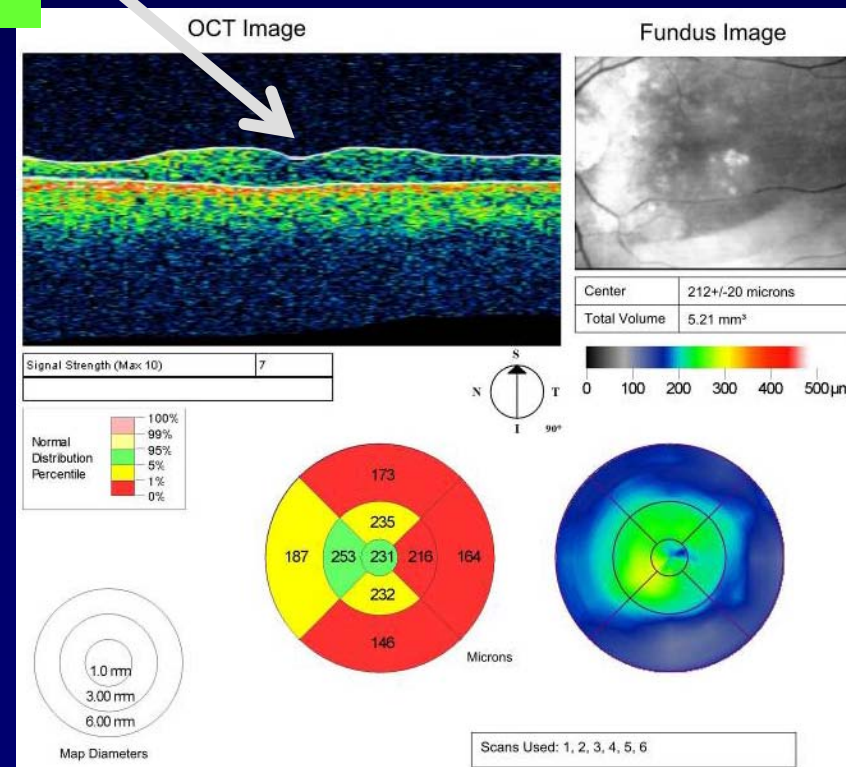
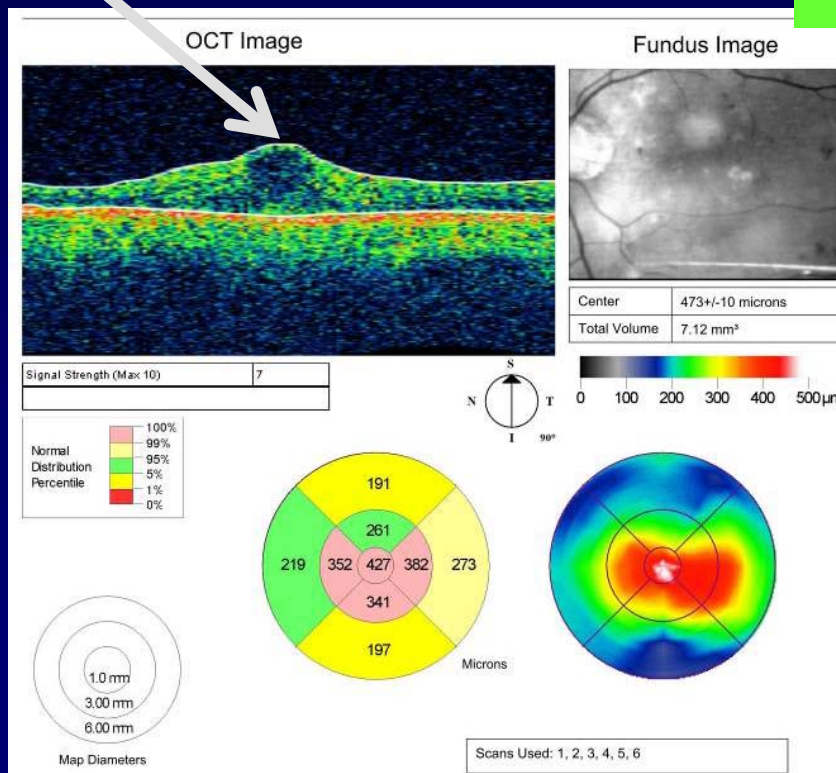
# Can We Treat Diabetic Macular Edema with Something Other than Laser?

*Retinal Thickening Readily Imaged  
And Quantified by Ocular Coherence Tomography (OCT)*

Retina swelling

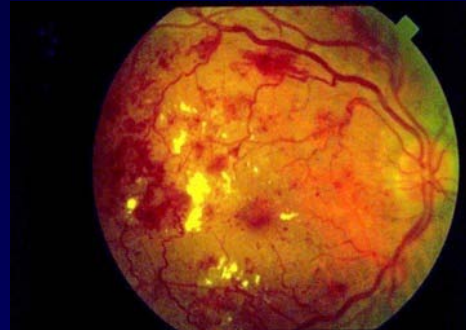
Rx

Retina swelling resolves



# The Diabetic Retinopathy Clinical Research Network

*Dedicated to multicenter clinical research of diabetic retinopathy, macular edema and associated*



Supported through a cooperative agreement from the National Eye Institute and the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services  
EY14231, EY14229, EY018817



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES  
National Institutes of Health  
National Eye Institute



# **DRCR.net Overview**

## **➤ Objective:**

- **The development of a collaborative network to facilitate multicenter clinical research on diabetic retinopathy, diabetic macular edema and associated conditions.**

## **➤ Funding (current award 2009 to 2013):**

- **National Institutes of Health**
- **Johns Hopkins University (Baltimore) – Network Chair (Neil Bressler)**
- **JAEB Center (Tampa) – Coordinating Center**

# **DRCR Network Recognition by Congress**

- **Recognized by the U.S. House of Representatives in House Resolution 366 on June 16, 2009, and the U.S. Senate in Senate Resolution 209 on July 7, 2009, and by the Senate Appropriations Committee in 2010 and 2011 for the contribution of its trials towards reducing blindness and disability due to diabetes**

# Senate Appropriations Bill - 2010

Page 108:  
Recommending \$723,220,000  
(2.34% increase)

108

cluding interstitial cystitis, fibromyalgia, temporomandibular joint and muscles disorders, irritable bowel syndrome, endometriosis, headache and chronic fatigue syndrome. The Committee strongly urges the creation of a trans-NIH research initiative that will support studies aimed at identifying common etiological pathways among these disorders, with the goal of developing potential therapeutic targets.

#### NATIONAL EYE INSTITUTE

Appropriations, 2010 .....	\$706,650,000
Budget estimate, 2011 .....	724,560,000
Committee recommendation .....	723,220,000

The Committee recommendation includes \$723,220,000 for the National Eye Institute (NEI). The budget request for fiscal year 2011 is \$724,560,000, and the comparable level for fiscal year 2010 is \$706,650,000.

**Cataracts.**—The Committee is encouraged by the NEI's collaboration with NASA in developing a new diagnostic technology that identifies those at risk for cataract development before it is clinically detectable.

**Improving Clinical Practice.**—The Committee recognizes the NEI's leadership in conducting several comparative effectiveness clinical trials to improve ophthalmic care, including the Diabetic Retinopathy Clinical Research Network's comparison of drug therapies as an alternative to laser treatment for diabetic macular edema and proliferative diabetic retinopathy. The Committee is also encouraged by the use of new analytic techniques to evaluate published data from clinical trials for therapies for Primary Open Angle Glaucoma that enable researchers to compare the merits of multiple interventions without conducting additional clinical trials, which will also substantially impact clinical practice.

**Leber Congenital Amaurosis.**—The Committee is encouraged by recent reports of initial success in treating Leber congenital amaurosis with gene therapy and is pleased that the NEI will evaluate gene transfer in younger patients with less severe disease. The Committee urges the Institute to pursue studies of this promising treatment on an expedited basis in other genetically inherited, retinal degenerative diseases. The Committee requests an update on such efforts in the fiscal year 2012 congressional budget justification.

**Trachoma.**—The Committee is pleased that a recent NEI clinical trial of a multi-dose treatment course of the antibiotic azithromycin in severely affected communities led to the eradication of trachoma, the leading cause of blindness in the developing world.

**Training Program.**—The Committee is pleased that the NEI is committed to developing the next generation of vision researchers by expanding its institutional training grant program with a program in ocular statistical genetics to provide the vision research community with expertise in mathematics, modeling, and computation.

**Improving Clinical Practice. —**  
The Committee recognizes the NEI's leadership in conducting several comparative effectiveness clinical trials to improve ophthalmic care, **including the Diabetic Retinopathy Clinical Research Network 's comparison of drug therapies** as an alternative to laser treatment for diabetic macular edema and proliferative diabetic retinopathy.

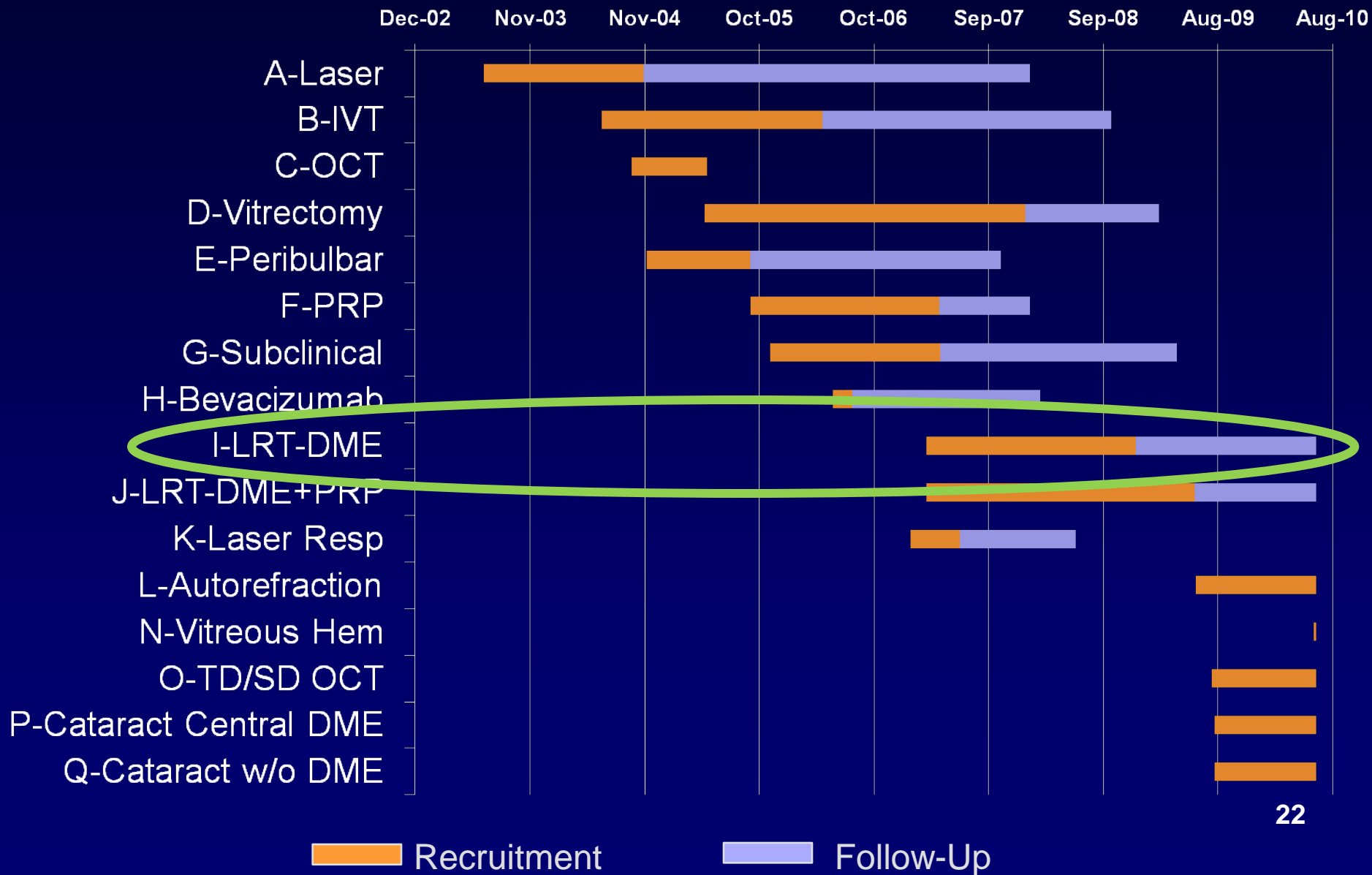


# Organization: Clinical Sites of the Network

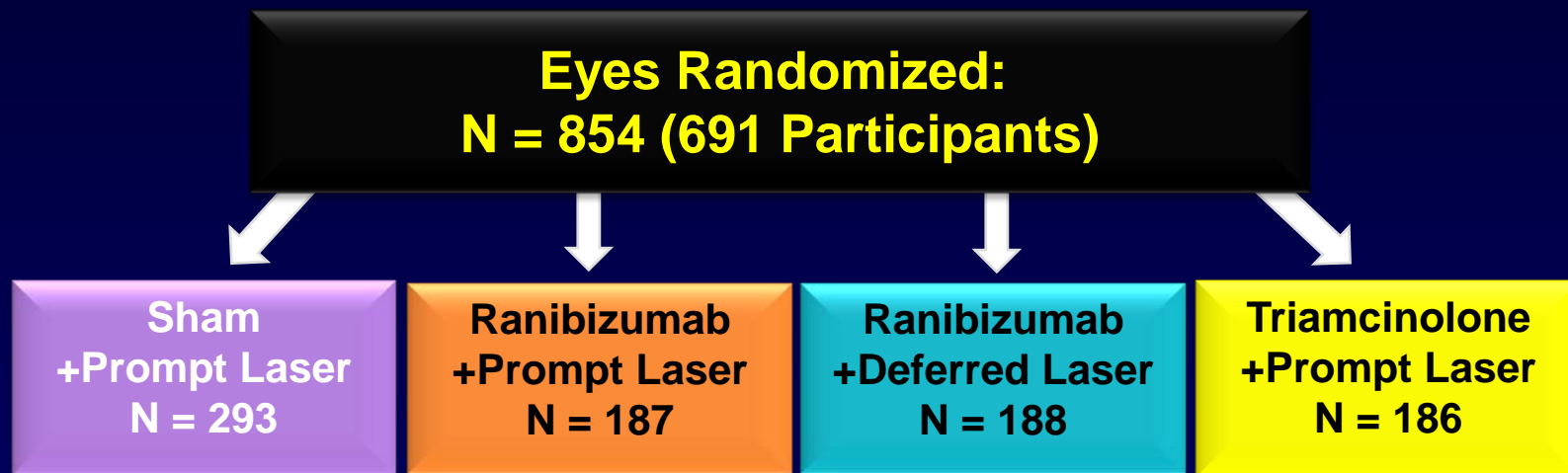
- **DRCR Network Participation (as of August 2011)**
  - 249 sites submitted application for Network
  - **868 total Investigators; 2666 additional personnel**
- **Current Participation**
  - **111 active sites; 10 pending sites**
    - 73 community based sites
  - 325 Investigators
  - 543 additional personnel
  - 38 States & 4 countries



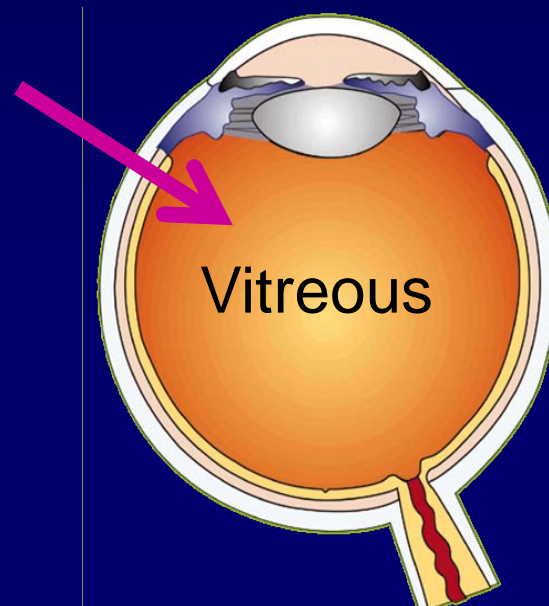
# Protocols through 2011



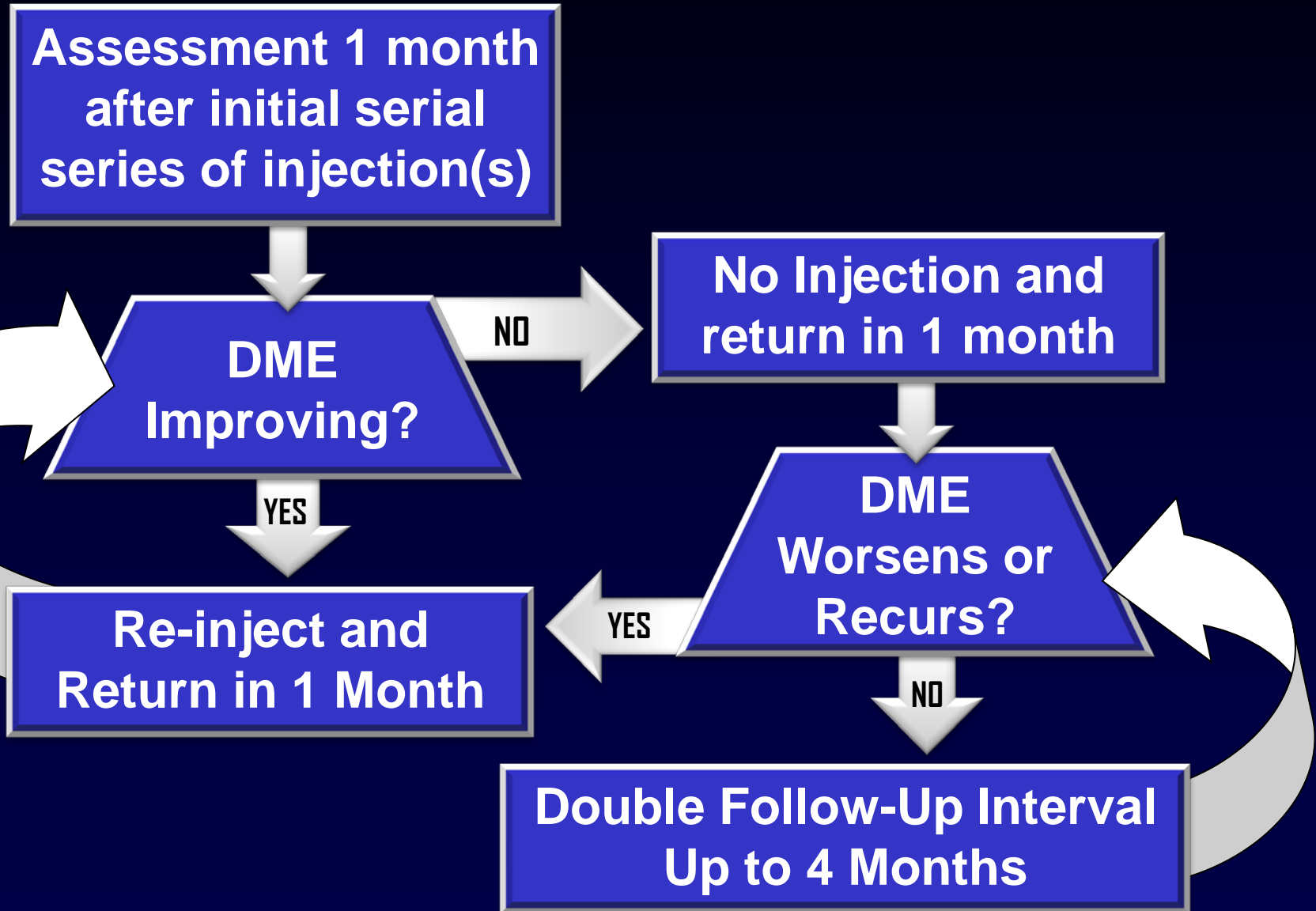
# Study Enrollment



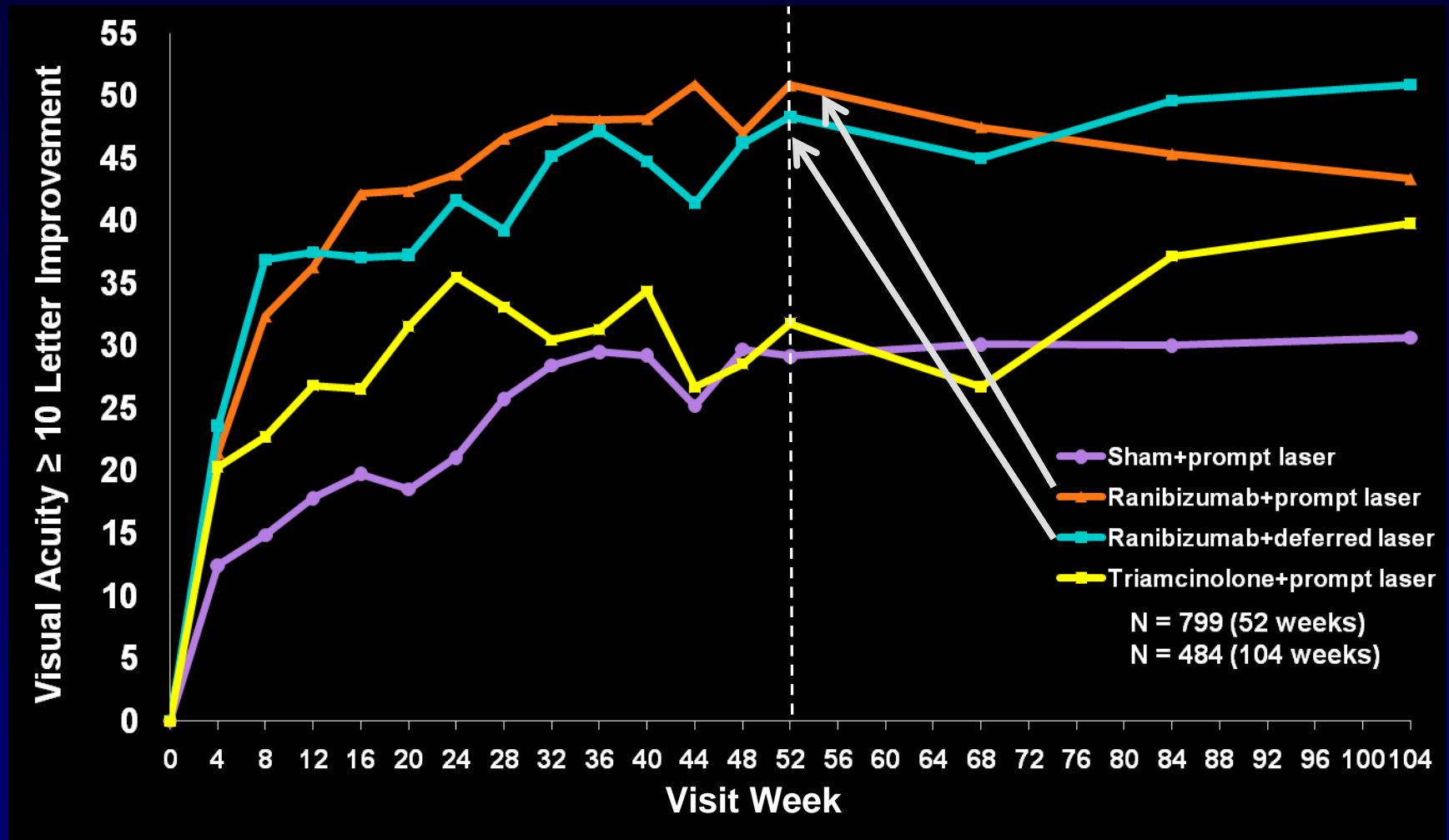
**All medications require  
INTRAVITREAL injection**



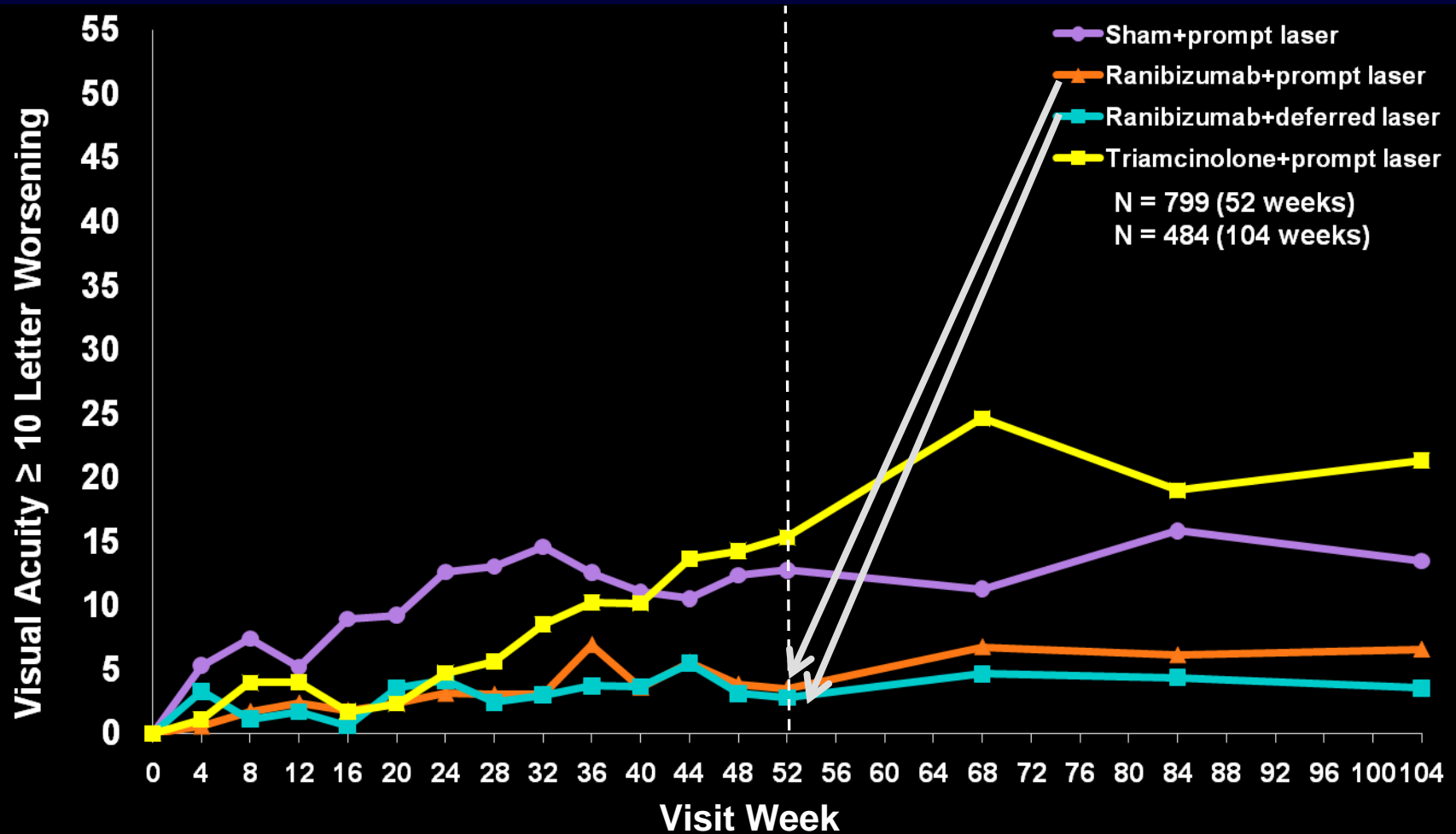
# **SIMPLIFIED** Retreatment and Follow-up of Center-Involved DME with Anti-VEGF



# Substantial Improvement in Vision at Follow-up Visits



# Substantial Loss of Vision at Follow-up Visits





# **Injectations Prior to 2-year Visit**

**(Restricted to eyes that completed 2-year visit)**

	<b>Ranibizumab + Prompt Laser N=136</b>	<b>Ranibizumab + Deferred Laser N=139</b>
<b>Maximal possible # of injections prior to 2- year visit</b>	<b>26</b>	<b>26</b>
<b>Median # of injections from baseline through week 24</b>	<b>6</b>	<b>6</b>
<b>Median # of injections from week 24 through week 48</b>	<b>3</b>	<b>3</b>
<b>Median # of injections from 1-year to (prior to) 2- year visit</b>	<b>2</b>	<b>3</b>

# Focal/Grid Laser Prior to 2 Years \*

	<b>Ranibizumab + Prompt Laser N=136</b>	<b>Ranibizumab + Deferred Laser N=139</b>
<b>Maximal possible number of focal/grid laser treatments prior to 2-year visit</b>	<b>8</b>	<b>6</b>
<b>Median number of focal/grid laser treatments from baseline to (prior to) 1-year visit</b>	<b>2</b>	<b>0</b>
<b>% of eyes that received focal/grid laser treatments from 1-year to (prior to) 2-year visit</b>	<b>40%</b>	<b>29%</b>

\* Restrict to eyes that completed 2 year visit

# Progression/Regression in Diabetic Retinopathy at 1 Year by Baseline Severity

	Sham +Prompt Laser	Ranibizumab +Prompt Laser or Deferred Laser	Triamcinolone +Prompt Laser
Change from baseline to 1-year visit*			
Baseline Severity: Moderately Severe NPDR or Better	N = 150	N = 182	N = 80
Improved by $\geq 2$ levels	4%	25%	25%
Worsened by $\geq 2$ levels	7%	3%	3%
<i>P</i> value for comparison with Sham		<i>P</i> = 0.08	<i>P</i> = 0.17

\*Photos were missing or ungradeable for 61 eyes in the sham+prompt laser group, 72 eyes in the ranibizumab groups, and 33 eyes in the triamcinolone+prompt laser group

# Progression/Regression in Diabetic Retinopathy at 1 Year by Baseline Severity

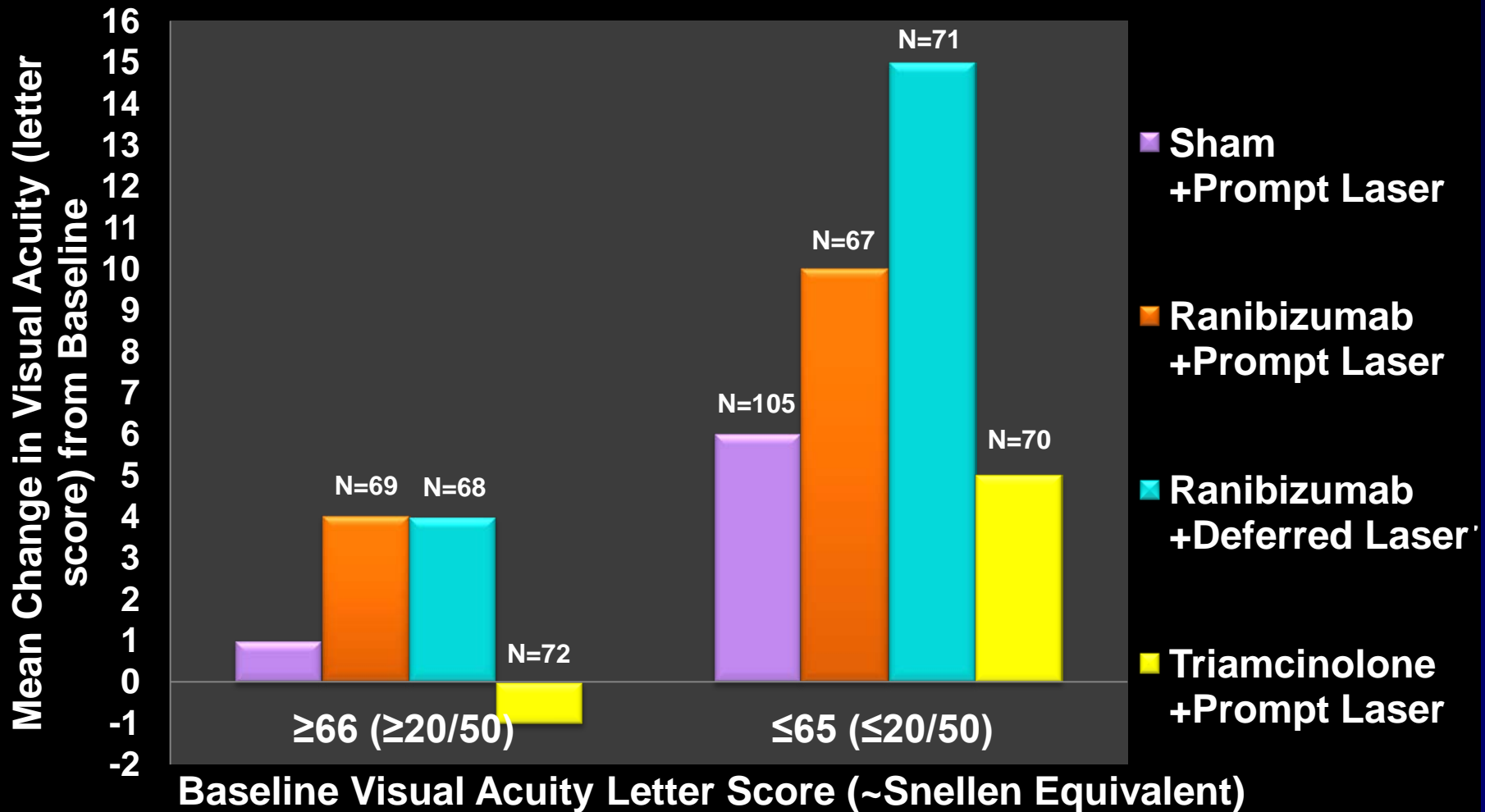
Change from baseline to 1-year visit*	Sham +Prompt Laser	Ranibizumab +Prompt Laser or Deferred Laser	Triamcinolone +Prompt Laser
<b>Baseline Severity: Severe NPDR or worse</b>	<b>N = 83</b>	<b>N = 121</b>	<b>N = 70</b>
<b>Improved by <math>\geq 2</math> levels</b>	<b>19%</b>	<b>28%</b>	<b>13%</b>
<b>Worsened by <math>\geq 2</math> levels</b>	<b>8%</b>	<b>1%</b>	<b>3%</b>
<b><i>P</i> value for comparison with Sham</b>		<b><i>P</i> = 0.03</b>	<b><i>P</i> = 0.17</b>

\*Photos were missing or ungradeable for 61 eyes in the sham+prompt laser group, 72 eyes in the ranibizumab groups, and 33 eyes in the triamcinolone+prompt laser group

# Retinopathy Progression During 1 Year of Follow-up

	<b>Sham N = 293</b>	<b>Ranibizumab N = 375</b>	<b>Triamcinolone N = 186</b>
<b>Reported vitreous hemorrhage OR received PRP</b>	<b>8%</b>	<b>3%</b>	<b>3%</b>
<b><i>P</i> Value for comparison with sham</b>	<b>--</b>	<b>0.002</b>	<b>0.02</b>

# Change in Visual Acuity at 2 Year Stratified by Baseline Visual Acuity





# BOLT study (42B, 38L): mean 5.6 letter gain; 31% 2-line gain, 12% 3-line gain; atypical laser results

Table 5. Efficacy Outcome Measures in the Two Treatment Groups

(unmasked)	Bevacizumab (ivB) Group	Laser (MLT) Group	P Value*
Baseline mean ETDRS BCVA	55.7±9.7 (range 34–69) (n = 42)	54.6±8.6 (range 36–68) (n = 38)	
12-mo mean ETDRS BCVA	61.3±10.4 (range 34–79) (n = 42)	50.0±16.6 (range 8–76) (n = 38)	0.0006
Median and [IQR] of change in ETDRS BCVA	8 [1–10] (n = 42)	−0.5 [−15 to 5] (n = 38)	0.0002
% of patients gaining ≥15 ETDRS letters	11.9 (5/42)	5.3 (2/38)	0.43
% of patients gaining ≥10 ETDRS letters	31.0 (13/42)	7.9 (3/38)	0.01
% of patients losing <15 ETDRS letters	97.6 (41/42)	73.7 (28/38)	0.002
% of patients losing ≥30 ETDRS letters	0 (0/42)	5.3 (2/38)	0.22
Baseline mean CMT (μm)	507±145 (range 281–900)	481±121 (range 279–844)	
12-mo mean CMT (μm)	378±134 (range 167–699)	413±135 (range 170–708)	
Mean change in CMT from baseline (μm)	−130±122 (range −475 to 92)	−68±171 (range −482 to 216)	0.06
Median and [IQR] of No. treatments	* 9 injections [8–9]	* 3 macular lasers [2–4]	

5.6 letters

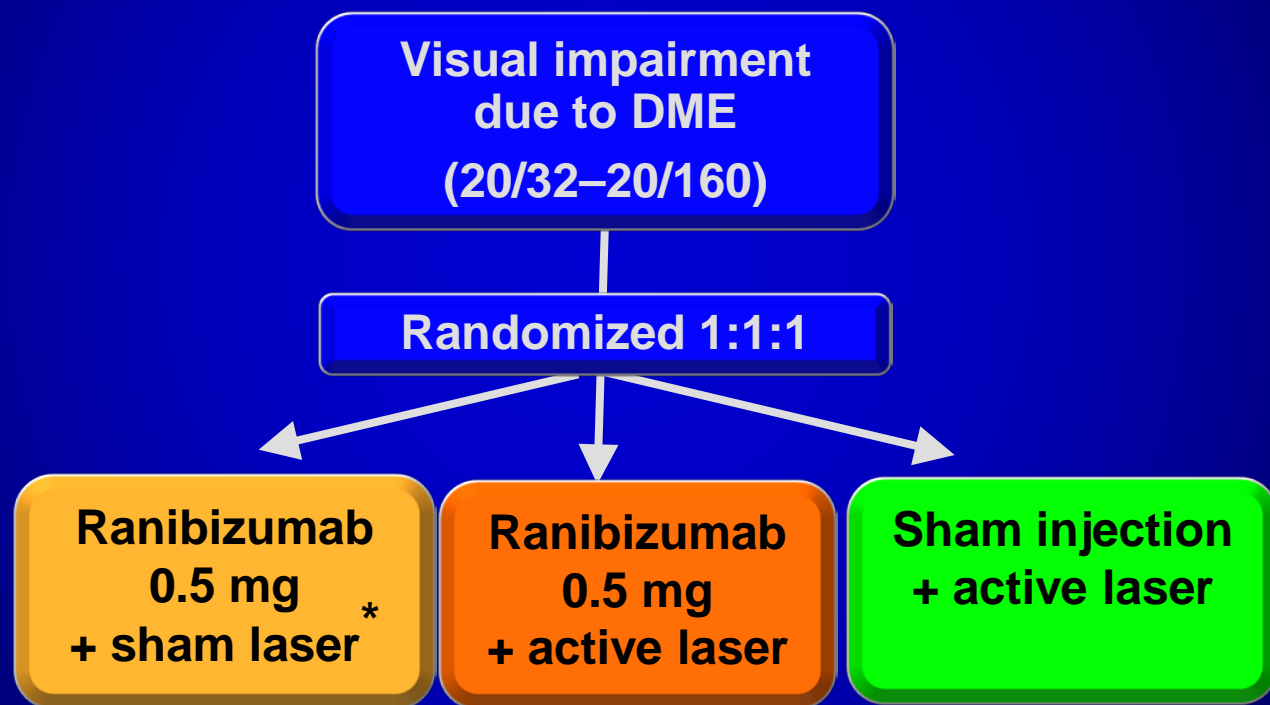
BCVA = best-corrected visual acuity; CMT = central macular thickness; ETDRS = Early Treatment of Diabetic Retinopathy Study; IQR = interquartile range; ivB = intravitreal bevacizumab; MLT = macular laser therapy.

\*Intention-to-treat analysis based on the last-observation-carried-forward method; (2 laser arm subjects did not complete 12 months of follow-up and were last reviewed at the 32-week time point).

# RESTORE Study:

## *Provides Complementary Evidence*

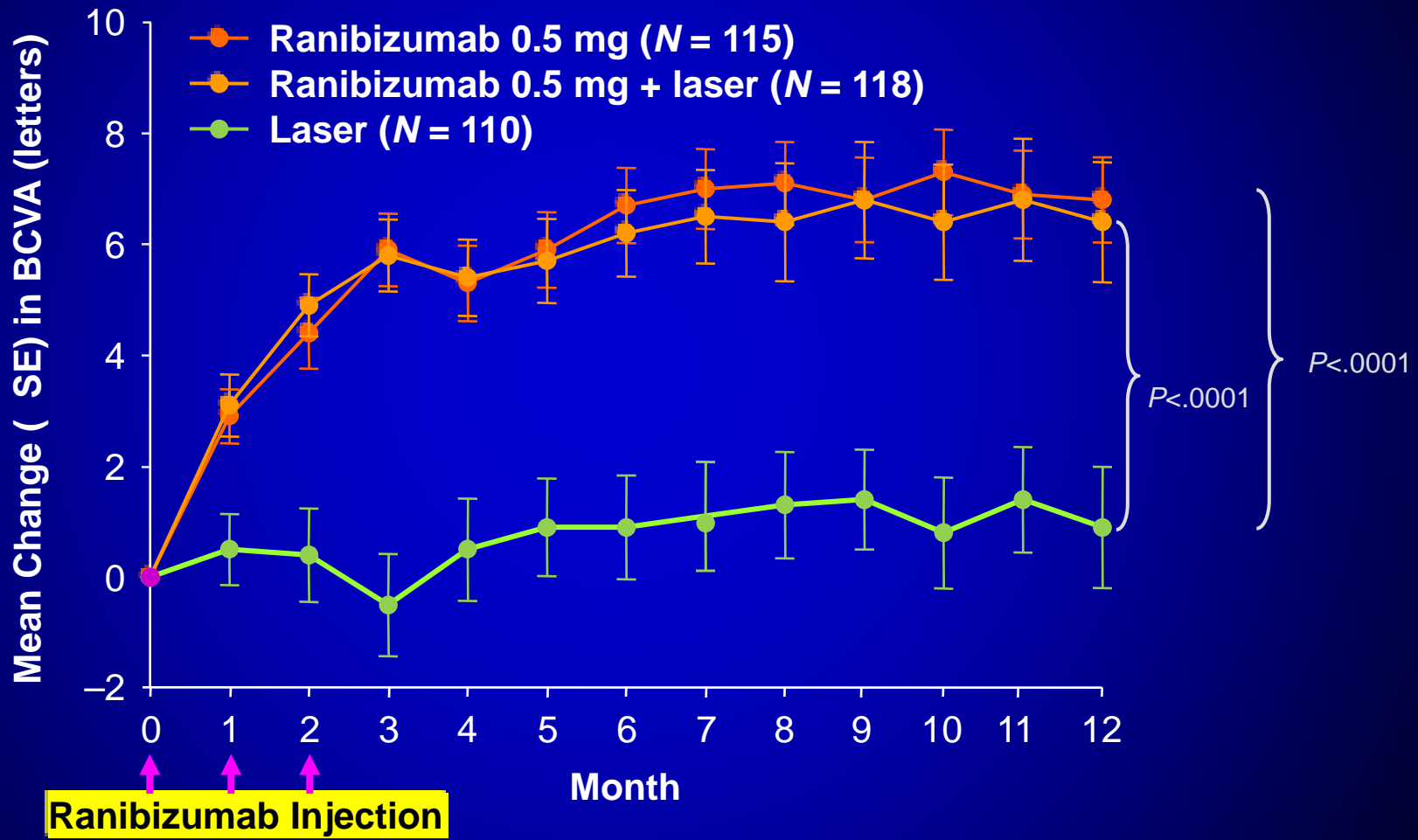
- Randomized, double-masked, multicenter, laser-controlled phase III (N = 345)



\*Laser possible on or after month 3

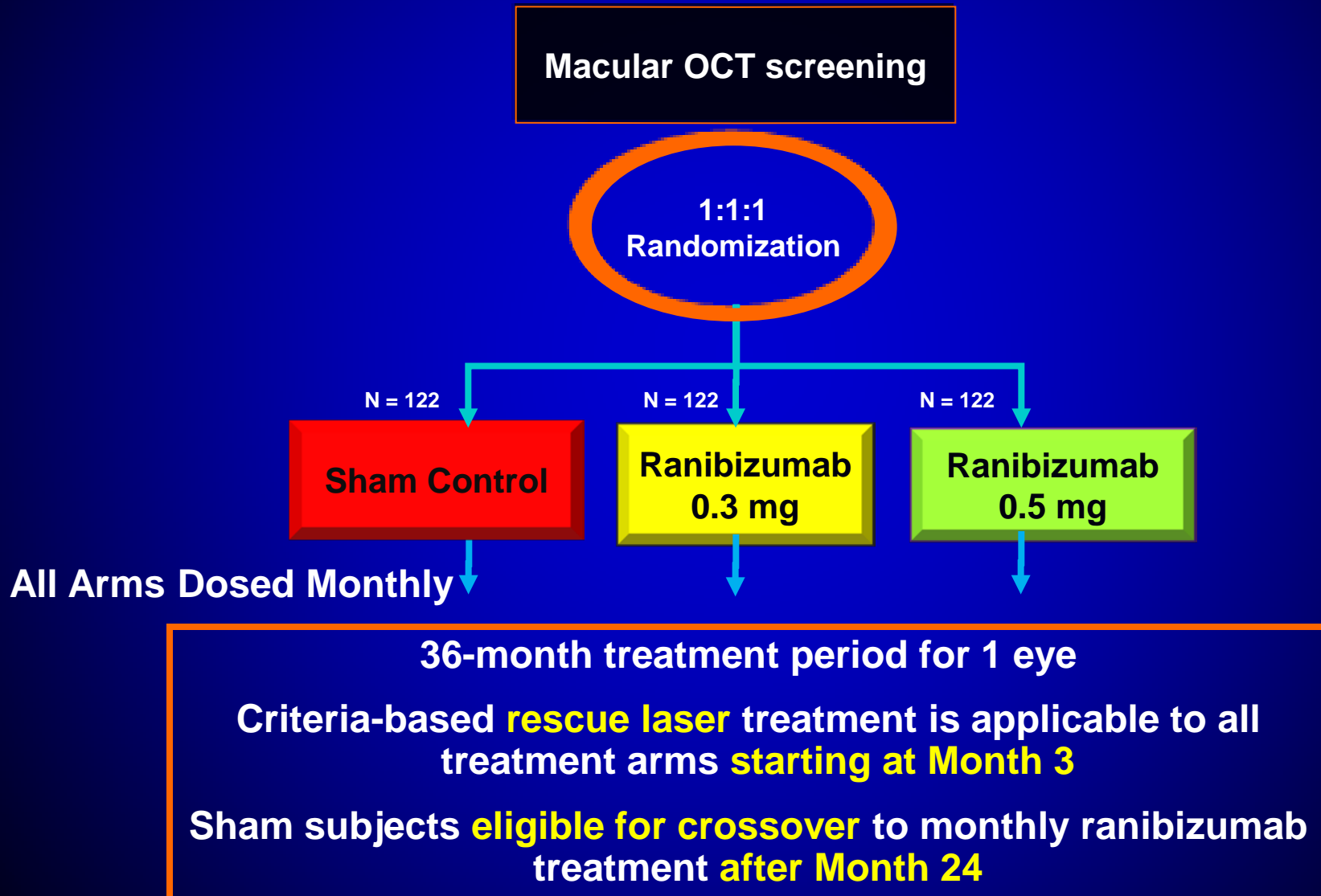
- **Primary endpoint:** mean change in BCVA from baseline to the average level from Month 1 to Month 12

# Mean BCVA Change from Baseline over Time



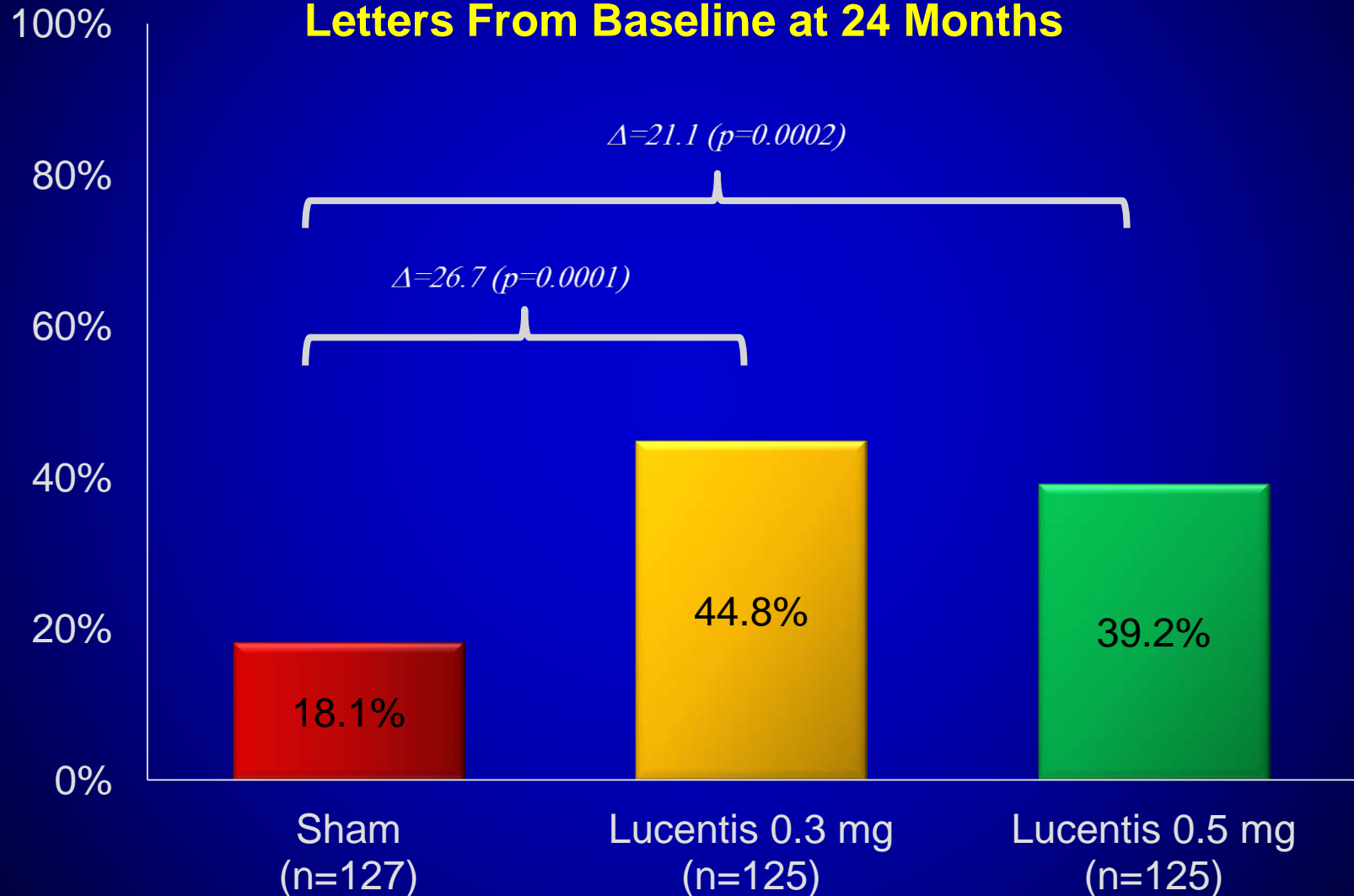
# RIDE and RISE Study Design

*Primary Endpoint at 24 Months; Study Duration of 36 Months*



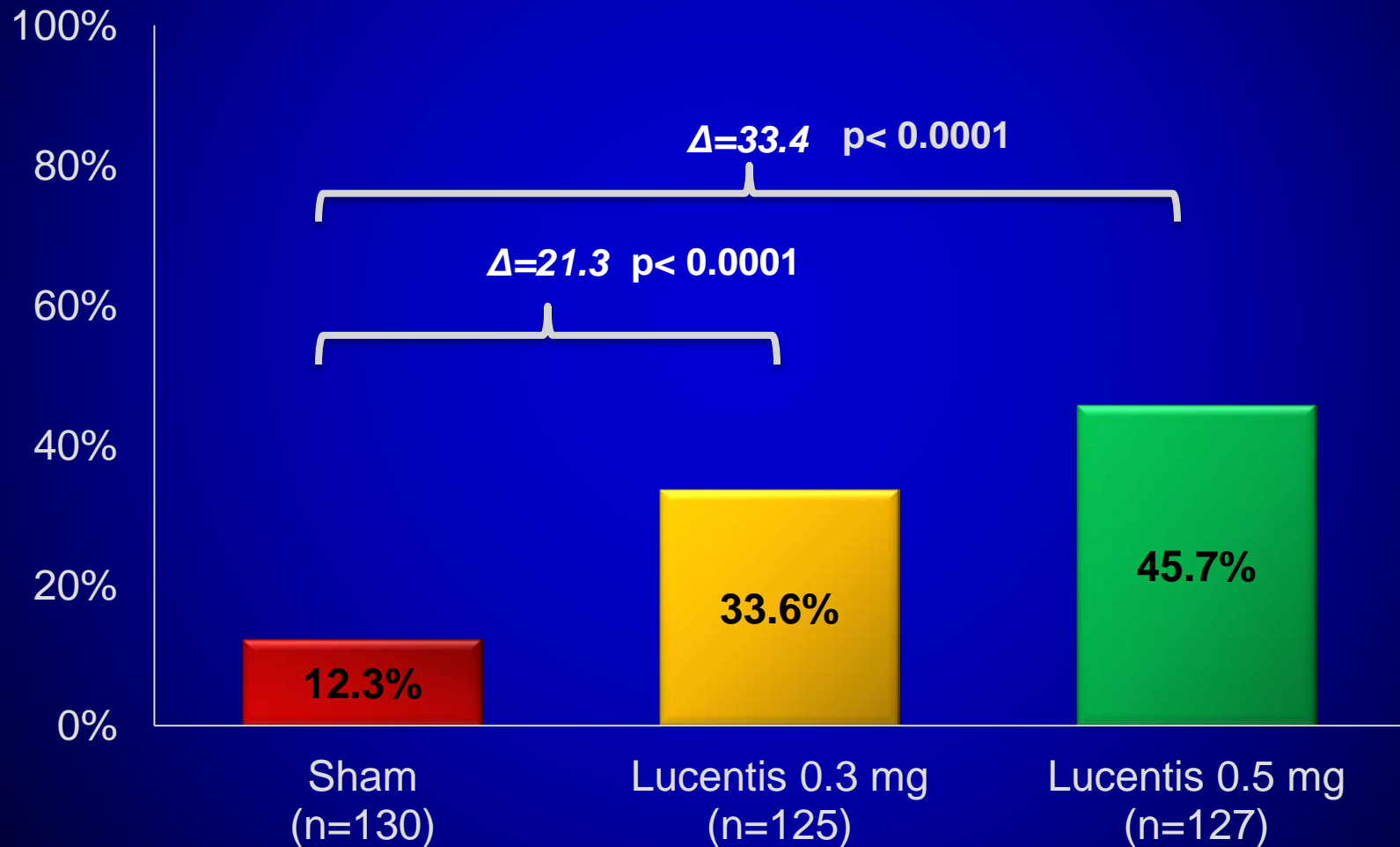
# RISE

## Proportions of Patients Gaining $\geq 15$ ETDRS Letters From Baseline at 24 Months

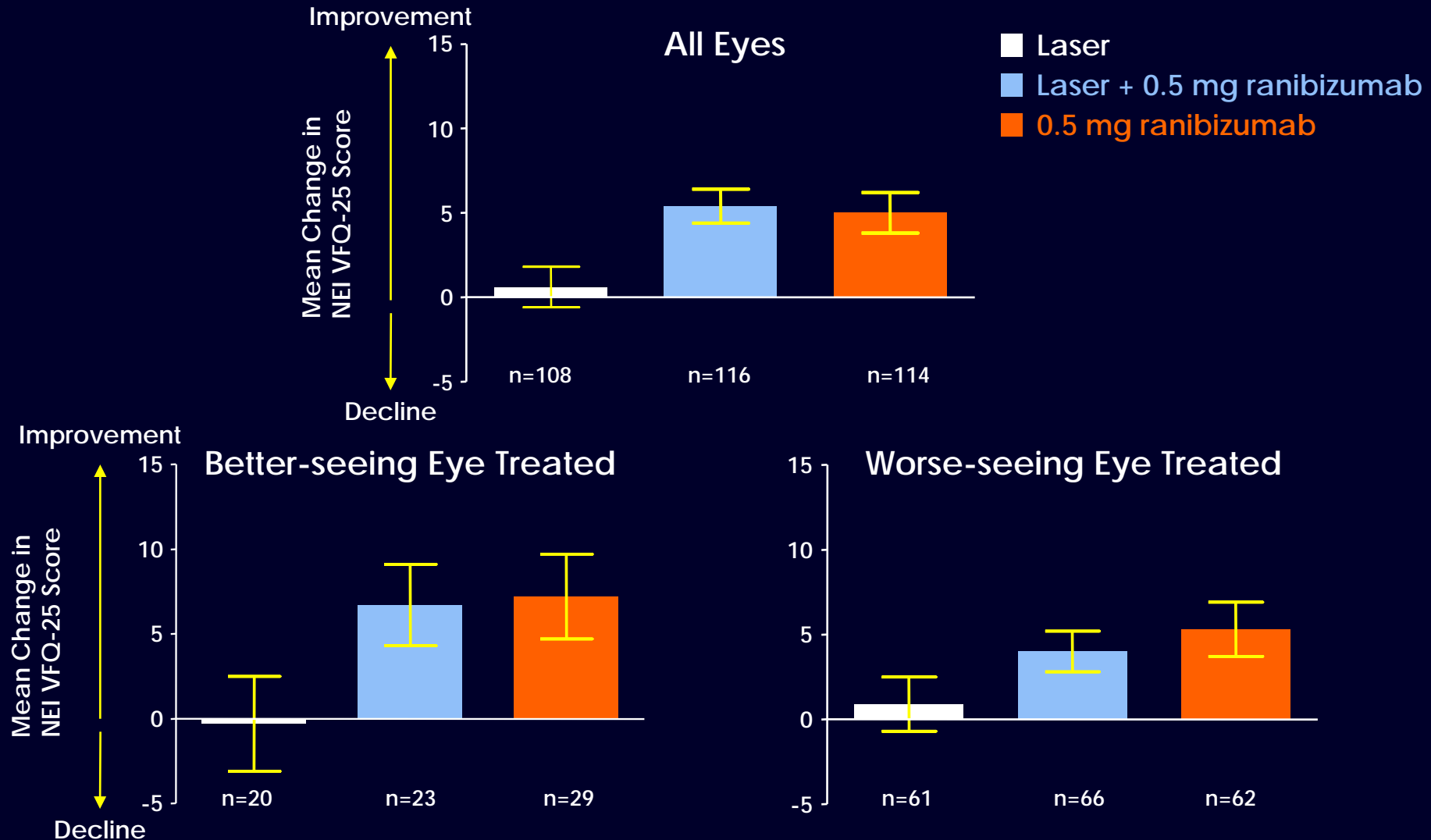


# RIDE

## Proportions of Patients Gaining $\geq 15$ ETDRS Letters From Baseline at 24 Months



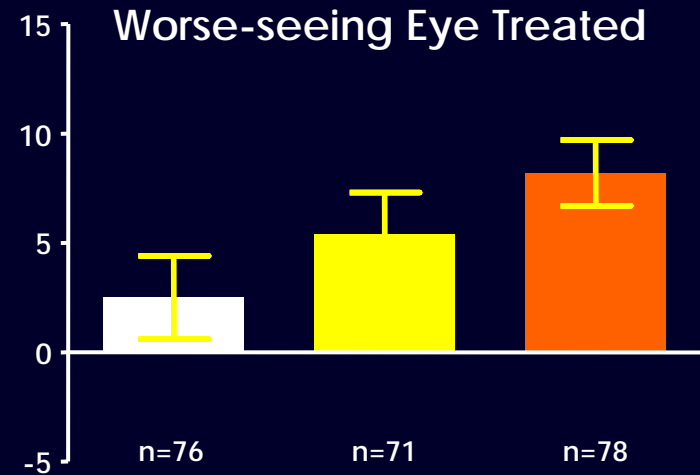
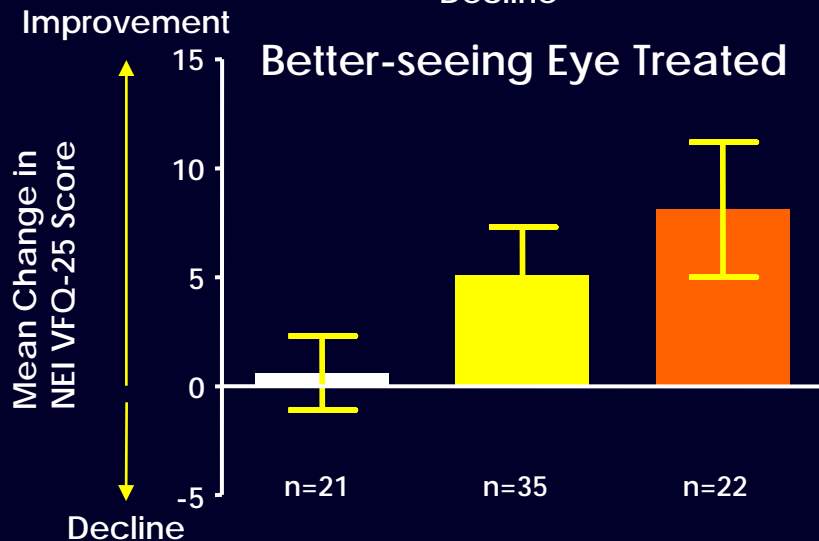
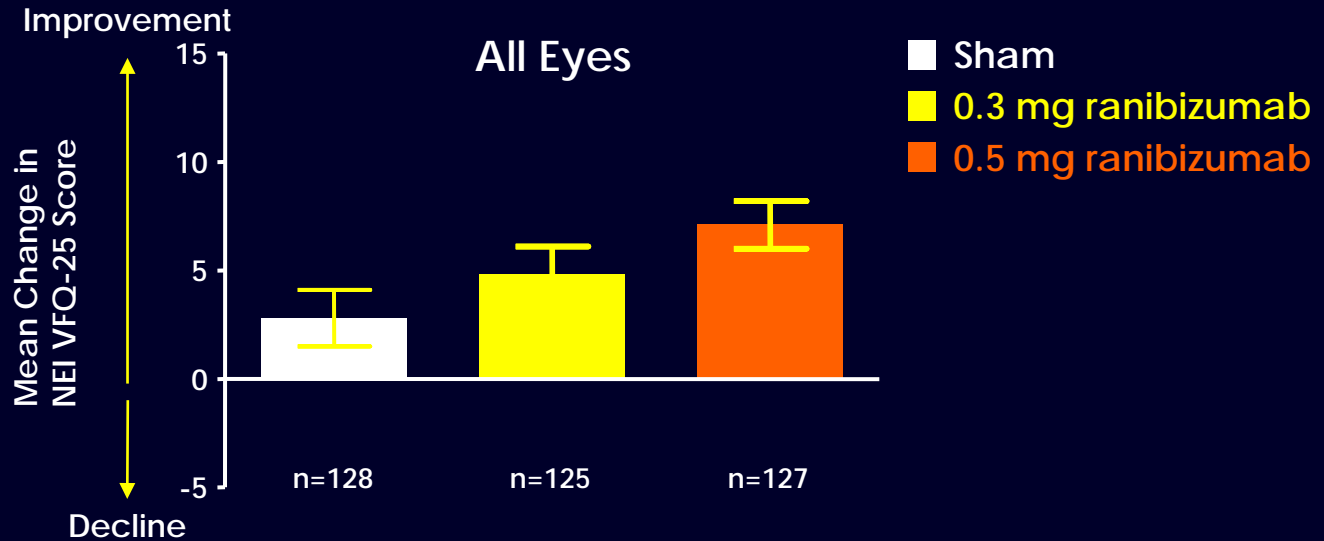
# RESTORE NEI VFQ-25 Composite Score: Mean Change From Baseline at 12 Months\*



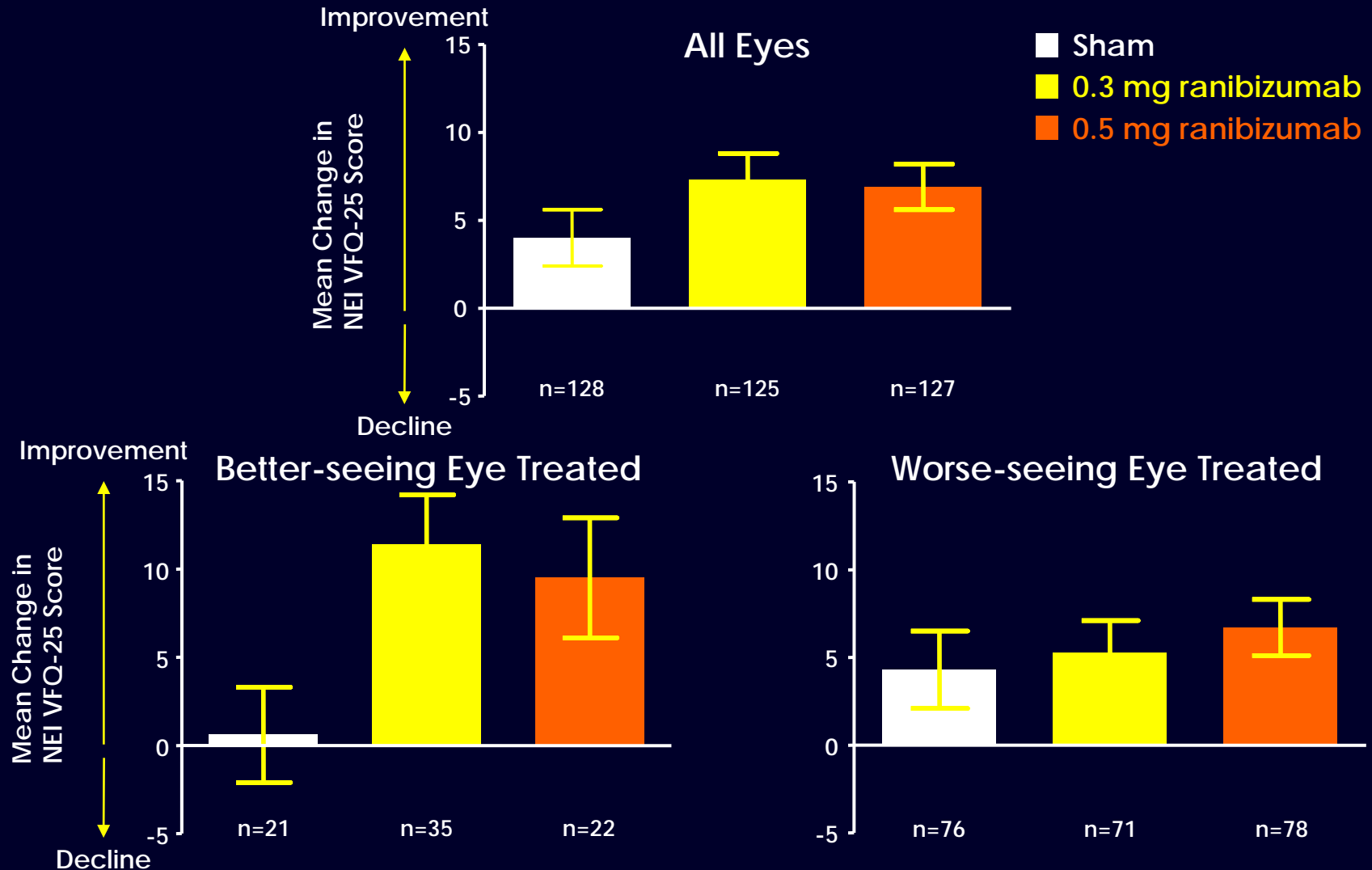
\*Data based on full analysis set: N=110 (sham), 118 (0.5 mg + laser), 115 (0.5 mg). Vertical bars are 1 standard error of the mean.



# RIDE NEI VFQ-25 Composite Score: Mean Change From Baseline at 12 Months

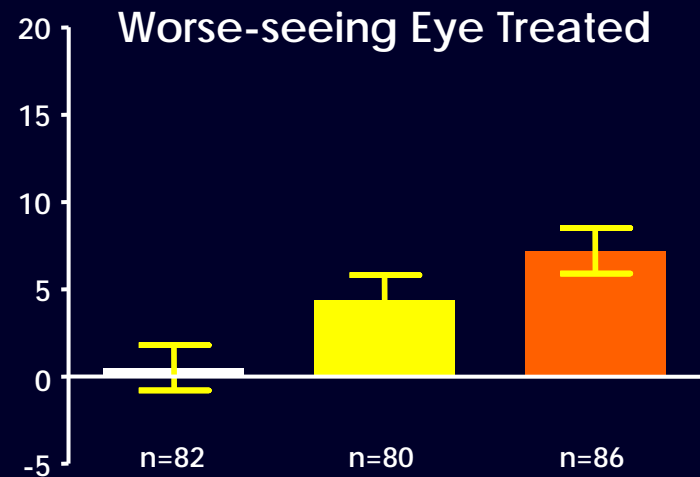
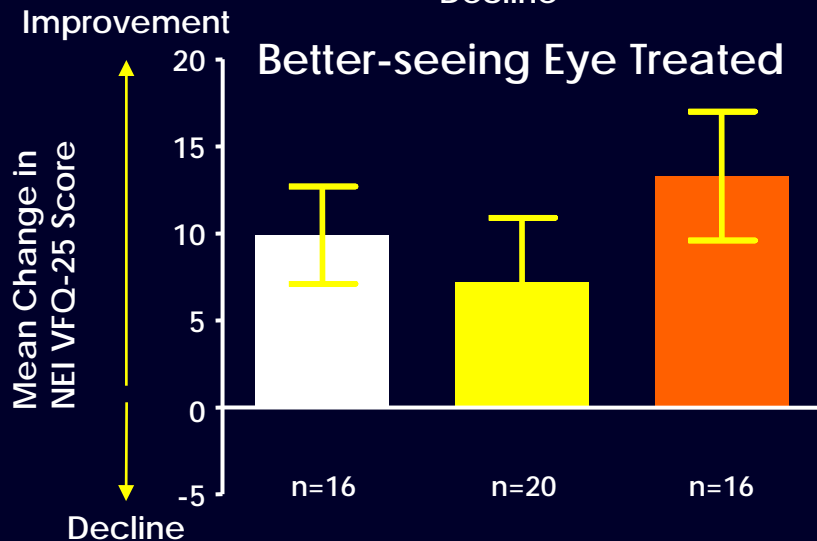
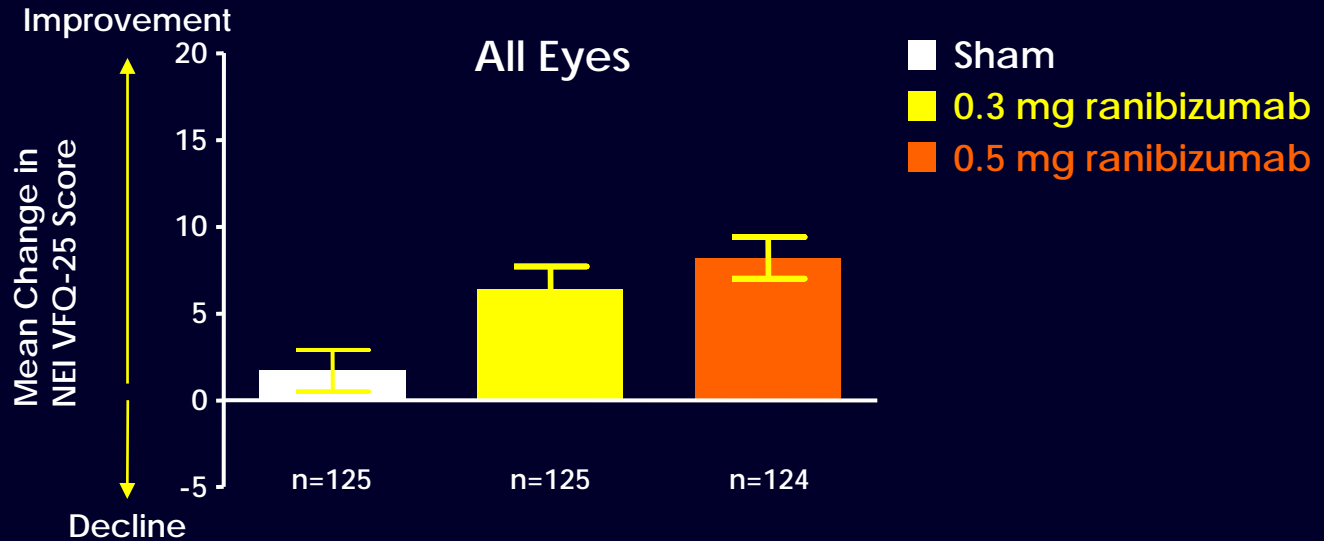


# RIDE NEI VFQ-25 Composite Score: Mean Change From Baseline at 24 Months

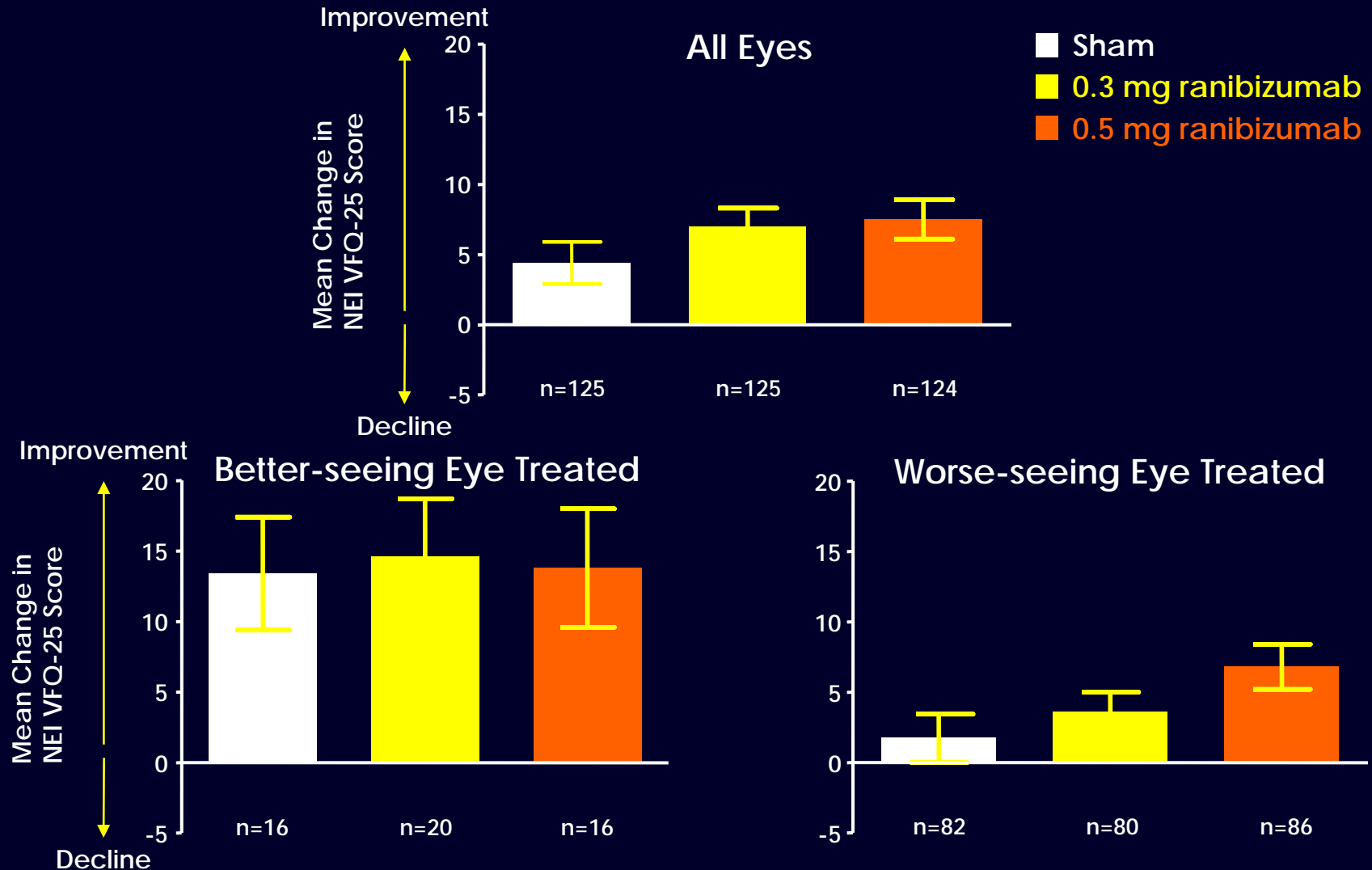


Vertical bars are 1 standard error of the mean.

# RISE NEI VFQ-25 Composite Score: Mean Change From Baseline at 12 Months



# RISE NEI VFQ-25 Composite Score: Mean Change From Baseline at 24 Months



Vertical bars are 1 standard error of the mean.

# Question #1

**In a 2005 MEDCAC on wet age-related macular degeneration (WAMD), the following commonly used outcomes or intermediate endpoint measures were discussed:**

**a. Visual acuity; b. VFQ 25; c. Dilated eye exam (to assess retinal damage); d. Grade of diabetic retinopathy (DR); e. Amsler grid; f. Extent/progression as measured by retinal photography; g. Fluorescein angiography (to assess blood flow/leakage in retina and choroid); h. Visual fields; i. Ocular coherence tomography (OCT) (to assess retinal thickening, other damage)**

**Please discuss the suitability of these measures for assessing DME treatment-related health outcomes, i.e., benefits and harms.**

## **Question #2**

**How confident are you that there is adequate evidence to determine whether or not DME management using intravitreal targeted anti-VEGF treatment improves patient health outcomes compared to DME management without intravitreal targeted anti-VEGF treatment?**

## Question #3

**If the result of Question 2 is at least intermediate (mean vote  $\geq 2.5$ ), how confident are you that there is adequate evidence to conclude that DME management using intravitreal targeted anti-VEGF treatment improves patient health outcomes compared to DME management without intravitreal targeted anti-VEGF treatment?**



## Question #4

**If the result of Question 3 is at least intermediate (mean vote  $\geq 2.5$ ), how confident are you that there is also adequate evidence to determine whether or not there are clinically meaningful differences in health outcomes among the available intravitreal targeted anti-VEGF treatments for the management of DME?**

## **Question #5**

**If the result of Question 4 is at least intermediate (mean vote  $\geq 2.5$ ), how confident are you that there is adequate evidence to conclude that there are clinically meaningful differences in the health outcomes when comparing the following available intravitreal targeted anti-VEGF treatments?**

- a. Ranibizumab vs pegatanib**
- b. Bevacizumab vs pegatanib**
- c. Ranibizumab vs bevacizumab**

**Please discuss whether your conclusions are based on evidence of:**

- a. Different benefits with similar harms**
- b. Similar benefits with different harms**
- c. Different benefits and different harms**

## **Question #6**

**How confident are you that the conclusions above are generalizable to:**

- a. Medicare beneficiaries?**
- b. Community-based settings?**

## **Discussion Questions #7 - 9**

- 7. To what extent are the conclusions above generalizable to the management of other forms of diabetic retinal vascular disease beyond DME?**
- 8. Are there significant gaps in the evidence base on the management of diabetic macula edema?**
- 9. What study designs would support the narrowing or closure of these gaps?**