How many American adults are diabetic or pre-diabetic?
How many American adults are diabetic or pre-diabetic?
Over 100M!
How many American adults are diabetic or pre-diabetic?
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Of the ~30M or so adults with full-blown diabetes, what proportion don’t even know they have it?
How many American adults are diabetic or pre-diabetic?
Over 100M!

Of the ~30M or so adults with full-blown diabetes, what proportion don’t even know they have it?
About 25%!
How many American adults are diabetic or pre-diabetic?
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Does diabetes prevalence vary with age?
How many American adults are diabetic or pre-diabetic?
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Does diabetes prevalence vary with age?
Yes, it increases with advancing age
**Diabetic Retinopathy: The Basics**

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Does diabetes prevalence vary with age?
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Does diabetes prevalence vary with ethnicity?
Yes. It is highest among Native Americans and Alaskan Natives, followed in order by non-Hispanic blacks, and Hispanics, Asians and non-Hispanic whites.
How many American adults are diabetic or pre-diabetic?
Over 100M!

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How many American adults are diabetic or pre-diabetic?
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Yes, rates are twice as high among individuals with less than a high-school education
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What proportion of diabetics receive screening eye exams at recommended intervals?
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Does diabetes prevalence vary with education level?
Yes, rates are twice as high among individuals with less than a high-school education

What proportion of diabetics receive screening eye exams at recommended intervals?
Only about 60%
Worldwide, what proportion of diabetics have retinopathy?
Worldwide, what proportion of diabetics have retinopathy?
About a third
Worldwide, what proportion of diabetics have retinopathy?
About a third

Of those diabetics with retinopathy, what proportion have vision-threatening retinopathy?
Worldwide, what proportion of diabetics have retinopathy?

About a third

Of those diabetics with retinopathy, what proportion have vision-threatening retinopathy?

Again, about a third
Worldwide, what proportion of diabetics have retinopathy? About a third

Of those diabetics with retinopathy, what proportion have vision-threatening retinopathy? Again, about a third

Per the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), what proportion of Type 2 diabetics have at least some retinopathy after 20 years?
Worldwide, what proportion of diabetics have retinopathy?
About a third

Of those diabetics with retinopathy, what proportion have vision-threatening retinopathy?
Again, about a third

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**Diabetic Retinopathy: The Basics**

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*Per the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), what proportion of Type 2 diabetics have at least some retinopathy after 20 years?*
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Of those diabetics with retinopathy, what proportion have vision-threatening retinopathy?
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Per the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), what proportion of Type 2 diabetics have at least some retinopathy after 20 years?
60%

Per the WESDR, what proportion of Type 1 diabetics have at least some retinopathy after 20 years?
99%! 
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Per the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), what proportion of Type 2 diabetics have at least some retinopathy after 20 years?
60%

Per the WESDR, what proportion of Type 2 diabetics have proliferative retinopathy (PDR) after 20 years?
25%

Per the WESDR, what proportion of Type 1 diabetics have at least some retinopathy after 20 years?
99%!
Worldwide, what proportion of diabetics have retinopathy?
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Of those diabetics with retinopathy, what proportion have vision-threatening retinopathy?
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**Diabetic Retinopathy: The Basics**

Worldwide, what proportion of diabetics have retinopathy? About a third

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Per the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), what proportion of Type 2 diabetics have at least some retinopathy after 20 years? 60%

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Per the WESDR, what proportion of Type 2 diabetics have proliferative retinopathy (PDR) after 20 years? 25%

Per the WESDR, what proportion of Type 1 diabetics have proliferative retinopathy (PDR) after 20 years? 50%!
Diabetic Retinopathy: The Basics

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About a third

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60%

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25%

(If you’re not sure what proliferative retinopathy is, no worries—it’ll be covered in this slide-set)

Per the WESDR, what proportion of Type 1 diabetics have proliferative retinopathy (PDR) after 20 years?
50%! 
What are the three histological vascular derangements in DBR?

1)
2)
3)
● What are the three histological vascular derangements in DBR?

1) Pericyte loss

2) BM thickening $\rightarrow$ ↓ lumen diameter

3) Loss of endothelial barrier function

BM = Basement membrane
What are the three histological vascular derangements in DBR?

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$BM = \text{Basement membrane}$
What are the three histological vascular derangements in DBR?

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With respect to the structure of retinal arterioles and capillaries, how are pericytes and endothelial cells related to one another?
What are the three histological vascular derangements in DBR?

1) Pericyte loss
2) BM thickening $\rightarrow$ lumen diameter ↓
3) Loss of endothelial barrier function

With respect to the structure of retinal arterioles and capillaries, how are pericytes and endothelial cells related to one another?
The endothelial cells line the lumen of the vessel. They are surrounded by their BM.
What are the three histological vascular derangements in DBR?

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*With respect to the structure of retinal arterioles and capillaries, how are pericytes and endothelial cells related to one another?*

The **endothelial** cells line the lumen of the vessel. They are surrounded by their **BM**. They are **fenestrated** or non-.
What are the three histological vascular derangements in DBR?

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With respect to the structure of retinal arterioles and capillaries, how are pericytes and endothelial cells related to one another? The endothelial cells line the lumen of the vessel. They are surrounded by their BM. They are nonfenestrated.
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With respect to the structure of retinal arterioles and capillaries, how are pericytes and endothelial cells related to one another?

The endothelial cells line the lumen of the vessel. They are surrounded by their BM. They are nonfenestrated. Tight junctions between cells form the so-called...
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What are the three histological vascular derangements in DBR?

1) Pericyte loss
2) BM thickening $\rightarrow$ ↓ lumen diameter
3) Loss of endothelial barrier function

**Do retinal vessels have an intimal lining?**
No

Do they possess a muscular wall?
No

With what nearby vascular bed do they share these features?
The cerebral vasculature (which makes sense, because the retina is in essence an extension of the CNS)
What are the three histological vascular derangements in DBR?

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2) **BM** thickening → ↓ lumen diameter
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That this is known as the inner blood-retina barrier implies the existence of what?

inner blood-retina barrier

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That this is known as the **inner** blood-retina barrier implies the existence of what? An **outer** blood-retina barrier

Diabetic Retinopathy: The Basics

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That this is known as the inner blood-retina barrier implies the existence of what?
An outer blood-retina barrier

Yup. What forms the outer blood-retina barrier?

inner blood-retina barrier
What are the three histological vascular derangements in DBR?
1) Pericyte loss
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An outer blood-retina barrier

Yup. What forms the outer blood-retina barrier?
Tight junctions between cells

inner blood-retina barrier
What are the three histological vascular derangements in DBR?

1) **Pericyte** loss
2) BM thickening → ↓ lumen diameter
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*That this is known as the inner blood-retina barrier implies the existence of what? An **outer** blood-retina barrier*

Yup. *What forms the outer blood-retina barrier?* Tight junctions between retinal pigment epithelium (RPE) cells

*Inner blood-retina barrier*
What are the three histological vascular derangements in DBR?

1) Pericyte loss
2) BM thickening $\rightarrow$ ↓ lumen diameter
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Which occurs first?
What are the three histological vascular derangements in DBR?

1) **Pericyte loss**
2) BM thickening $\rightarrow$ ↓ lumen diameter
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*Which occurs first? Pericyte loss*
The dark nuclei belong to pericytes; the lighter, to endothelial cells. *Note that the ratio between them is roughly 1:1.*
Trypsin mount of DBR retina--
low and high mag

But in a retina that with damage 2ndry
to diabetes, the ratio of endothelial
cells to pericytes is many-to-one.
Trypsin mount of DBR retina--low and high mag

What are these things?
Trypsin mount of DBR retina--low and high mag

What are these things?
Microaneurysms
What are the three histological vascular derangements in DBR?

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What pathological state is the endpoint of decreasing lumen diameter?
What are the three histological vascular derangements in DBR?

1) Pericyte loss

2) **BM thickening** \(\rightarrow\) ↓ **lumen diameter**

3) Loss of endothelial barrier function

*What pathological state is the endpoint of decreasing lumen diameter?*  
Occlusion of the retinal vessel
What are the three histological vascular derangements in DBR?

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*What pathological state is the endpoint of decreasing lumen diameter?*
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*Vessel occlusion leads to what pathological event?*
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*What pathological state is the endpoint of decreasing lumen diameter?*
Occlusion of the retinal vessel

*Vessel occlusion leads to what pathological event?*
Ischemia of the retinal area serviced by the vessel
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Retinal ischemia leads to what pathological state?
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What pathological state is the endpoint of decreasing lumen diameter?
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Retinal ischemia leads to what pathological state?
Hypoxia of the affected retinal cells
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Retinal ischemia leads to what pathological state?
Hypoxia of the affected retinal cells

Hypoxic retinal cells release a signaling molecule that is central to the pathogenesis of DBR. What is that signaling molecule?

Diabetic Retinopathy: The Basics
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Hypoxia of the affected retinal cells

Hypoxic retinal cells release a signaling molecule that is central to the pathogenesis of DBR. What is that signaling molecule?
VEGF (we will have much more to say about VEGF shortly)
What are the three histological vascular derangements in DBR?

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2) BM thickening $\rightarrow$ lumen diameter
3) Loss of endothelial barrier function

*Loss of endothelial barrier function leads to what pathologic event?*
What are the three histological vascular derangements in DBR?

1) Pericyte loss
2) BM thickening $\rightarrow$ lumen diameter
3) Loss of endothelial barrier function

Loss of endothelial barrier function leads to what pathologic event?
Leaching of serum into the retina
What are the three histological vascular derangements in DBR?

1) Pericyte loss

2) BM thickening → ↓ lumen diameter

3) **Loss of endothelial barrier function**

*Loss of endothelial barrier function leads to what pathologic event?*
Leaching of serum into the retina

*Leaching of serum into the retina leads to what pathological state?*
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2) BM thickening $\rightarrow$ ↓ lumen diameter

3) **Loss of endothelial barrier function**

*Loss of endothelial barrier function leads to what pathologic event?*
Leaching of serum into the retina

*Leaching of serum into the retina leads to what pathological state?*
Retinal edema
Classification of diabetic retinopathy

Two broad categories of DBR

Nonproliferative diabetic retinopathy (NPDR)
- Mild
- Moderate
- Severe: Any of the 4:2:1 rule
  - 15% chance of high-risk PDR within 1 year
- Very severe: Any 2 of the 4:2:1 rule
  - 45% chance of high-risk PDR within 1 year
- Pre-proliferative: Severe or very severe NPDR + CWS

Proliferative diabetic retinopathy (PDR)
- High-risk PDR
  - Any NVD associated with vitreous heme (VH)
  - Large (at least ¼ DD) area of NVD with or without VH
  - Large (at least ½ DD) area of NVE with VH
Classification of diabetic retinopathy

- Nonproliferative diabetic retinopathy (NPDR)
  - Mild
  - Moderate
  - Severe
  - Very severe

- Proliferative diabetic retinopathy (PDR)
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Two broad categories of DBR

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Classification of diabetic retinopathy

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    - Large (at least ¼ DD) area of NVD with or without VH
    - Large (at least ½ DD) area of NVE with VH

What is the histological definition of proliferation in this context?

Retinal neovascularization that breaks through the internal limiting membrane (ILM)
Classification of diabetic retinopathy

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  - Mild
  - Moderate
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Two broad categories of DBR

What is the histological definition of proliferation in this context?
Retinal neovascularization that breaks through the internal limiting membrane (ILM)
Classification of diabetic retinopathy

Nonproliferative diabetic retinopathy (NPDR)

- Three basic levels of NPDR

Proliferative diabetic retinopathy (PDR)

Diabetic Retinopathy: The Basics
Classification of diabetic retinopathy

Nonproliferative diabetic retinopathy (NPDR)

- Mild
- Moderate
- Severe

Proliferative diabetic retinopathy (PDR)
Classification of diabetic retinopathy

- Nonproliferative diabetic retinopathy (NPDR)
  - Mild
  - Moderate
  - Severe

- Proliferative diabetic retinopathy (PDR)

Three basic levels of NPDR

One more level (not universally used)
Classification of diabetic retinopathy

- Nonproliferative diabetic retinopathy (NPDR)
  - Mild
  - Moderate
  - Severe

- Very severe

Three basic levels of NPDR

Proliferative diabetic retinopathy (PDR)
Classification of diabetic retinopathy

Nonproliferative diabetic retinopathy (NPDR)

- Mild
- Moderate
- Severe

- Very severe

Three basic levels of NPDR

Proliferative diabetic retinopathy (PDR)

One level of concern

Three basic levels of NPDR

One more level (not universally used)
**Classification of diabetic retinopathy**

- **Nonproliferative diabetic retinopathy (NPDR)**
  - **Mild**
  - **Moderate**
  - **Severe**
  - **Very severe**

Three basic levels of NPDR

- **Proliferative diabetic retinopathy (PDR)**
  - **High-risk PDR**

One level of concern
Classification of diabetic retinopathy

- Nonproliferative diabetic retinopathy (NPDR)
  - Mild
  - Moderate
  - Severe
  - Very severe

- Proliferative diabetic retinopathy (PDR)
  - High-risk PDR

What landmark clinical trial provided this system of DBR classification?

The Early Treatment of Diabetic Retinopathy Study.
Classification of diabetic retinopathy

- Nonproliferative diabetic retinopathy (NPDR)
  - Mild
  - Moderate
  - Severe
  - Very severe

- Proliferative diabetic retinopathy (PDR)
  - High-risk PDR

What landmark clinical trial provided this system of DBR classification?
The Early Treatment of Diabetic Retinopathy Study. Note that the ETDRS is one of the studies you are expected to be familiar with by name.
Classification of diabetic retinopathy

Nonproliferative diabetic retinopathy (NPDR)
- **Mild**
- **Moderate**
- **Severe**
- **Very severe**

Proliferative diabetic retinopathy (PDR)
- **High-risk PDR**

How are mild and moderate NPDR defined?
Classification of diabetic retinopathy

Nonproliferative diabetic retinopathy (NPDR)
- **Mild**
- **Moderate**
- **Severe**

Very severe

Proliferative diabetic retinopathy (PDR)
- **High-risk PDR**

How are mild and moderate NPDR defined? With respect to the standard photographs employed in the DRS.
Classification of diabetic retinopathy

- Nonproliferative diabetic retinopathy (NPDR)
  - **Mild:**
  - Moderate
  - Severe
  - Very severe

- Proliferative diabetic retinopathy (PDR)
  - High-risk PDR
Classification of diabetic retinopathy

Nonproliferative diabetic retinopathy (NPDR)

- **Mild**: Any DBR < moderate
- Moderate
- Severe
- Very severe

Proliferative diabetic retinopathy (PDR)

- High-risk PDR
Diabetic Retinopathy: The Basics

Mild nonproliferative diabetic retinopathy
Classification of diabetic retinopathy

- Nonproliferative diabetic retinopathy (NPDR)
  - **Mild:** Any DBR < moderate
  - **Moderate:**
  - **Severe**
  - **Very severe**

- Proliferative diabetic retinopathy (PDR)
  - **High-risk PDR**

Diabetic Retinopathy: The Basics
Classification of diabetic retinopathy

Nonproliferative diabetic retinopathy (NPDR)
- **Mild**: Any DBR < moderate
- **Moderate**: DBR > mild but < severe
- **Severe**
- **Very severe**

Proliferative diabetic retinopathy (PDR)
- **High-risk PDR**
Diabetic Retinopathy: The Basics

Moderate nonproliferative diabetic retinopathy
**Classification of diabetic retinopathy**

- **Nonproliferative diabetic retinopathy (NPDR)**
  - **Mild:** Any DBR < moderate
  - **Moderate:** DBR > mild but < severe
  - **Severe:** Presence of any 1 of the 4:2:1 rule
    - 15% chance of high-risk PDR within 1 year

- **Very severe**
  - Severe or very severe NPDR + CWS

- **Proliferative diabetic retinopathy (PDR)**
  - **High-risk PDR**
Classification of diabetic retinopathy

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- **Mild**: Any DBR < moderate
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Proliferative diabetic retinopathy (PDR)

What is the 4:2:1 rule?
- 4 retinal quadrants of...
- 2 retinal quadrants of...
- 1 retinal quadrant of...

Diabetic Retinopathy: The Basics
Classification of diabetic retinopathy

Nonproliferative diabetic retinopathy (NPDR)

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Proliferative diabetic retinopathy (PDR)

What is the 4:2:1 rule?
- 4 retinal quadrants of extensive retinal hemorrhages
- 2 retinal quadrants of...
- 1 retinal quadrant of...
Severe nonproliferative diabetic retinopathy:
Extensive hemorrhages
Classification of diabetic retinopathy

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  - Mild: Any DBR < moderate
  - Moderate: DBR > mild but < severe
  - Severe: Presence of any 1 of the 4:2:1 rule
    - 4 retinal quadrants of...
    - 2 retinal quadrants of...
    - 1 retinal quadrant of...
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  - Very severe: Any 2 of the 4:2:1 rule
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- Proliferative diabetic retinopathy (PDR)
Classification of diabetic retinopathy

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Proliferative diabetic retinopathy (PDR)

What is the 4:2:1 rule?
- 4 retinal quadrants of... **extensive retinal hemorrhages**
- 2 retinal quadrants of... **venous beading**
- 1 retinal quadrant of...
Severe nonproliferative diabetic retinopathy:
Venous beading
Classification of diabetic retinopathy

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- **Mild:** Any DBR < moderate
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Proliferative diabetic retinopathy (PDR)

*What is the 4:2:1 rule?*
- 4 retinal quadrants of... *extensive retinal hemorrhages*
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Proliferative diabetic retinopathy (PDR)

Diabetic Retinopathy: The Basics

What is the 4:2:1 rule?
- 4 retinal quadrants of extensive retinal hemorrhages
- 2 retinal quadrants of venous beading
- 1 retinal quadrant of IRMA
Classification of diabetic retinopathy

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  - **Mild**: Any DBR < moderate
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- Proliferative diabetic retinopathy (PDR)

**What is the 4:2:1 rule?**
- 4 retinal quadrants of extensive retinal hemorrhages
- 2 retinal quadrants of venous beading
- 1 retinal quadrant of IRMA

**What does IRMA stand for?**
- Intraretinal microvascular anomalies
- Think of it as neovascularization that has not broken through the ILM
Classification of diabetic retinopathy

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- **Mild**: Any DBR < moderate
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Proliferative diabetic retinopathy (PDR)

What does IRMA stand for?
Intraretinal microvascular anomalies

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- 4 retinal quadrants of extensive retinal hemorrhages
- 2 retinal quadrants of venous beading
- 1 retinal quadrant of IRMA

What does IRMA mean?
Think of it as neovascularization that has not broken through the ILM
Classification of diabetic retinopathy

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A

Diabetic Retinopathy: The Basics

Classification of diabetic retinopathy

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What does **IRMA** stand for?
Intraretinal microvascular anomalies

What does that mean?
Think of it as neovascularization that has **not** broken through the ILM

Proliferative diabetic retinopathy (PDR)

What is the histological definition of **proliferation** in this context?
Retinal neovascularization that breaks through the internal limiting membrane (ILM) has **not** broken
Diabetic Retinopathy: The Basics

Severe nonproliferative diabetic retinopathy:

IRMA

4 patches of IRMA (Airlie House Slide 6a). Note that they are more visible in the right-hand red-free image.

severe IRMA
Classification of diabetic retinopathy

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Very severe: 

Proliferative diabetic retinopathy (PDR)
- **High-risk PDR**
Classification of diabetic retinopathy

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Proliferative diabetic retinopathy (PDR)

- **High-risk PDR**

What % of very severe NPDR cases will progress to high-risk PDR in 1 year?
Classification of diabetic retinopathy

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45% chance of high-risk PDR within 1 year

Pre-proliferative: Severe or very severe NPDR + CWS

Proliferative diabetic retinopathy (PDR)

How should NPDR be managed?

There is a clear role for controlling three systemic risk factors:

--Blood glucose
--Blood pressure
--Lipid profile

What's less clear (at the time of this writing) is the role of two modalities that have shown considerable potential:

--Intravitreal anti-VEGF injections
--Intravitreal steroids

There is good clinical-trial data demonstrating that these interventions can lessen the severity of NPDR—substantially so in some cases. What is uncertain at this time is whether the cost/benefit ratio of these interventions is favorable enough to warrant mandating their use. Trials addressing this issue are ongoing.
Classification of diabetic retinopathy

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Classification of diabetic retinopathy

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Pre-proliferative

Proliferative diabetic retinopathy (PDR)
Classification of diabetic retinopathy

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Proliferative diabetic retinopathy (PDR)

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Classification of diabetic retinopathy

Nonproliferative diabetic retinopathy (NPDR)

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  - How should NPDR be managed?
  - There is a clear role for controlling three systemic risk factors:
    - Blood glucose
    - Blood pressure
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  - What’s less clear (at the time of this writing) is the role of two modalities that have shown considerable potential:
    - Intravitreal anti-VEGF injections
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Proliferative diabetic retinopathy (PDR)
- **High-risk PDR**
  - OR
  - OR
  - OR
Classification of diabetic retinopathy

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- Proliferative diabetic retinopathy (PDR)
  - High-risk PDR
    - Any NVD associated with vitreous heme (VH), OR
      - Large (at least ¼ DD) area of NVD with or without VH, OR
      - Large (at least ½ DD) area of NVE with VH

\(NVD = \text{Neovascularization of the disc}\)
High-risk proliferative diabetic retinopathy:
NVD + vitreous hemorrhage
**Classification of diabetic retinopathy**

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*DD = Disc diameter*

**definition 3**
High-risk proliferative diabetic retinopathy:
Extensive NVD
Classify diabetic retinopathy

Nonproliferative diabetic retinopathy (NPDR)

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Proliferative diabetic retinopathy (PDR)

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  - Any NVD associated with vitreous heme (VH), *OR*
  - Large (at least ¼ DD) area of NVD with or without VH, *OR*
  - Large (at least ½ DD) area of NVE with VH

*NVE* = Neovascularization elsewhere (ie, anywhere but the disc)
Diabetic Retinopathy: The Basics

High-risk proliferative diabetic retinopathy:
Large area NVE + associated vitreous heme
Classification of diabetic retinopathy

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How big is a DD in microns?

1500 (1.5 mm)
Diabetic Retinopathy: The Basics

Classification of diabetic retinopathy

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Circling back for a minute…We said that PDR consists of retinal neovascularization. What sequence of events leads to retinal neovascularization?

What is the histological definition of proliferation in this context?

**Retinal neovascularization**

- Large (at least ½ DD) area of NVE with VH
Classification of diabetic retinopathy

What pathological state is the endpoint of decreasing lumen diameter?
Occlusion of the retinal vessel

Vessel occlusion leads to what pathological event?
Ischemia of the retinal area serviced by the vessel

Retinal ischemia leads to what pathological state?
Hypoxia of the affected retinal cells

Hypoxic retinal cells release a signaling molecule that is central to the pathogenesis of DBR. What is that signaling molecule?
VEGF (we will have much more to say about VEGF shortly)

Circling back for a minute…We said that PDR consists of retinal neovascularization. What sequence of events leads to retinal neovascularization?
The answer can be found in this set of questions/answers from earlier in the slide-set:

What is the histological definition of proliferation in this context?
Retinal neovascularization

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High-risk PDR

Pre-proliferative: Severe or very severe NPDR + CWS

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High-risk PDR
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The answer can be found in this set of questions/answers from earlier in the slide-set:

- What pathological state is the endpoint of decreasing lumen diameter?
  - Occlusion of the retinal vessel

Vessel occlusion leads to what pathological event?

To summarize: Occlusive vasculopathy secondary to diabetic derangements produces retinal ischemia.

What is the histological definition of proliferation in this context?

**Retinal neovascularization**

Retinal neovascularization that breaks through the internal limiting membrane (ILM)
Classification of diabetic retinopathy

What pathological state is the endpoint of decreasing lumen diameter?
Occlusion of the retinal vessel

Vessel occlusion leads to what pathological event?

To summarize: Occlusive vasculopathy secondary to diabetic derangements produces retinal ischemia. In a desperate attempt to recruit a blood supply, hypoxic retinal cells release VEGF, which diffuses throughout the vitreous cavity promoting neovascularization.

What is that signaling molecule?
VEGF

Circling back for a minute…We said that PDR consists of retinal neovascularization. What sequence of events leads to retinal neovascularization?
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- Occlusion of the retinal vessel
- Vessel occlusion leads to ischemia of the retinal area serviced by the vessel
- Hypoxia of the affected retinal cells
- Hypoxic retinal cells release VEGF, which diffuses throughout the vitreous cavity promoting neovascularization.
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Obviously, VEGF plays a central role in the pathogenesis of DBR. Let’s take a closer look at it.

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Pre-proliferative:
Severe or very severe NPDR + CWS
What does VEGF stand for?

**VEGF-A**

165
What does VEGF stand for?
Vascular endothelial growth factor
What does VEGF stand for?
Vascular endothelial growth factor

Broadly speaking, what is it?
What does VEGF stand for?
Vascular endothelial growth factor

Broadly speaking, what is it?
An extracellular signaling protein involved in vascular development
What does VEGF stand for?
Vascular endothelial growth factor

Broadly speaking, what is it?
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Does VEGF do anything besides grow new blood vessels?

**VEGF-A** 165
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Does VEGF do anything besides grow new blood vessels?
Yes, it also is a potent vasodilator (it was known originally as vascular permeability factor)

VEGF-A

VEGF-A

VEGF-A

VEGF-A

VEGF-A

VEGF-A
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How potent?

VEGF-A_{165}
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Vascular endothelial growth factor

Broadly speaking, what is it?
An extracellular signaling protein involved in vascular development

Does VEGF do anything besides grow new blood vessels?
Yes, it also is a potent vasodilator (it was known originally as vascular permeability factor)

How potent?
About 10,000x more potent than histamine!
What does VEGF stand for? 
Vascular endothelial growth factor

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Yes, it also is a potent vasodilator (it was known originally as vascular permeability factor)

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About 10,000x more potent than histamine!

VEGF-A\textsubscript{165}

This property accounts for VEGF’s role in the development of diabetic macular edema, and explains why anti-VEGF meds can treat this condition!

*(Diabetic macular edema is addressed in slide-set R32)*
What does VEGF stand for?
Vascular endothelial growth factor

Broadly speaking, what is it?
An extracellular signaling protein involved in vascular development

How does VEGF work?

VEGF-A

165
**A**

**Diabetic Retinopathy: The Basics**

*What does VEGF stand for?*
Vascular endothelial growth factor

*Broadly speaking, what is it?*
An extracellular signaling protein involved in vascular development

*How does VEGF work?*
Extracellular VEGF binds to VEGF receptors (VEGFR), which are transmembrane receptor tyrosine kinase (RTK) structures.

*VEGF-A*
**What does VEGF stand for?**
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**Broadly speaking, what is it?**
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**How does VEGF work?**
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**What does the A signify?**
VEGF-A165
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How does VEGF work?
Extracellular VEGF binds to VEGF receptors (VEGFR), which are transmembrane receptor tyrosine kinase (RTK) structures.

What does the A signify?
VEGF is not a single entity—a number of similar-but-different proteins comprise the ‘VEGF family.’ These are differentiated as VEGF-A through VEGF-F. (One family member, placental growth factor [PlGF], is the exception to the naming rule.) When the term VEGF is used in the ophthalmology literature without a subfamily designation, it is understood to mean VEGF-A.
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What does 165 signify?
VEGF-A is not a single entity either. At least 4 isoforms exist; these differ in the number of peptides they contain, and that number is used as a subscript to identify specific isoforms.
What does VEGF stand for?
Vascular endothelial growth factor

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What does 165 signify?
VEGF-A is not a single entity either. At least 4 isoforms exist; these differ in the number of peptides they contain, and that number is used as a subscript to identify specific isoforms.

Why focus on isoform 165?
What does VEGF stand for? 
Vascular endothelial growth factor

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Extracellular VEGF binds to VEGF receptors (VEGFR), which are transmembrane receptor tyrosine kinase (RTK) structures.

VEGF-A

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What does 165 signify? 
VEGF-A is not a single entity either. At least 4 isoforms exist; these differ in the number of peptides they contain, and that number is used as a subscript to identify specific isoforms.

Why focus on isoform 165? 
It seems to be the most important with respect to pathologic angiogenesis in the human eye.
Classification of diabetic retinopathy

- Nonproliferative diabetic retinopathy (NPDR)
  - **Mild**: Any DBR < moderate
  - **Moderate**: DBR > mild but < severe
  - **Severe**: Presence of any 1 of the 4:2:1 rule
    - 15% chance of high-risk PDR within 1 year
  - **Very severe**: Any 2 of the 4:2:1 rule
    - 45% chance of high-risk PDR within 1 year

- Proliferative diabetic retinopathy (PDR)
  - **High-risk PDR**
    - Any NVD associated with vitreous heme (VH), OR
    - Large (at least ¼ DD) area of NVD with or without VH, OR
    - Large (at least ½ DD) area of NVE with VH

What landmark clinical trial provided this system of PDR classification?
The Diabetic Retinopathy Study (DRS)

What question did the DRS seek to answer?
'Is PRP effective in treating PDR/severe NPDR?'

And the answer was…?
We'll get to that in a few slides
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Pre-proliferative
- Severe or very severe NPDR + CWS

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Panretinal photocoagulation
Classification of diabetic retinopathy

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We’ll get to that in a few slides.

Let’s drill down on PRP for a minute…
Diabetic Retinopathy: The Basics

First, let’s talk about laser-tissue interaction …
What are the five modes of laser-tissue interaction?
What are the five modes of laser-tissue interaction?

- Photo-chemical aka *photoactivation*
- Thermal
- Photo-ablation
- Plasma-induced ablation
- Photo-disruption aka *plasma-induced disruption*
Which mode is PRP an exemplar of?
Which mode is PRP an exemplar of?
Thermal
Thermal effects on tissue exist on a continuum. What are the five degrees (see what I did there?) of tissue effects?
The five modes of laser-tissue interaction

Thermal effects on tissue exist on a continuum. What are the five degrees (see what I did there?) of tissue effects?

--Hyperthermia
--Coagulation
--Vaporization
--Carbonization
--Melting
The five modes of laser-tissue interaction

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--Hyperthermia?
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Which thermal effect is employed most frequently?
Thermal effects on tissue exist on a continuum. What are the five degrees (see what I did there?) of tissue effects?

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Which thermal effect is employed most frequently?

Coagulation
Thermal effects on tissue exist on a continuum. What are the five degrees of tissue effects?

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Which thermal process is employed most frequently? Coagulation

What does it mean to say that tissue has 'coagulated'?

It means the proteins have been denatured.

What does it mean to say a protein has been 'denatured'?

It means the protein has been forced out of its native conformation by some sort of applied stress (in this case, heat).

Because a protein's function is inextricably tied to its shape, denatured proteins do not behave as they do in their native form.

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Can you give an example of protein denaturation?

Consider egg albumin. In its native state, it's a clear liquid. But if sufficient heat is applied, it becomes a white solid. (And if sufficient salsa is applied to the white solid, it becomes delish.)
Thermal effects on tissue exist on a continuum. What are the five degrees of tissue effects?

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Which thermal effect is employed most frequently?

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- Photothermal
- Photothermal ablation
- Plasma-induced ablation
- Photo-disruption aka plasma-induced disruption

Thermal effects on tissue exist on a continuum. What are the five degrees?
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At what temperature does retinal tissue start to coagulate?
65°C

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For more info on lasers, see slide-set FELT26
Which laser is used to perform PRP?
Which laser is used to perform PRP?
Argon green or blue-green
Q

- Which laser is used to perform PRP? Argon green or blue-green
- How many shots constitute a full compliment of PRP?
● Which laser is used to perform PRP? Argon green or blue-green
● How many shots constitute a full compliment of PRP? About 1200-1400
Which laser is used to perform PRP? Argon green or blue-green

How many shots constitute a full compliment of PRP? About 1200-1400

What spot size should be used?
Which laser is used to perform PRP? Argon green or blue-green

How many shots constitute a full compliment of PRP? About 1200-1400

What spot size should be used? 500 \( \mu \text{m} \)
Which laser is used to perform PRP? Argon green or blue-green

How many shots constitute a full compliment of PRP? About 1200-1400

What spot size should be used? 500 μm

How much power?
Q/A

Diabetic Retinopathy: The Basics

- Which laser is used to perform PRP? Argon green or blue-green
- How many shots constitute a full compliment of PRP? About 1200-1400
- What spot size should be used? 500 μm
- How much power? Enough to produce a gray or light beige-colored burn
• Which laser is used to perform PRP? Argon green or blue-green
• How many shots constitute a full compliment of PRP? About 1200-1400
• What spot size should be used? 500 μm
• How much power? Enough to produce a gray or light cream-colored burn
Q

- Which laser is used to perform PRP? Argon green or blue-green
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- How much power? Enough to produce a gray or light cream-colored burn
- How much distance between burns?
Which laser is used to perform PRP? Argon green or blue-green

How many shots constitute a full compliment of PRP? About 1200-1400

What spot size should be used? 500 μm

How much power? Enough to produce a gray or light cream-colored burn

How much distance between burns? About half a burn’s width
Diabetic Retinopathy: The Basics

PRP
Q

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- Should it be done in one, or multiple sessions?
Which laser is used to perform PRP? Argon **green** or **blue-green**

How many shots constitute a full compliment of PRP? **About 1200-1400**

What spot size should be used? **500 \( \mu \text{m} \)**

How much power? **Enough to produce a gray or light cream-colored burn**

How much distance between burns? **About half a burn’s width**

Should it be done in one, or multiple sessions? **It doesn’t matter**
What are known complications of PRP?

- Reduced vision
- Reduced color vision
- Reduced contrast sensitivity
- Loss of 1-2 lines BCVA
What are known complications of PRP?

- Reduced **peripheral** vision
- Reduced **color** vision
- Reduced **contrast sensitivity**
- Loss of 1-2 lines BCVA
What are known complications of PRP?

- Reduced peripheral vision
- Reduced color vision
- Reduced contrast sensitivity
- Loss of 1-2 lines BCVA
- Decreased parasympathetic function
- Decreased two words
What are known complications of PRP?

- Reduced *peripheral* vision
- Reduced *color* vision
- Reduced *contrast sensitivity*
- Loss of 1-2 lines BCVA
- Decreased *accommodation*
- Decreased *corneal sensitivity*
Q

What are known complications of PRP?

- Reduced peripheral vision
- Reduced color vision
- Reduced contrast sensitivity
- Loss of 1-2 lines BCVA
- Decreased accommodation
- Decreased corneal sensitivity

What do accommodation and corneal sensitivity have in common?
What are known complications of PRP?

- Reduced *peripheral* vision
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*What do accommodation and corneal sensitivity have in common? Both are mediated by the* long ciliary nerves

---

**Diabetic Retinopathy: The Basics**
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What do accommodation and corneal sensitivity have in common? Both are mediated by the long ciliary nerves

OK, but what do the long ciliary nerves have to do with PRP?
Q/A

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- Reduced contrast sensitivity
- Loss of 1-2 lines BCVA
- Decreased accommodation
- Decreased corneal sensitivity

What do accommodation and corneal sensitivity have in common?
Both are mediated by the long ciliary nerves

OK, but what do the long ciliary nerves have to do with PRP?
The long ciliary nerves run pretty deep (ie, just under the choroid) in the meridian.
What are known complications of PRP?

- Reduced peripheral vision
- Reduced color vision
- Reduced contrast sensitivity
- Loss of 1-2 lines BCVA
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OK, but what do the long ciliary nerves have to do with PRP?
The long ciliary nerves run pretty deep (ie, just under the choroid) in the horizontal meridian.
What are known complications of PRP?

- Reduced peripheral vision
- Reduced color vision
- Reduced contrast sensitivity
- Loss of 1-2 lines BCVA
- Decreased accommodation
- Decreased corneal sensitivity

What do accommodation and corneal sensitivity have in common?
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How can one minimize the risk to the long ciliary nerves?
By avoiding the horizontal meridian during PRP.
What are known complications of PRP?

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- Macular
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(CNVM = Choroidal neovascular membrane)
Diabetic Retinopathy: The Basics

What does the term high-risk PDR mean? High risk of what?

Proliferative diabetic retinopathy (PDR)

High-risk PDR

- Any NVD associated with vitreous heme (VH), OR
- Large (at least \( \frac{1}{4} \) DD) area of NVD with or without VH, OR
- Large (at least \( \frac{1}{2} \) DD) area of NVE with VH

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In the DRS, patients with this level of neovascularization were found to be at high risk of severe vision loss (SVL).

What was the definition of SVL in the DRS?

Snellen acuity ≤ 5/200 (20/800)

Why was this level of vision chosen as the benchmark?

At or below 5/200, visually-guided ambulation becomes problematic.

What is the clinical implication of finding high-risk PDR in a patient?

High-risk PDR is the formal justification for performing PRP (I say 'formal' because many clinicians will offer PRP at lesser levels of DBR if they feel it is warranted).

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The goal is to kill most of the cells in the peripheral retina.

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What is the therapeutic rationale? Why kill the peripheral retina?
To answer an earlier question: Per the DRS, is PRP effective at preventing SVL? Indeed it is—it reduces the risk by 50% at 5 years post-treatment

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The goal is to kill most of the cells in the peripheral retina.

*What is the therapeutic rationale? Why kill the peripheral retina?*
As stated several times now: DBR renders portions of the retina hypoxic, and hypoxic cells release VEGF, initiating a cascade of deleterious events.

*To answer an earlier question. Per the DRS, is PRP effective at preventing SVL?*
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**What is the therapeutic rationale? Why kill the peripheral retina?**
As stated several times now: DBR renders portions of the retina hypoxic, and hypoxic cells release VEGF, initiating a cascade of deleterious events.

OTOH, dead cells do not release VEGF. So by euthanizing the hypoxic retina, the intraocular VEGF burden is reduced, neovascularization is halted, and SVL is avoided.
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What is the goal of PRP; ie, what are we trying to do?
The goal is to kill most of the cells in the peripheral retina

What is the therapeutic rationale? Why kill the peripheral retina?
As stated several times now: DBR renders portions of the retina hypoxic, and hypoxic cells release VEGF, initiating a cascade of deleterious events. OTOH, dead cells do not release VEGF. So by euthanizing the hypoxic retina, the intraocular VEGF burden is reduced, neovascularization is halted, and SVL is avoided.

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**Classification of diabetic retinopathy**

- **Nonproliferative diabetic retinopathy (NPDR)**
  - **Mild?** Any DBR < moderate
  - **Moderate?** DBR > mild but < severe
  - **Severe?** Presence of any 1 of the 4:2:1 rule

The ETDRS looked at whether PRP for mild, moderate and/or severe NPDR reduced the risk of SVL. What did it find in this regard?

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- **Mild?** **Nope**
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- **Severe?** **Yes!**

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The ETDRS looked at whether PRP for mild, moderate and/or severe NPDR reduced the risk of SVL. What did it find in this regard?
It found that PRP resulted in a modest reduction of SVL in severe NPDR (especially in pts with Type 2 DM), but not in mild or moderate dz

Per the DRS, is PRP effective at preventing SVL?
It is for severe NPDR (but not mild or moderate)
Take note: DBR is a **progressive** condition, one that passes through a well-defined series of stages on its way to blinding a pt. If DBR is identified at an early stage, the pt has a chance to enact lifestyle modifications that will lead to its resolution. If it is recognized at a later (but pre-SVL) stage, treatment can be performed that may prevent it from blinding the pt. *This is why we screen DM pts on the reg.*
**Classification of diabetic retinopathy**

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  - **Mild**: Any DBR < moderate
  - **Moderate**: DBR > mild but < severe
  - **Severe**: Presence of any 1 of the 4:2:1 rule
    - 15% chance of high-risk PDR within 1 year
  - **Very severe**: Any 2 of the 4:2:1 rule
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And finally: With respect to DBR, what does DME stand for?

Diabetic macular edema (DME) can occur at any level of NPDR or PDR.
Classification of diabetic retinopathy

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Pre-proliferative: Severe or very severe NPDR + CWS

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And finally: With respect to DBR, what does DME stand for?
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Where does DME fit into this classification scheme?

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*DME is addressed in detail in its own slide-set*

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*Diabetic Retinopathy: The Basics*