How many American adults are diabetic or pre-diabetic?
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Over 100M!
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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%!
Diabetic Retinopathy: The Basics

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?
About 25%!

Does diabetes prevalence vary with age?
How many American adults are diabetic or pre-diabetic?
Over 100M!

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Does diabetes prevalence vary with age?
Yes, it increases with advancing age
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Does diabetes prevalence vary with ethnicity?
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Over 100M!

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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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Does diabetes prevalence vary with age?
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Does diabetes prevalence vary with education level?
Diabetic Retinopathy: The Basics

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
How many American adults are diabetic or pre-diabetic?
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What proportion of diabetics receive screening eye exams at recommended intervals?
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

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?
Diabetic Retinopathy: The Basics

*Worldwide, what proportion of diabetics have retinopathy?*
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*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

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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?
Worldwide, what proportion of diabetics have retinopathy?
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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?
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**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?*
60%

*Per the WESDR, what proportion of Type 1 diabetics have at least some retinopathy after 20 years?*
Worldwide, what proportion of diabetics have 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 I 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?
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? 60%

Per the WESDR, what proportion of Type 1 diabetics have at least some retinopathy after 20 years? 99%! 
Diabetic Retinopathy: The Basics

**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 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?
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?
60%

Per the WESDR, what proportion of Type 1 diabetics have at least some retinopathy after 20 years?
99%

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?
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?

60%

Per the WESDR, what proportion of Type 1 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%

Per the WESDR, what proportion of Type 1 diabetics have proliferative retinopathy (PDR) after 20 years?

50%!
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? 60%

Per the WESDR, what proportion of Type 1 diabetics have at least some retinopathy after 20 years? 99%

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%

(If you’re not sure what proliferative retinopathy is, no worries—it’ll be covered in this slide-set)
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?
60%

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Diabetes also causes CAD, CVA, nephropathy, and neuropathy. (Thanks Captain Obvious.) However, only one has onset that is strongly correlated with the onset of retinopathy. Which one?
Worldwide, what proportion of diabetics have retinopathy?
About a third

Of those diabetics with retinopathy, what proportion have vision-threatening retinopathy?
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99%!

Diabetes also causes CAD, CVA, nephropathy, and neuropathy. (Thanks Captain Obvious.) However, only one has on onset that is strongly correlated with the onset of retinopathy. Which one?
Nephropathy—when a pt develops one of the two, it’s a lock s/he’s going to develop the other very soon
What are the three histological vascular derangements in DBR?

1) Pericyte loss
2) BM thickening → ↓ lumen diameter
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?

1) **Pericyte loss**

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

3) **Loss of endothelial barrier function**
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?
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?

1) Pericyte loss
2) BM thickening $\rightarrow$ ↓ lumen diameter
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1) Pericyte loss
2) BM thickening $\rightarrow$ ↓ lumen diameter
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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?

1) Pericyte loss
2) BM thickening → ↓ 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. They are nonfenestrated.
What are the three histological vascular derangements in DBR?

1) Pericyte loss
2) BM thickening $\rightarrow$ lumen diameter decrease
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. They are nonfenestrated. Tight junctions between cells form the so-called inner blood-retina barrier.
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. They are nonfenestrated. Tight junctions between cells form the so-called *inner blood-retina barrier*.
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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**. They are **nonfenestrated**. Tight junctions between cells form the so-called **inner blood-retina barrier**. The pericytes surround the vessel, and are embedded in the BM of the endothelial cells.*
What are the three histological vascular derangements in DBR?

1) Pericyte loss
2) BM thickening → ↓ 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 this lack of 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?

1) **Pericyte** loss
2) BM thickening → ↓ lumen diameter
3) Loss of **endothelial** barrier function

---

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No

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2) **BM** thickening → ↓ lumen diameter
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What are the three histological vascular derangements in DBR?

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

That this is known as the inner blood-retina barrier implies the existence of what?
What are the three histological vascular derangements in DBR?

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

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**Diabetic Retinopathy: The Basics**

- **Pericyte**
- BM thickening $\rightarrow$ ↓ lumen diameter
- Loss of **endothelial** barrier function

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

An **outer** 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

Yup. What forms the outer blood-retina barrier?

inner blood-retina barrier
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1) Pericyte loss
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Tight junctions between retinal pigment epithelium (RPE) cells

The pericytes surround the vessel, and are embedded in the BM of the endothelial cells.
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inner blood-retina barrier
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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.*
But in a retina with damage secondary 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?

1) Pericyte loss

2) **BM thickening** $\rightarrow$ $\downarrow$ lumen diameter

3) Loss of endothelial barrier function

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
What are the three histological vascular derangements in DBR?

1) Pericyte loss

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

3) Loss of endothelial barrier function

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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?

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

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

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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?*
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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 $\rightarrow$ ↓ 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?*
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

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

- **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

Two broad categories of DBR

- 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: 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

- 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

Two broad categories of DBR

- Diabetic Retinopathy: The Basics
Classification of diabetic retinopathy

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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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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)
Classification of diabetic retinopathy

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

Proliferative diabetic retinopathy (PDR)

Three basic levels of NPDR:
- 15% chance of high-risk PDR within 1 year
- 45% chance of high-risk PDR within 1 year

Pre-proliferative:
- Severe or very severe NPDR + CWS

Classification of diabetic retinopathy

Diabetic Retinopathy: The Basics
Classification of diabetic retinopathy

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

- Pre-proliferative
  - Severe or very severe NPDR + CWS

- 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

- Proliferative diabetic retinopathy (PDR)

Three basic levels of NPDR:
- Mild
- Moderate
- Severe

One more level (not universally used):
- Very severe
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
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
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:** Any DBR < moderate
- 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
Mild nonproliferative diabetic retinopathy
Classification of diabetic retinopathy

Nonproliferative diabetic retinopathy (NPDR)

- **Mild**: Any DBR < moderate
- **Moderate**: Any DBR > mild but < severe
- **Severe**: 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

- Severe or very severe NPDR + CWS

Proliferative diabetic retinopathy (PDR)

- High-risk PDR
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:** Any 2 of the 4:2:1 rule
  - 45% chance of high-risk PDR within 1 year

- Severe or very severe NPDR + CWS

Proliferative diabetic retinopathy (PDR)

- **High-risk PDR**
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

- Very severe

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

What is the 4:2:1 rule?
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)

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)
- **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)

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

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)

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

*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

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

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

Proliferative diabetic retinopathy (PDR)
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
    - 45% chance of high-risk PDR within 1 year
  - **Very severe:** Any 2 of the 4:2:1 rule
    - 90% chance of high-risk PDR within 1 year

- 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
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

- **Pre-proliferative:** Severe

- **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

- 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

- Pre-proliferative

- 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
 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)

*What does IRMA stand for?*
Intraretinal microvascular anomalies

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

- Pre-proliferative

Proliferative diabetic retinopathy (PDR)

**What is the histological definition of proliferation in this context?**
Retinal neovascularization that hasn't broken through the internal limiting membrane (ILM)

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

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

- **Very severe:**

Proliferative diabetic retinopathy (PDR)

- **High-risk PDR**
Classification of diabetic retinopathy

Nonproliferative diabetic retinopathy (NPDR)

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Proliferative diabetic retinopathy (PDR)

- High-risk PDR
Classification of diabetic retinopathy

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- **High-risk PDR**
Classification of diabetic retinopathy

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Classification of diabetic retinopathy

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- **High-risk PDR**
Classification of diabetic retinopathy

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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

Nonproliferative diabetic retinopathy (NPDR)

Mild: Any DBR < moderate

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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:

- Lipid profile
- S -
- V -
- W

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

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- Pre-proliferative

- Proliferative diabetic retinopathy (PDR)

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Pre-proliferative

Proliferative diabetic retinopathy (PDR)

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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:

- 
- 

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Classification of diabetic retinopathy

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Moderate: DBR > mild but < severe

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  - 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)

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

Diabetic Retinopathy: The Basics
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

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

Nonproliferative diabetic retinopathy (NPDR)
- **Mild**: Any DBR < moderate
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- **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**
  - definition 1
  - definition 2
  - definition 3
**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

* definitions:
  - NVD = Neovascularization of the disc
  - OR
High-risk proliferative diabetic retinopathy: NVD + vitreous hemorrhage
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

\[DD = \text{Disc diameter}\]
\[\text{definition 3}\]
High-risk proliferative diabetic retinopathy: Extensive NVD
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

NVE = Neovascularization elsewhere (ie, anywhere but the disc)
High-risk proliferative diabetic retinopathy: Large area NVE + associated vitreous heme
**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 $\frac{1}{4}$ DD) area of NVD with or without VH, OR
    - Large (at least $\frac{1}{2}$ DD) area of NVE with VH

*How big is a DD in microns?*  
1500 (1.5 mm)
Classification of diabetic retinopathy

Nonproliferative diabetic retinopathy (NPDR)

- **Mild:** Any DBR < moderate
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- **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 + VH, OR
  - Large (at least ½ DD) area of NVE with VH

How big is a DD in microns?

1500 (1.5 mm)
Classification of diabetic retinopathy

- Nonproliferative diabetic retinopathy (NPDR)
  - **Mild:** Any DBR < moderate
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  - **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

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

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

---

**Diabetic Retinopathy: The Basics**

**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)

---

**Retinal neovascularization**

**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 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)
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.

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
Classification of diabetic retinopathy

Nonproliferative diabetic retinopathy (NPDR)

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Pre-proliferative

Proliferative diabetic retinopathy (PDR)

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Diabetic Retinopathy: The Basics

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.

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 that breaks through the internal limiting membrane (ILM)

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

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- Pre-proliferative
  - Severe or very severe NPDR + CWS

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    - 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)

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:

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

2. 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. Unfortunately, the resulting new fibrovascular tissue is highly abnormal—it is prone to bleeding and contraction, leading to vitreous hemorrhages and/or tractional retinal detachment.

Pathogenesis of DBR: What is that signaling molecule?
VEGF (we will have much more to say about VEGF shortly)
Classification of diabetic retinopathy

- Nonproliferative diabetic retinopathy (NPDR)
  - Mild: Any DBR < moderate
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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. Unfortunately, the resulting new fibrovascular tangle is highly abnormal—it is prone to bleeding and contraction, leading to vitreous hemorrhages and/or tractional retinal detachment.

Obviously, VEGF plays a central role in the pathogenesis of DBR. Let’s take a closer look at it.
What does VEGF stand for?
What does VEGF stand for?
Vascular endothelial growth factor
What does VEGF stand for? 
Vascular endothelial growth factor

Broadly speaking, what is it?

VEGF-A$_{165}$
What does **VEGF** stand for?
Vascular endothelial growth factor

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

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Does VEGF do anything besides grow new blood vessels?

VEGF-A\textsubscript{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)

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How potent?

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How potent?
About 10,000x more potent than histamine!
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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-$A_{165}$

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}
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Extracellular VEGF binds to VEGF receptors (VEGFR), which are transmembrane receptor tyrosine kinase (RTK) structures.
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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 [PIGF], 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.
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Why focus on isoform 165?
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**Why focus on isoform 165?**
It seems to be the most important with respect to pathologic angiogenesis in the human eye.
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Pre-proliferative: Severe or very severe NPDR + CWS

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
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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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Panretinal photocoagulation
Classification of diabetic retinopathy

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**Diabetic Retinopathy: The Basics**

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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?
The five modes of laser-tissue interaction

- Photo-chemical
  aka photoactivation
- Thermal
- Photo-ablation
- Plasma-induced ablation
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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:

- Photo-chemical (aka photoactivation)
- Photo-thermal ablation
- Plasma-induced ablation
- Photo-disruption (aka plasma-induced disruption)
The five modes of laser-tissue interaction

Thermal

Photo-chemical
aka photoactivation

Photo-ablation

Plasma-induced ablation

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

--Hyperthermia
--Coagulation
--Vaporization
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--Melting?

Which thermal effect is employed most frequently?
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The five modes of laser-tissue interaction

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What does it mean to say that tissue has ‘coagulated’?

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

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What does it mean to say that tissue has ‘coagulated’? It means the proteins have been denatured.

Which thermal effect is employed most frequently?

Coagulation
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Which thermal effect is employed most frequently?

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What does it mean to say that tissue has ‘coagulated’?

It means the proteins have been denatured.

OK, 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.

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.)
The five modes of laser-tissue interaction

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- Photo-chemical ablation
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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.)

At what temperature does retinal tissue start to coagulate?

65°C
Thermal effects on tissue exist on a continuum. What are the five degrees of tissue effects?
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--- Coagulation
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Which thermal mode is employed most frequently?

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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
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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
Q

- Which laser is used to perform PRP? Argon green or blue-green
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- What spot size should be used?
Diabetic Retinopathy: The Basics

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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

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
Which laser is used to perform PRP? Argon green or blue-green

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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?
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

- 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
- 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 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

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

- Reduced vision
- Reduced vision
- Reduced two words
- Loss of # to # 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**
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
- 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? Both are mediated by the two words long ciliary nerves.
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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What do accommodation and corneal sensitivity have in common? Both are mediated by the long ciliary nerves.
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? Both are mediated by the long ciliary nerves*

*OK, but what do the long ciliary nerves have to do with PRP?*
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? 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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- 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 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?
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 (i.e., just under the choroid) in the horizontal meridian. Because of their location, they are vulnerable to damage during PRP.
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

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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. Because of their location, they are vulnerable to damage during PRP.

How can one minimize the risk to the long ciliary nerves?
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?
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 horizontal meridian. Because of their location, they are vulnerable to damage during PRP.

How can one minimize the risk to the long ciliary nerves?
By avoiding the horizontal meridian during PRP
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
- Macular
- Inadvertent burn
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**
- Macular **edema**
- Inadvertent **foveal** burn
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**
- Macular **edema**
- Inadvertent **foveal** burn
- Choroidal
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**
- Macular **edema**
- Inadvertent **foveal** burn
- Choroidal **detachment**
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- Loss of 1-2 lines BCVA
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- Decreased *corneal sensitivity*
- Macular *edema*
- Inadvertent *foveal* burn
- Choroidal *detachment*
- Iatrogenic break in Bruch’s→
What are known complications of PRP?

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- Decreased *accommodation*
- Decreased *corneal sensitivity*
- Macular *edema*
- Inadvertent *foveal* burn
- Choroidal *detachment*
- Iatrogenic break in Bruch’s → *CNVM*  

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

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

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?

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- Any NVD associated with vitreous heme (VH), OR
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- Large (at least $\frac{1}{2}$ DD) area of NVE with VH
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
- Pre-proliferative: Severe or very severe NPDR + CWS

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There is another ‘informal’ justification for performing PRP that has yet to be mentioned—what is it?

The presence of extensive neovascularization of the iris (NVI), or any neovascularization of the angle (NVA)

What is the concern vis a vis extensive NVI, or NVA?

Their presence is very worrisome for the development of neovascular glaucoma (NVG), a potentially blinding condition

In very general terms, what type of glaucoma is NVG, ie, what causes the IOP elevation?

It is a type of angle-closure glaucoma
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What was the definition of SVL in the DRS?

Snellen acuity ≤ 5/200 (20/800).

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

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Extensive NVI
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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.

Proliferative diabetic retinopathy (PDR)
Diabetic Retinopathy: The Basics

There is another ‘informal’ justification for PRP that has yet to be mentioned—what is it? The presence of extensive neovascularization of the iris (NVI) or any neovascularization of the angle (NVA) is the informal 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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Proliferative diabetic retinopathy (PDR)

High-risk PDR

- Any NVD associated with vitreous heme (VH), OR
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The presence of extensive neovascularization of the iris (NVI), or any neovascularization of the angle (NVA), is the informal justification for performing PRP.

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Pupillary vascular tufts
Diabetic Retinopathy: The Basics

There is another ‘informal’ justification for PRP that has yet to be mentioned—what is it? The presence of extensive neovascularization of the iris (NVI), or any neovascularization of the angle (NVA).

My diabetic pt has a small area of NVI at the pupillary margin—should I PRP him? Not necessarily. So-called ‘tufts’ of NVI are a common occurrence in diabetics, and do not of themselves warrant PRP. That said, they do warrant a careful evaluation of the retina (consider wide-field FA to assess for extensive nonperfusion and/or subtle NVE), as well as close follow up (including frequent undilated gonioscopy to check for NVA).

In very general terms, what type of glaucoma is NVG, ie, what causes the IOP elevation? It is a type of angle-closure glaucoma.

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Diabetic Retinopathy: The Basics

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

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 $\leq 5/200$ (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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LPI?

I’m confused—if extensive NVI or NVA is concerning for the development of angle-closure glaucoma, shouldn’t I be performing laser peripheral iridotomy (LPI) rather than PRP?

No. LPI is effective only if/when the mechanism of angle closure is pupillary block. In NVA, the mechanism of angle closure is occlusion via peripheral anterior synechiae (PAS). (If you’re unclear on the difference between the two, it’s really important that you review slide-set G16 in the not-too-distant future.)
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It is an angle-closure glaucoma. What causes angle closure in NVG?

Peripheral anterior synechiae (PAS), or consecutive neovascularization of the iris (NVI) and angle (NVA).

In our discussion of high-risk PDR, we considered high-risk PDR defined as:

- Any NVD associated with vitreous heme (VH), OR
- Large (at least ¼ DD) area of NVD with or without VH, OR
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These findings predict a high risk for the development of angle-closure glaucoma.

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Classification of diabetic retinopathy

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What is the goal of PRP, ie, what are we trying to do?

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

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As stated several times now: DBR renders portions of the retina hypoxic, and hypoxic cells release VEGF, initiating a cascade of deleterious events.

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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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  - 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

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Diabetic Retinopathy: The Basics

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

**PRP has two other salutary effects on oxygen tension in the retina—what are they?**

**To answer an earlier question: Per the DRS, is PRP effective at preventing SVL?**
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What does the term high-risk PDR mean? High risk of what?

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What is the goal of PRP, i.e., what are we trying to do?

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

PRP has two other salutary effects on oxygen tension in the retina—what are they?

--By decreasing the number of living retinal cells competing for oxygen, the remaining ones receive a greater portion of the oxygen delivered to the retina

--The PRP scars facilitate the diffusion of oxygen from the choroidal circulation into the retinal space

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Diabetic Retinopathy: The Basics

What does the term high-risk PDR mean? High risk of what?
In the DRS, patients with this level of neovascularization were found to be at high risk of severe vision loss (SVL).

An important aside: The ETDRS looked at whether PRP reduced the risk of SVL in pts with mild, moderate and/or severe NPDR. It found a modest reduction in the risk among pts with severe NPDR, but not for those with mild or moderate dz. Thus, PRP is justified in severe NPDR, but not in mild or moderate dz.

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Classification of diabetic retinopathy

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  - **Mild?** Any DBR < moderate
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  - **Severe?** Presence of any 1 of the 4:2:1 rule

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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?

Per the DRS, is PRP effective at preventing SVL?
Classification of diabetic retinopathy

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  - **Mild?** Nope
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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 reduction of SVL in severe NPDR (especially in pts with Type 2 DM), but not in mild or moderate dz

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Per the DRS, is PRP effective at preventing SVL?

It is for severe NPDR (but not mild or moderate).

Diabetic Retinopathy: The Basics

To answer an earlier question: 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.*
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- Severe or very severe NPDR + CWS

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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.
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Diabetic Retinopathy: The Basics

**And finally:** With respect to DBR, what does DME stand for?

DME is addressed in detail in its own slide-set

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Diabetic Retinopathy: The Basics