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 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**

*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

*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 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.*
What are the three histological vascular derangements in DBR?

1) Pericyte loss
2) BM thickening → ↓ 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-fenestrated.
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.
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. Tight junctions between cells form the so-called...
What are the three histological vascular derangements in DBR?

1) Pericyte loss
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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 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. 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 $\rightarrow$ ↓ 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?

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

**Diabetic Retinopathy: Classification**

Do retinal vessels have an intimal lining?

No
What are the three histological vascular derangements in DBR?

1) **Pericyte** loss
2) **BM** thickening $\rightarrow$ ↓ lumen diameter
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**Do retinal vessels have an intimal lining?**
No

**Do they possess a muscular wall?**
No
What are the three histological vascular derangements in DBR?

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**Diabetic Retinopathy: Classification**

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  - No

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  - No
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Do retinal vessels have an intimal lining?
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With what nearby vascular bed do they share the lack of these features?

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What are the three histological vascular derangements in DBR?

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**Diabetic Retinopathy: Classification**

- Do retinal vessels have an intimal lining?
  - No

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  - No

- With what nearby vascular bed do they share the 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 $\rightarrow$ $\downarrow$ 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

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

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.
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1) Pericyte loss
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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
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? 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
3) 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

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
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

Which occurs first? Pericyte loss
Trypsin mount of normal retina--
low and high mag

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?

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?
What are the three histological vascular derangements in DBR?

1) Pericyte loss

2) **BM thickening** → **↓ 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?

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?
What are the three histological vascular derangements in DBR?

1) Pericyte loss

2) **BM thickening** → ↓ *lumen diameter*

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
What are the three histological vascular derangements in DBR?

1) Pericyte loss

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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?
What are the three histological vascular derangements in DBR?

1) Pericyte loss

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

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 → ↓ 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

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

Diabetic Retinopathy: Classification
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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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)
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?*
A

Diabetic Retinopathy: Classification

- 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

- 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

Two broad categories of DBR
Classification of diabetic retinopathy

- Nonproliferative diabetic retinopathy (NPDR)
  - Mild
  - Moderate
  - Severe: Any of the 4:2:1 rule
    - 15% chance of high-risk PDR within 1 year
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    - 45% chance of high-risk PDR within 1 year
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  - High-risk PDR
    - Any NVD associated with vitreous heme (VH)
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Classifciation of diabetic retinopathy

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- 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

What is the histological definition of proliferation in this context?

Diabetic Retinopathy: Classification
Diabetic Retinopathy: Classification

- Classification of diabetic retinopathy
  - Nonproliferative diabetic retinopathy (NPDR)
    - Mild
    - Moderate
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      - 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

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)
**Diabetic Retinopathy: Classification**

**Classification of diabetic retinopathy**

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

  Three basic levels of NPDR

- **Proliferative diabetic retinopathy (PDR)**

  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

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

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

Three basic levels of NPDR: Any of the 4:2:1 rule

- 15% chance of high-risk PDR within 1 year
- 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)
  - One level of concern

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**
- **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
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: Classification

Mild nonproliferative diabetic retinopathy
Classification of diabetic retinopathy

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

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**
Diabetic Retinopathy: Classification

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

**What is the 4:2:1 rule?**
- 4 retinal quadrants of...
- 2 retinal quadrants of...
- 1 retinal quadrant of...
Nonproliferative diabetic retinopathy (NPDR)

- **Mild:** Any DBR < moderate
- **Moderate:** DBR > mild but < severe
- **Severe:** Presence of any 1 of the 4:2:1 rule

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

Proliferative diabetic retinopathy (PDR)
Diabetic Retinopathy: Classification

Severe nonproliferative diabetic retinopathy: Extensive hemorrhages
Diabetic Retinopathy: Classification

Classification of diabetic retinopathy

- Nonproliferative diabetic retinopathy (NPDR)
  - **Mild:** Any DBR < moderate
  - **Moderate:** DBR > mild but < severe
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    - 4 retinal quadrants of... extensive retinal hemorrhages
    - 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)
Classifications of diabetic retinopathy

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**Proliferative diabetic retinopathy (PDR)**
Diabetic Retinopathy: Classification

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

- **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...
Classification of diabetic retinopathy

- Nonproliferative diabetic retinopathy (NPDR)
  - **Mild:** Any DBR < moderate
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    - 15% chance of high-risk PDR within 1 year
  - **Very severe:** Any 2 of the 4:2:1 rule
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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
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
  - 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
- Proliferative diabetic retinopathy (PDR)

What does IRMA stand for?
Intraretinal microvascular anomalies

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

45% chance of high-risk PDR within 1 year if any 2 of the 4:2:1 rule are present.
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
  - 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? IRMA

Think of it as neovascularization that has not broken through the ILM.

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
Diabetic Retinopathy: Classification

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

- 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

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

What is the histological definition of proliferation in this context?
Retinal neovascularization that breaks through the internal limiting membrane (ILM) hasn’t broken through
Diabetic Retinopathy: Classification

Severe nonproliferative diabetic retinopathy: 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

- Very severe: [definition]

- 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**: Any 2 of the 4:2:1 rule

Proliferative diabetic retinopathy (PDR)

- *High-risk PDR*
Classification of diabetic retinopathy

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  - Mild: Any DBR < moderate
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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

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

Per the DRS, what % of severe NPDR cases will progress to high-risk PDR in 1 year?
Classification of diabetic retinopathy

Nonproliferative diabetic retinopathy (NPDR)

- **Mild**: Any DBR < moderate
- **Moderate**: DBR > mild but < severe
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Proliferative diabetic retinopathy (PDR)

- **High-risk PDR**
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Proliferative diabetic retinopathy (PDR)
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What % of very severe NPDR cases will progress to high-risk PDR in 1 year?
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Pre-proliferative

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.
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- **Proliferative diabetic retinopathy (PDR)**

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**How should NPDR be managed?**

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- **Blood pressure**
- **Blood glucose level**

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Proliferative diabetic retinopathy (PDR)

- High-risk PDR

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Diabetic Retinopathy: Classification
Classification of diabetic retinopathy

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Proliferative diabetic retinopathy (PDR)
- **High-risk PDR**
  - definition 1
  - definition 2
  - definition 3
**Classification of diabetic retinopathy**

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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

**Definitions**

- NVD = Neovascularization of the disc
- definition 2
- definition 3
Diabetic Retinopathy: Classification

High-risk proliferative diabetic retinopathy: NVD + vitreous hemorrhage
Classification of diabetic retinopathy

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\[ DD = \text{Disc diameter} \]

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

Diabetic Retinopathy: Classification

Classification of diabetic retinopathy

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

NVE = Neovascularization elsewhere (ie, anywhere but the disc)
Classification of diabetic retinopathy

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**How big is a DD in microns?**
1500 (1.5 mm)
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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**
- That breaks through the internal limiting membrane (ILM)
  - Large (at least ½ DD) area of NVE with VH
Diabetic Retinopathy: Classification

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)

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)

(No question—proceed when ready)
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.

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Retinal neovascularization

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High-risk PDR
• Any NVD associated with vitreous heme (VH),
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Diabetic Retinopathy: Classification (No question—proceed when ready)

**What pathological state is the endpoint of decreasing lumen diameter?**
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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.

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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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Very severe:
Severe or very severe NPDR + CWS

What pathological state is the endpoint of decreasing lumen diameter?
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What does VEGF stand for?
What does VEGF stand for?
Vascular endothelial growth factor

VEGF-A165
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

VEGF-A$_{165}$

Diabetic Retinopathy: Classification
What does VEGF stand for?
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Does VEGF do anything besides grow new blood vessels?

VEGF-A\textsuperscript{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?

VEGF-A \(_{165}\)
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**How potent?**
About 10,000x more potent than histamine!

**VEGF-A**

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**Diabetic Retinopathy: Classification**
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Yes, it also is a potent vasodilator (it was known originally as vascular permeability factor)

How potent?
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?
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How does VEGF work?

VEGF-A_{165}
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How does VEGF work?
Extracellular VEGF binds to VEGF receptors (VEGFR), which are transmembrane receptor tyrosine kinase (RTK) structures.
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What does the A signify?

Diabetic Retinopathy: Classification
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.

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.

Diabetic Retinopathy: Classification
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What does VEGF-A 165 signify?
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VEGF-A

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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VEGF-A

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Why focus on isoform 165?
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**Broadly speaking, what is it?**
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**VEGF-A**

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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
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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
Diabetic Retinopathy: Classification

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And the answer was…?

We’ll get to that in a few slides.

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

First, let’s talk about laser-tissue interaction…
What are the five modes of laser-tissue interaction?
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<table>
<thead>
<tr>
<th>Mode</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Photo-chemical</td>
<td>aka photoactivation</td>
</tr>
<tr>
<td>Thermal</td>
<td></td>
</tr>
<tr>
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Diabetic Retinopathy: Classification

The five modes of laser-tissue interaction:

- Photo-chemical (aka photoactivation)
- Thermal
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Which mode is PRP an examplar of?
The five modes of laser-tissue interaction

- Photo-chemical (aka photoactivation)
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Which mode is PRP an example of?
Thermal
The five modes of laser-tissue interaction

- **Thermal**
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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?_
The five modes of laser-tissue interaction

- Photo-chemical (aka photoactivation)
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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?
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Which thermal effect is employed most frequently?

**Diabetic Retinopathy: Classification**

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

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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

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.)
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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?
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What spot size should be used?
Diabetic Retinopathy: Classification

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

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

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How can one minimize the risk to the long ciliary nerves?
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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? 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
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- Decreased accommodation
- Decreased corneal sensitivity
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- Choroidal
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- Choroidal **detachment**
- Iatrogenic break in Bruch’s
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- Macular edema
- Inadvertent foveal burn
- Choroidal detachment
- Iatrogenic break in Bruch’s → CNVM

(CNVM = Choroidal neovascular membrane)
Diabetic Retinopathy: Classification

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

Snellen acuity ≤ 5/200 (20/800)

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

Indeed it is--it reduces the risk by 50% at 5 years post-treatment
Diabetic Retinopathy: Classification

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).

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

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).

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.
Diabetic Retinopathy: Classification

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?

Proliferative diabetic retinopathy (PDR)

High-risk PDR

- Any NVD associated with vitreous heme (VH), OR
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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)

To answer an earlier question: Per the DRS, is PRP effective at preventing SVL?
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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. 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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Diabetic Retinopathy: Classification

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
    - 45% chance of high-risk PDR within 1 year

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

- Proliferative diabetic retinopathy (PDR)
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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?

ET early

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

Nonproliferative diabetic retinopathy (NPDR)

- **Mild?** No
- **Moderate?** No
- **Severe?** Yes!

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
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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.

Per the DRS, is PRP effective at preventing SVL? It is for severe NPDR (but not mild or moderate).
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Diabetic Retinopathy: Classification

Classification of diabetic retinopathy

- Nonproliferative diabetic retinopathy (NPDR)
  
  **Mild? Nope**
  
  **Moderate? Nope**
  
  **Severe? Yes!**

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.

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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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- **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?

DME can occur at any level of NPDR or PDR

Diabetic Retinopathy: Classification
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And finally: With respect to DBR, what does DME stand for? 
Diabetic macular edema

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

Where does DME fit into this classification scheme?

**Diabetic Macular Edema (DME)**

DME can occur at any level of NPDR or PDR.
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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: Classification