What are the three histological vascular derangements in DBR?

1) Pericyte loss

2) BM thickening

3) ↓ lumen diameter
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

BM = Basement membrane

cell type

diff dell type
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$BM = Basement\ membrane$
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*With respect to the structure of retinal arterioles and capillaries, how are pericytes and endothelial cells related to one another?*
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The cell type cells line the lumen of the vessel. They are surrounded by their BM.
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The endothelial cells line the lumen of the vessel. They are surrounded by their BM.
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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.
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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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**Do retinal vessels have an intimal lining?**
No

Do they possess a muscular wall?
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?

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

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

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Diabetic Retinopathy: Classification
What are the three histological vascular derangements in DBR?

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

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

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 $\rightarrow$ ↓ 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

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

In the context of diabetic retinopathy, pericytes 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
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That this is known as the inner blood-retina barrier implies the existence of what?
An outer blood-retina barrier

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

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

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

Which occurs first?
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*
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

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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 $\rightarrow \downarrow$ lumen diameter

3) Loss of endothelial barrier function

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

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

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

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What pathological state is the endpoint of decreasing lumen diameter?
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Retinal ischemia leads to what pathological state?
Hypoxia of the affected retinal cells
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What pathological state is the endpoint of decreasing lumen diameter?
Occlusion of the retinal vessel

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

Hypoxic retinal cells release a signaling molecule that is central to the pathogenesis of DBR. What is that signaling molecule?
What are the three histological vascular derangements in DBR?

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

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

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

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

Three basic levels of NPDR
Classification of diabetic retinopathy

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

- Proliferative diabetic retinopathy (PDR)

Three basic levels of NPDR
Classification of diabetic retinopathy

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

Proliferative diabetic retinopathy (PDR)

Three basic levels of NPDR

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

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

Three basic levels of NPDR

Proliferative diabetic retinopathy (PDR)

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

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

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

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

Very severe

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
Classification of diabetic retinopathy

Nonproliferative diabetic retinopathy (NPDR)

- **Mild:** Any DBR < moderate
- **Moderate**
- **Severe**
- **Very severe:** Any 2 of the 4:2:1 rule
  - 15% 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
  - 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
  - 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

- 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**: Any 2 of the 4-2-1 rule
  - 15% chance of high-risk PDR within 1 year
- **Very severe**: Any 3 of the 4-2-1 rule
  - 45% chance of high-risk PDR within 1 year

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

- **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: 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
  - 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...
Diabetic Retinopathy: Classification

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
  - 45% 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

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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... 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

- 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)

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- **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

Very severe: Any 2 of the 4:2:1 rule

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 untreated retinal microvascular abnormalities
- Any 2 of...extensive retinal hemorrhages
- Any 1 of...venous beading
- Any 1 of...untreated retinal microvascular abnormalities

What does IRMA stand for?

Intraretinal microvascular anomalies
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
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- **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 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 4:2:1 rule?
  - 4 retinal quadrants of extensive retinal hemorrhages
  - 2 retinal quadrants of venous beading
  - 1 retinal quadrant of IRMA

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**Diabetic Retinopathy: Classification**

- **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
  - **Pre-proliferative**

- **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
  - 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)

- **IRMA**: Intraretinal microvascular anomalies
  - What does IRMA stand for?
  - 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 ILM
Diabetic Retinopathy: Classification

Severe nonproliferative diabetic retinopathy: IRMA
Classification of diabetic retinopathy

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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
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Proliferative diabetic retinopathy (PDR)

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

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Proliferative diabetic retinopathy (PDR)

- **High-risk PDR**

Next Q

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

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Pre-proliferative

Proliferative diabetic retinopathy (PDR)

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

Diabetic Retinopathy: Classification
Diabetic Retinopathy: Classification

Classification of diabetic retinopathy

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Proliferative diabetic retinopathy (PDR)

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

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

- **Nonproliferative diabetic retinopathy (NPDR)**
  - *Mild:* Any DBR < moderate
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  - *Severe:* Presence of any 1 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

*DD = Disc diameter*
High-risk proliferative diabetic retinopathy:
Extensive NVD
Classification of diabetic retinopathy

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- **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)
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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 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**

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Pre-proliferative: Severe or very severe NPDR + CWS

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

- 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)
**Classification of diabetic retinopathy**

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**Diabetic Retinopathy: Classification**

What pathological state is the endpoint of decreasing lumen diameter?

- Occlusion of the retinal vessel

Vessel occlusion leads to what pathological event?

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

What is the histological definition of proliferation in this context?

- **Retinal neovascularization**
  - Neovascularization that breaks through the internal limiting membrane (ILM)

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

- 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)

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.
Diabetic Retinopathy: Classification

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

What is the histological definition of proliferative diabetic retinopathy (PDR)?

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

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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.

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

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Diabetic Retinopathy: Classification
Classification of diabetic retinopathy

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

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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 tissue 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.

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:

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Diabetic Retinopathy: Classification
What does VEGF stand for?

**VEGF-A**165
What does VEGF stand for?
Vascular endothelial growth factor
What does VEGF stand for?
Vascular endothelial growth factor

Broadly speaking, what is it?

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
What does VEGF stand for?
Vascular endothelial growth factor

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

VEGF-A\textsubscript{165}
What does VEGF stand for?
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Does VEGF do anything besides grow new blood vessels?
Yes, it also is a potent vasodilator (it was known originally as vascular permeability factor)

VEGF-A\textsubscript{165}
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How potent?

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

VEGF-A165
What does \textbf{VEGF} stand for? Vascular endothelial growth factor.

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

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

\textbf{How potent?} About 10,000x more potent than histamine!

\textbf{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!

\textit{(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\textsubscript{165}
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Extracellular VEGF binds to VEGF receptors (VEGFR), which are transmembrane receptor tyrosine kinase (RTK) structures.
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VEGF-A

What does the A signify?
VEGF is not a single entity—a number of similar-but-different proteins comprise the ‘VEGF family.’ These are differentiated as VEGF-A through VEGF-F. (One family member, placental growth factor [PlGF], is the exception to the naming rule.) When the term VEGF is used in the ophthalmology literature without a subfamily designation, it is understood to mean VEGF-A.
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What does the A signify?

What does 165 signify?

VEGF-A¹⁶⁵
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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.
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
  - 15% chance of high-risk PDR within 1 year
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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**
  - Large (at least ½ DD) area of NVE with VH

What landmark clinical trial provided this system of PDR classification?

The Diabetic Retinopathy Study (DRS)

What question did the DRS seek to answer?

'Is PRP effective in treating PDR/severe NPDR?'

And the answer was…?

We’ll get to that in a few slides
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- What landmark clinical trial provided this system of PDR classification?
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- What does PRP stand for in this context?
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What landmark clinical trial provided this system of PDR classification?
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What are the five modes of laser-tissue interaction?
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<tr>
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<tbody>
<tr>
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</tr>
<tr>
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*Are these thrown up here rando, or are they in an order of some sort?*
What are the five modes of laser-tissue interaction?

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Are these thrown up here rando, or are they in an order of some sort?
Not rando. Although there is some overlap (especially between plasma-induced ablation and photodisruption), overall these are listed in order of increasing intensity.
What are the five modes of laser-tissue interaction?

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Which mode is PRP an examplar of?
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Diabetic Retinopathy: Classification

The five modes of laser-tissue interaction:

- Photochemical (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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The five modes of laser-tissue interaction:

- Thermal effects on tissue exist on a continuum. What are the five degrees (see what I did there?) of tissue effects?
  - Hyperthermia
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## Diabetic Retinopathy: Classification

### The five modes of laser-tissue interaction:

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

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--Hyperthermia
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Thermal effects on tissue exist on a continuum. What are the five degrees?  
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*What does it mean to say that tissue has ‘coagulated’?*

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

Diabetic Retinopathy: Classification
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What does it mean to say that tissue has ‘coagulated’?

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OK, what does it mean to say a protein has been ‘denatured’?

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

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Can you give an example of protein denaturation?

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**Thermal**

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

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**Can you give an example of protein denaturation?**

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At what temperature does retinal tissue start to coagulate?

65°C

Diabetic Retinopathy: Classification
The five modes of laser-tissue interaction:

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*The five modes of laser-tissue interaction:*

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For more info on lasers, see slide-set FELT26

At what temperature does retinal tissue start to coagulate? 65°C
Which laser is used to perform PRP?
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How many shots constitute a full compliment of PRP?
Diabetic Retinopathy: Classification

- Which laser is used to perform PRP? Argon green or blue-green
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How much power?
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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
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- 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? 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: Classification

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.

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

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

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

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

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

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

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

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

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

- Reduced vision
- Reduced vision
- Reduced vision
- Loss of # to # lines BCVA

Diabetic Retinopathy: Classification

Effects on vision
What are known complications of PRP?

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

Diabetic Retinopathy: Classification

Effects on vision
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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- 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?

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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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Diabetic Retinopathy: Classification
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.

OK, but what do the long ciliary nerves have to do with PRP?
What are known complications of PRP?

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

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

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

- Reduced peripheral vision
- Reduced color vision
- Reduced contrast sensitivity
- Loss of 1-2 lines BCVA
- 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.
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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How can one minimize the risk to the long ciliary nerves? By avoiding the horizontal meridian during PRP.
Q

Diabetic Retinopathy: Classification

- What are known complications of PRP?
  - Reduced **peripheral** vision
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  - Reduced **contrast sensitivity**
  - Loss of 1-2 lines BCVA
  - Decreased **accommodation**
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  - Macular
  - Inadvertent burn
What are known complications of PRP?

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- Choroidal detachment
- Iatrogenic break in Bruch’s → CNVM

(CNVM = Choroidal neovascular membrane)
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What does the term high-risk PDR mean? High risk of what?

- **High-risk PDR**
  - Any NVD associated with vitreous heme (VH), OR
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Proliferative diabetic retinopathy (PDR)

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?

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

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What is the therapeutic rationale? Why kill the peripheral retina?

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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.

**To answer an earlier question: Per the DRS, is PRP effective at preventing SVL?** Indeed it is—*it reduces the risk by 50%* at 5 years post-treatment

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

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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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**Classification of diabetic retinopathy**

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

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

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Classification of diabetic retinopathy

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- **Mild?** **Nope**
- **Moderate?** **Nope** mild but < severe
- **Severe?** **Yes!** presence of any 1 of the 4:2:1 rule

Proliferative diabetic retinopathy (PDR)

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It found that PRP resulted in a modest reduction of SVL in severe NPDR (especially in pts with Type-2 DM), but not in mild or moderate dz.

Per the DRS, is PRP effective at preventing SVL?

It is for severe NPDR (but not mild or moderate).
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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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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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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Where does DME fit into this classification scheme?

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DME is addressed in detail in its own slide-set

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Diabetic Retinopathy: Classification