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

Of the ~30M or so adults with full-blown diabetes, what proportion don’t even know they have it?
About 25%!
How many American adults are diabetic or pre-diabetic?
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About 25%!

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

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

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

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

Of those diabetics with retinopathy, what proportion have vision-threatening retinopathy?
Again, about a third
Diabetic Retinopathy: The Basics

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

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

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

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

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

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

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

Per the WESDR, what proportion of Type I diabetics have at least some retinopathy after 20 years?
Worldwide, what proportion of diabetics have retinopathy?
About a third

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

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

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

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

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

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

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

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

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Diabetic Retinopathy: The Basics

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

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

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

*Per the WESDR, what proportion of Type 1 diabetics have proliferative retinopathy (PDR) after 20 years? 25%*

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

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

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

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

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Diabetic Retinopathy: The Basics

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

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

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

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

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

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

1) Pericyte loss
2) BM thickening → ↓ lumen diameter
3)
What are the three histological vascular derangements in DBR?

1) Pericyte loss

2) BM thickening $\rightarrow$ ↓ lumen diameter

3) Loss of endothelial barrier function

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

1) **Pericyte loss**

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*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 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
3) Loss of endothelial barrier function

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

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

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

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

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

The endothelial cells line the lumen of the vessel. They are surrounded by their BM. They are nonfenestrated.
What are the three histological vascular derangements in DBR?

1. Pericyte loss
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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?

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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. 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?

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Do retinal vessels have an intimal lining?
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Do they possess a muscular wall?
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With what nearby vascular bed do they share the lack of these features?

---

With 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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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
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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?

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?

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

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

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 $\rightarrow$ ↓ 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 **three words** 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

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 → ↓ lumen diameter
3) Loss of endothelial barrier function
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 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 $\rightarrow$ ↓ lumen diameter

3) Loss of endothelial barrier function

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

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?
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?

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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
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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?
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

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 \(\rightarrow\) \(\downarrow\) 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 → ↓ lumen diameter
3) Loss of endothelial barrier function

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

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

Two broad categories of DBR
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

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

  - 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)
  - 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

What is the histological definition of proliferation in this context?
Classification of diabetic retinopathy

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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

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)**
Classification of diabetic retinopathy

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

Three basic levels of NPDR

One more level (not universally used)

Proliferative diabetic retinopathy (PDR)
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

  Three basic levels of NPDR

  Very severe

  One more level (not universally used)

- 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

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

Nonproliferative diabetic retinopathy (NPDR)

- Mild
- Moderate
- Severe

- Very severe

Proliferative diabetic retinopathy (PDR)

- High-risk PDR
Classification of diabetic retinopathy

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

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

Nonproliferative diabetic retinopathy (NPDR)

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

- Very severe

Proliferative diabetic retinopathy (PDR)

- High-risk PDR
Mild nonproliferative diabetic retinopathy
Classification of diabetic retinopathy

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

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?

- 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:

Proliferative diabetic retinopathy (PDR)

What is the 4:2:1 rule?

- 4 retinal quadrants of...
- 2 retinal quadrants of...
- 1 retinal quadrant of...

Diabetic Retinopathy: The Basics
Classification of diabetic retinopathy

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

- Proliferative diabetic retinopathy (PDR)

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

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

- Proliferative diabetic retinopathy (PDR)

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

Diabetic Retinopathy: The Basics
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

4:2:1 rule:
- 4 retinal quadrants of...extensive retinal hemorrhages
- 2 retinal quadrants of...venous beading
- 1 retinal quadrant of...

Proliferative diabetic retinopathy (PDR)
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
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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...
Classification of diabetic retinopathy

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

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

45% chance of high-risk PDR within 1 year

- Pre-proliferative
  - Severe

- 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
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  - **Severe:** Presence of any 1 of the 4:2:1 rule
    - 15% chance of high-risk PDR within 1 year
    - **4:2:1 rule**
      - 4 retinal quadrants of extensive retinal hemorrhages
      - 2 retinal quadrants of venous beading
      - 1 retinal quadrant of IRMA (Intraretinal microvascular anomalies)

- **Proliferative diabetic retinopathy (PDR)**

**What does IRMA stand for?**
Intraretinal microvascular anomalies
Classification of diabetic retinopathy

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

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**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.
Classification of diabetic retinopathy

Nonproliferative diabetic retinopathy (NPDR)
- Mild: Any DBR < moderate
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  - 45% chance of high-risk PDR within 1 year

Proliferative diabetic retinopathy (PDR)

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

Severe nonproliferative diabetic retinopathy:
IRMA

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

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

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

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- High-risk PDR
Classification of diabetic retinopathy

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

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

Nonproliferative diabetic retinopathy (NPDR)

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- **High-risk PDR**
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
- **Pre-proliferative**: Severe or very severe NPDR + CWS

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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- Severe or very severe NPDR + CWS

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Proliferative diabetic retinopathy (PDR)

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

- **Proliferative diabetic retinopathy (PDR)**

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- There is a clear role for controlling three systemic risk factors:
  - Blood glucose
  - Blood pressure
  - Lipid profile

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

- --
- --

**Diabetic Retinopathy: The Basics**
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

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
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Classification of diabetic retinopathy

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Moderate: DBR > mild but < severe

Severe: Presence of any 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

How should NPDR be managed?

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

- Blood glucose
- Blood pressure
- Lipid profile

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

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

Diabetic Retinopathy: The Basics
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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- **Very severe**: Any 2 of the 4:2:1 rule
  - 45% chance of high-risk PDR within 1 year

Proliferative diabetic retinopathy (PDR)

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

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

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

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

\[ \text{definition 3} \]
Diabetic Retinopathy: The Basics

High-risk proliferative diabetic retinopathy:  
Extensive NVD
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
  - 45% chance of high-risk PDR within 1 year

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

\[\text{NVE} = \text{Neovascularization elsewhere (ie, anywhere but the disc)}\]
Diabetic Retinopathy: The Basics

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

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

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

Nonproliferative diabetic retinopathy (NPDR)

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

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How big is a DD in microns? 1500 (1.5 mm)
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

**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: The Basics

Classification of diabetic retinopathy

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

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

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

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

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

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

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

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

Diabetic Retinopathy: The Basics

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

Vessel occlusion leads to what pathological event?
- To summarize: Occlusive vasculopathy secondary to diabetic derangements produces retinal ischemia.

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

Retinal neovascularization that breaks through the internal limiting membrane (ILM)
- 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?
    - To summarize: Occlusive vasculopathy secondary to diabetic derangements produces retinal ischemia.
  - What is the histological definition of proliferation in this context?
    - Retinal neovascularization
Classification of diabetic retinopathy

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

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

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

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

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

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

High-risk PDR

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

Severe or very severe NPDR + CWS

Diabetic Retinopathy: The Basics
**Classification of diabetic retinopathy**

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**Diabetic Retinopathy: The Basics**

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

- Vessel occlusion leads to what pathological event?

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

---

**What is the histological definition of proliferation in this context?**

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

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

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.
What does VEGF stand for?

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

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

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

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

Does VEGF do anything besides grow new blood vessels?

VEGF-A₁₆₅
What does VEGF stand for? Vascular endothelial growth factor.

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

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

VEGF-A_{165}
What does VEGF stand for?
Vascular endothelial growth factor

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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)

How potent?

VEGF-A

Diabetic Retinopathy: The Basics
What does VEGF stand for?
Vascular endothelial growth factor

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

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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)

How potent?
About 10,000x more potent than histamine!

VEGF-A_{165}

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

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

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

How does VEGF work?

VEGF-A

Diabetic Retinopathy: The Basics
What does VEGF stand for?
Vascular endothelial growth factor

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How does VEGF work?
Extracellular VEGF binds to VEGF receptors (VEGFR), which are transmembrane receptor tyrosine kinase (RTK) structures.
**What does VEGF stand for?**
Vascular endothelial growth factor

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

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 sub-family designation, it is understood to mean VEGF-A.
**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?**
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**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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VEGF-A 165

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

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

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

- Nonproliferative diabetic retinopathy (NPDR)
  - **Mild**: Any DBR < moderate
  - **Moderate**: DBR > mild but < severe
  - **Severe**: Presence of any 1 of the 4:2:1 rule
    - 15% chance of high-risk PDR within 1 year
  - **Very severe**: Any 2 of the 4:2:1 rule
    - 45% chance of high-risk PDR within 1 year
- 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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And the answer was... We'll get to that in a few slides

What does PRP stand for in this context? Panretinal photocoagulation
Classification of diabetic retinopathy

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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
First, let’s talk about laser-tissue interaction…
What are the five modes of laser-tissue interaction?
Diabetic Retinopathy: The Basics

What are the five modes of laser-tissue interaction?

Photochemical
aka photoactivation

Thermal

Photoablation

Plasma-induced ablation

Photo-disruption
aka plasma-induced disruption
Which mode is PRP an exemplar of?
Which mode is PRP an exemplar of?
Thermal
Thermal effects on tissue exist on a continuum. What are the five degrees (see what I did there?) of tissue effects?
Thermal effects on tissue exist on a continuum. What are the five degrees (see what I did there?) of tissue effects?

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

**Thermal**

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

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

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

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

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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

Diabetic Retinopathy: The Basics
Thermal effects on tissue exist on a continuum. What are the five degrees?

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Which thermal Coagulation

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

It means the proteins have been denatured.
Thermal effects on tissue exist on a continuum. What are the five degrees?

--- Hyperthermia

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

It means the proteins have been denatured.

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

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

Consider egg albumin. In its native state, it’s a clear liquid. But if sufficient heat is applied, it becomes a white solid. (And if sufficient salsa is applied to the white solid, it becomes delish.)
The five modes of laser-tissue interaction

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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.

Which thermal? Coagulation
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Can you give an example of protein denaturation?

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Which thermal mode are we focusing on today? Coagulation

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At what temperature does retinal tissue start to coagulate?
65°C

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For more info on lasers, see slide-set FELT26
Which laser is used to perform PRP?
Which laser is used to perform PRP?
Argon **green** or **blue-green**
Which laser is used to perform PRP? Argon green or blue-green
How many shots constitute a full compliment of PRP?
Which laser is used to perform PRP? 
Argon green or blue-green

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

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

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

What spot size should be used? 500 \( \mu \text{m} \)
- Which laser is used to perform PRP? Argon green or blue-green
- How many shots constitute a full compliment of PRP? About 1200-1400
- What spot size should be used? 500 μm
- How much power?
Q/A

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

How many shots constitute a full compliment of PRP?
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What spot size should be used?
500 μm

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

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

How much distance between burns?
Diabetic Retinopathy: The Basics

- Which laser is used to perform PRP? Argon green or blue-green
- How many shots constitute a full compliment of PRP? About 1200-1400
- What spot size should be used? 500 μm
- How much power? Enough to produce a gray or light cream-colored burn
- How much distance between burns? About half a burn’s width
Diabetic Retinopathy: The Basics

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 μm

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

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

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

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

What spot size should be used? 500 μm

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

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

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

- Reduced vision
- Reduced vision
- Reduced vision
- Loss of lines BCVA

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: The Basics

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 parasymptathetic function
- Decreased *two words*
What are known complications of PRP?

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

What do accommodation and corneal sensitivity have in common?
Q/A

What are known complications of PRP?

- Reduced peripheral vision
- Reduced color vision
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- Loss of 1-2 lines BCVA
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What do accommodation and corneal sensitivity have in common? Both are mediated by the long ciliary nerves.
What are known complications of PRP?
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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
- 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?

- 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?

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

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

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

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

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

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

How can one minimize the risk to the long ciliary nerves?
What are known complications of PRP?

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

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

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

*How can one minimize the risk to the long ciliary nerves?*
By avoiding the horizontal meridian during PRP
What are known complications of PRP?

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

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

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

- Reduced peripheral vision
- Reduced color vision
- Reduced contrast sensitivity
- Loss of 1-2 lines BCVA
- Decreased accommodation
- Decreased corneal sensitivity
- Macular edema
- Inadvertent foveal burn
- Choroidal detachment
What are known complications of PRP?

- Reduced **peripheral** vision
- Reduced **color** vision
- Reduced **contrast sensitivity**
- Loss of 1-2 lines BCVA
- Decreased **accommodation**
- Decreased **corneal sensitivity**
- Macular **edema**
- Inadvertent **foveal** burn
- Choroidal **detachment**
- Iatrogenic break in Bruch’s
What are known complications of PRP?

- Reduced peripheral vision
- Reduced color vision
- Reduced contrast sensitivity
- Loss of 1-2 lines BCVA
- Decreased accommodation
- Decreased corneal sensitivity
- Macular edema
- Inadvertent foveal burn
- Choroidal detachment
- Iatrogenic break in Bruch’s

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

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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
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- **Mild:** Any DBR < moderate
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- **Severe:** Presence of any 1 of the 4:2:1 rule
  - 15% chance of high-risk PDR within 1 year
- **Very severe:** Any 2 of the 4:2:1 rule
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Diabetic Retinopathy: The Basics

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

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Diabetic Retinopathy: The Basics

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

**What is the goal of PRP, ie, what are we trying to do?**
The goal is to kill most of the cells in the peripheral retina.

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.

- **High-risk PDR**
  - Any NVD associated with vitreous heme (VH), **OR**
  - Large (at least \( \frac{1}{4} \) DD) area of NVD with or without VH, **OR**
  - Large (at least \( \frac{1}{2} \) DD) area of NVE with VH.
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What is the goal of PRP, ie, what are we trying to do?
The goal is to kill most of the cells in the peripheral retina.

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

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Diabetic Retinopathy: The Basics

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

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

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

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Classification of diabetic retinopathy

Nonproliferative diabetic retinopathy (NPDR)

- **Mild**?
  - Any DBR < moderate

- **Moderate**?
  - DBR > mild but < severe

- **Severe**?
  - Presence of any 1 of the 4:2:1 rule
  - 15% chance of high-risk PDR within 1 year

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

Proliferative diabetic retinopathy (PDR)

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

Diabetic Retinopathy: The Basics

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

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

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.
**Classification of diabetic retinopathy**

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

**Classification of diabetic retinopathy**

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Classification of diabetic retinopathy

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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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Pre-proliferative: Severe or very severe NPDR + CWS

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

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

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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) can occur at any level of NPDR or PDR.
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**DME is addressed in detail in its own slide-set**

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