眼睛的解剖學與生理學
EYE ANATOMY AND PHYSIOLOGY

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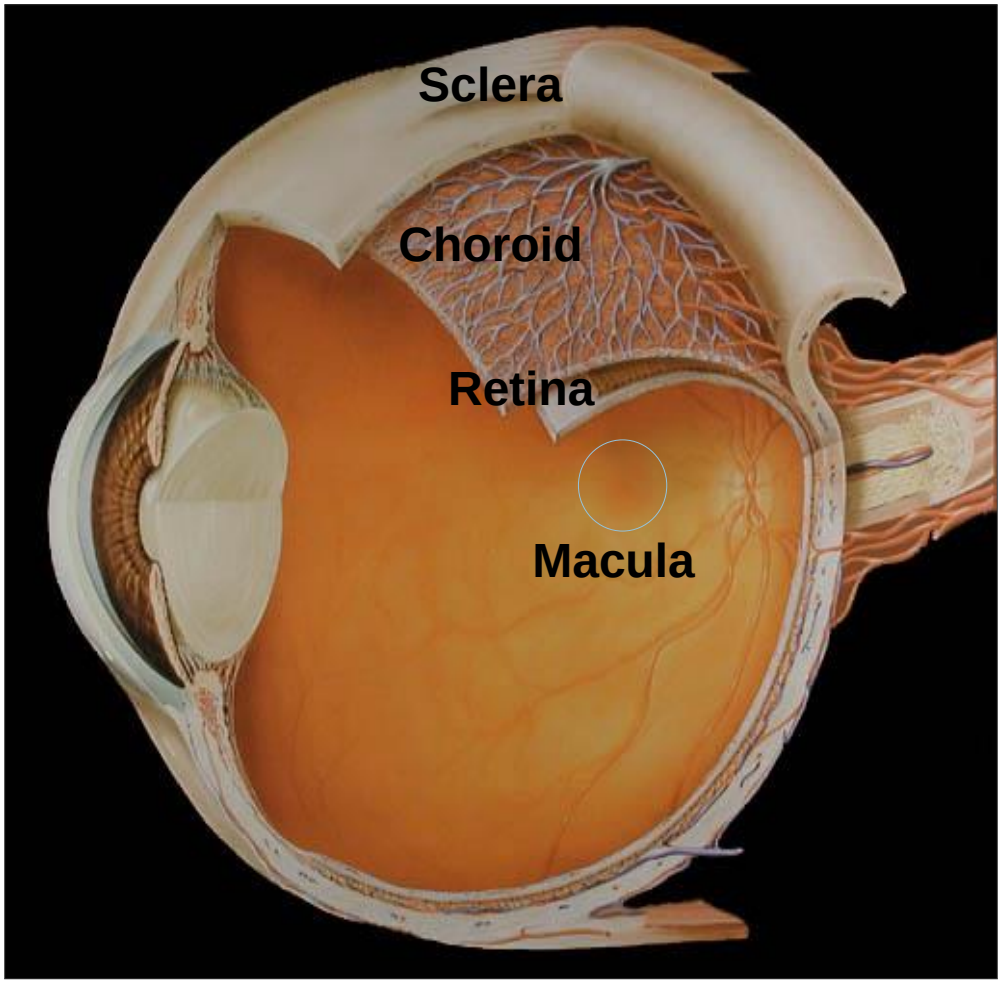
EYLEA®
(aflibercept ophthalmic solution)

視覺的形成就像照相機顯影一樣

- 我們可將眼睛的結構想像成照相機
  - 光圈 (瞳孔- pupil)
  - 鏡頭 (角膜- cornea & 水晶體- lens)
  - 底片 (視網膜- retina)
- 視覺的形成: 透過光線在物體上反射的傳導到眼睛，經過角膜與水晶體將光線聚集，最終光線聚焦呈像於視網膜。
- 位於視網膜中央區域我們稱之為黃斑部- macula, 其直徑約為 5.5 mm, 此區域負責中央視力。
- 位於黃斑部中央區域名為中心凹-fovea, 此區域負責高解析度的中央視力。

Eye structure



Macula is responsible for central fine vision

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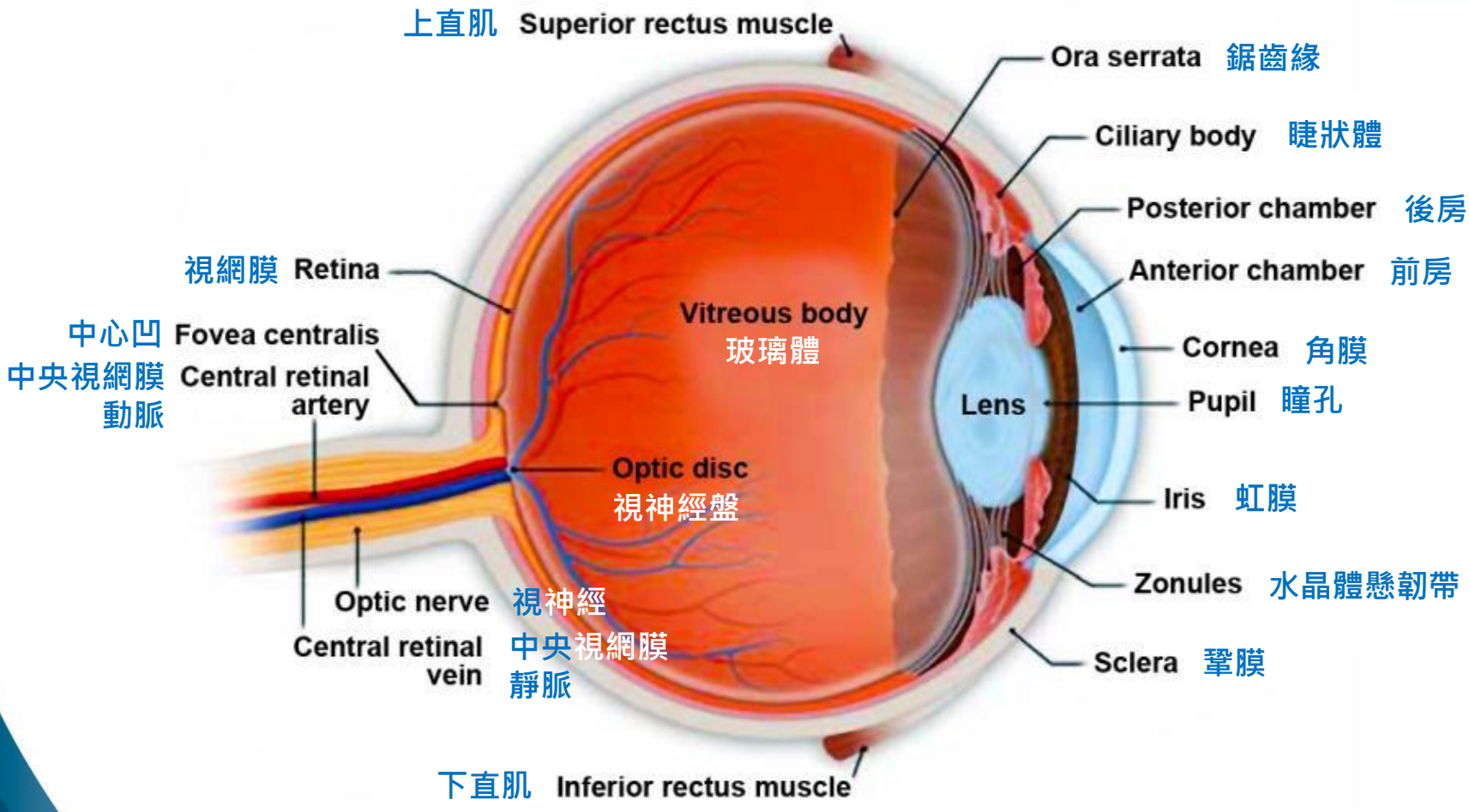
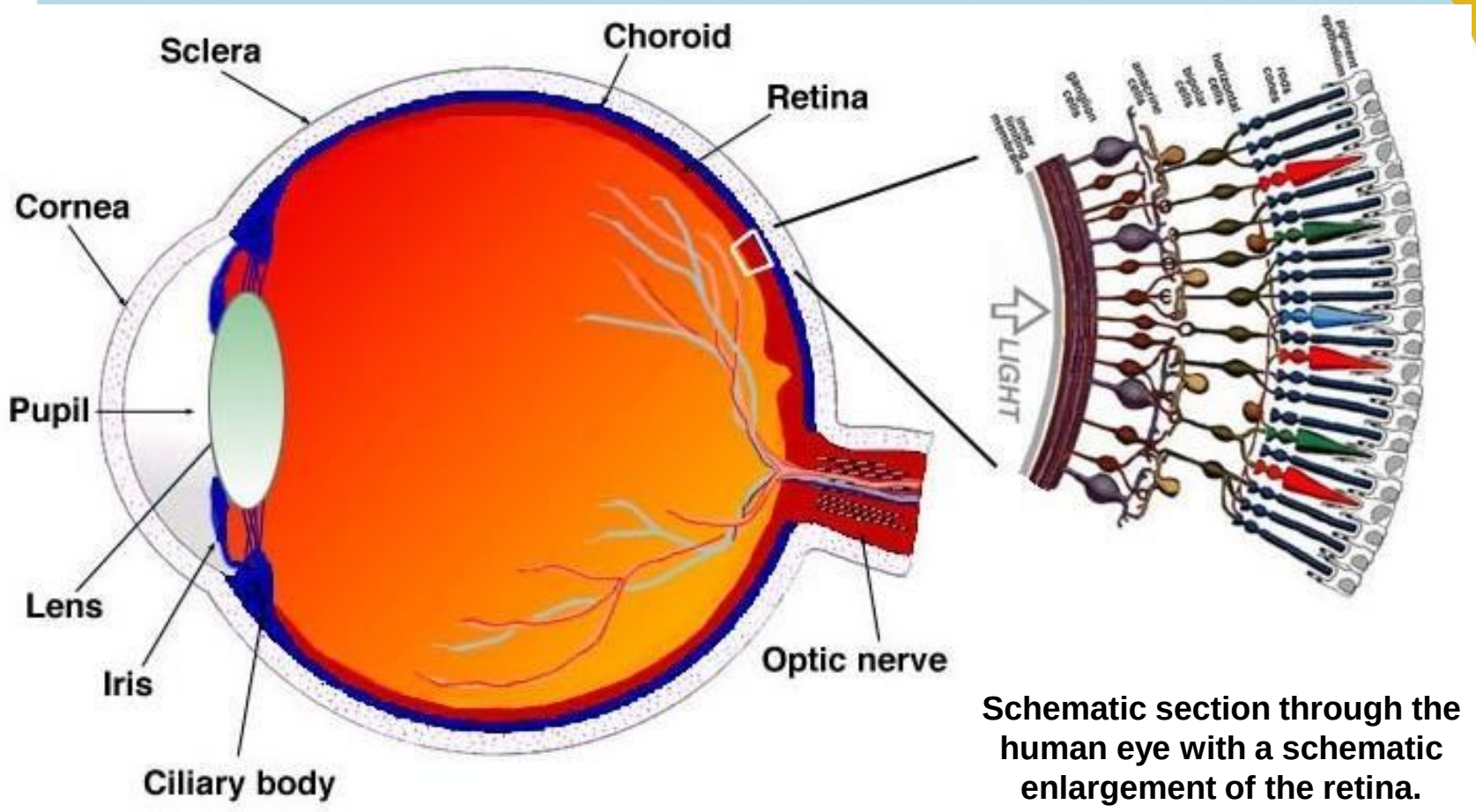
CORETRAINING

一般眼球解剖學



The Human Retina



Schematic section through the human eye with a schematic enlargement of the retina.

The Organization of the Retina and Visual System. **Kolb H, Fernandez E, Nelson R. University of Utah Health Sciences Center, 2011.**

The Human Retina

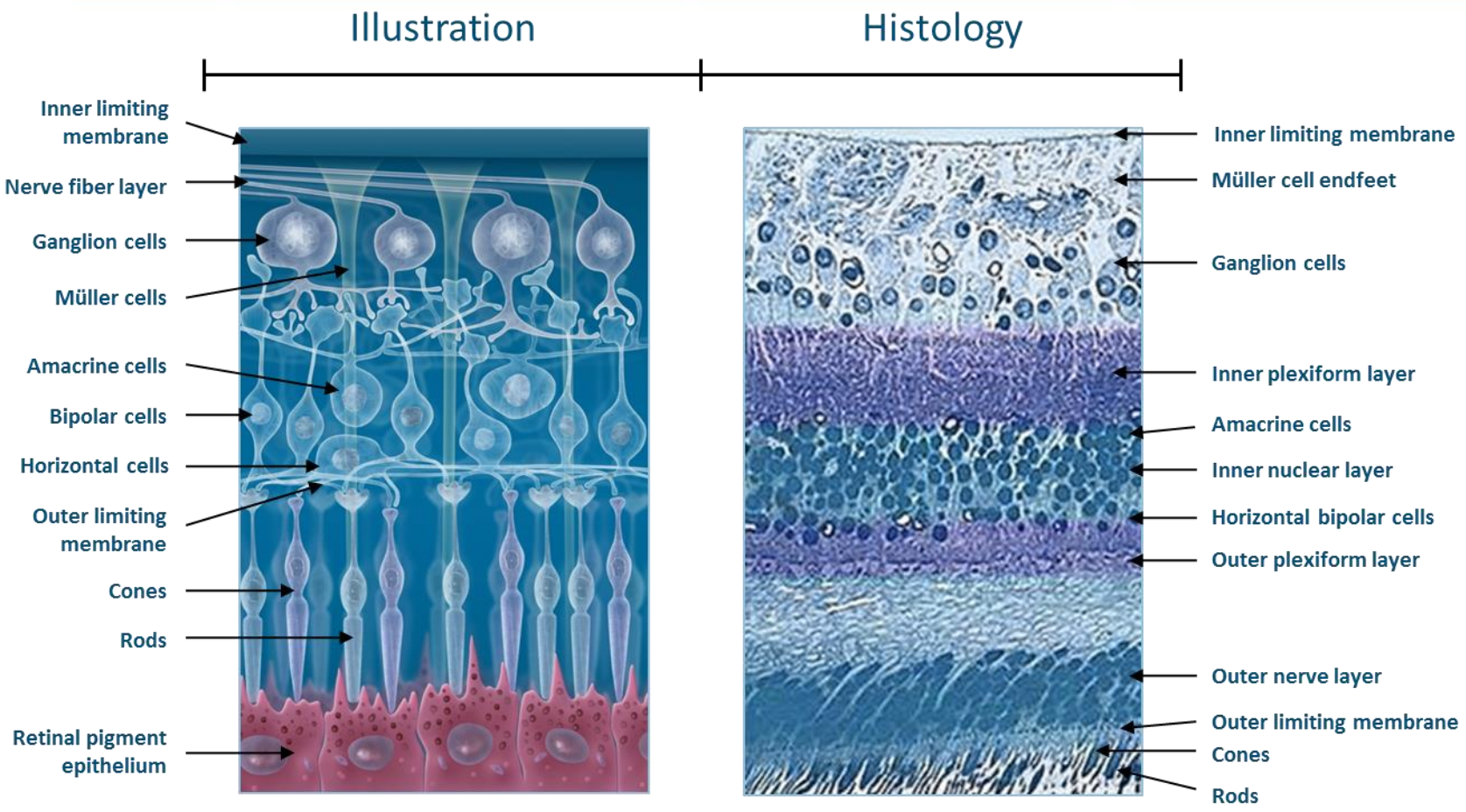


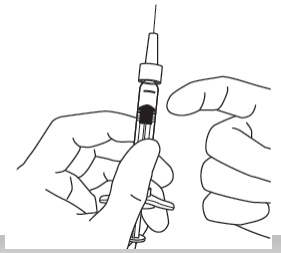
Illustration courtesy of Bayer HealthCare

Micrograph image adapted from Kolb H. *The Organization of the Retina and Visual System.* 2012.

1. Kolb H. Simple anatomy of the retina. In: *The Organization of the Retina and Visual System.* 2012.

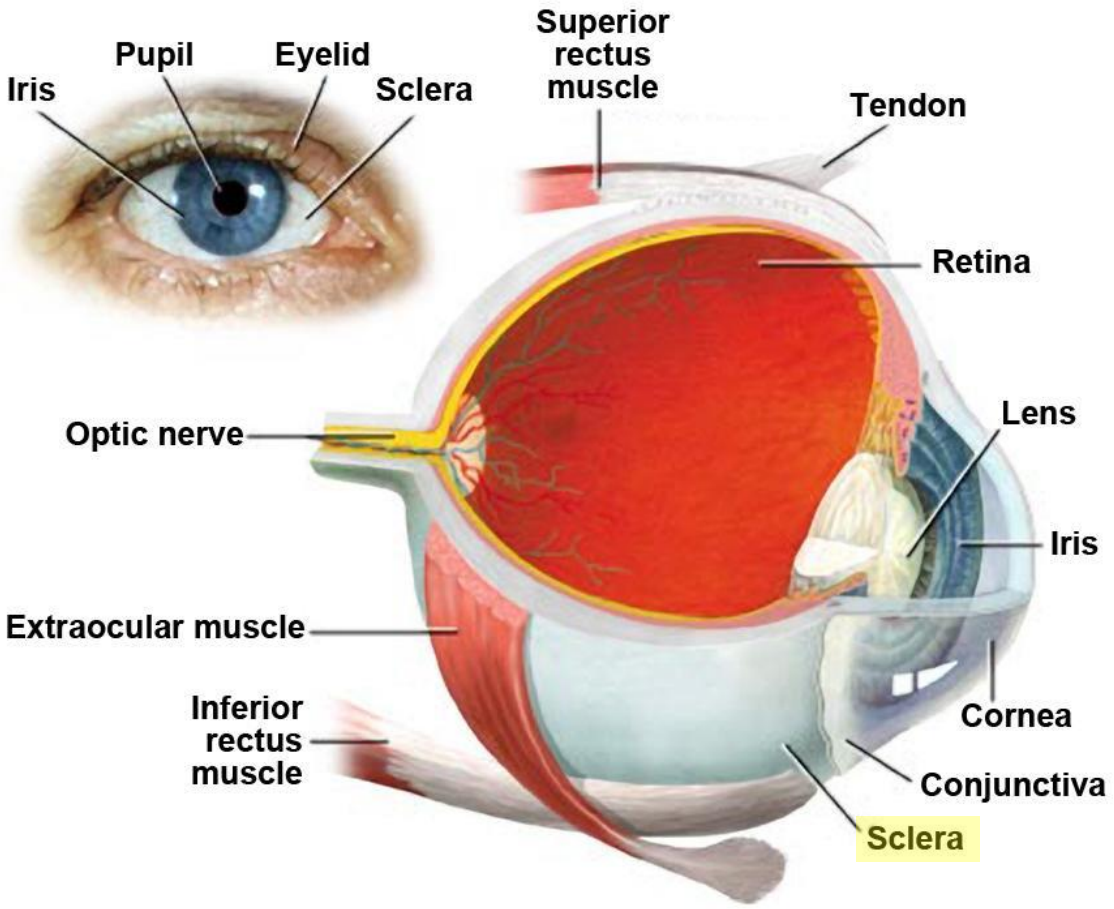
“Back of the Eye Disease”

Major Front of Eye Conditions	Major Back of the Eye Conditions
• Allergic Conjunctivitis • Dry Eye • Glaucoma • Cataract • Anterior Uveitis • Infection • Inflammation	Macular Disease – Dry AMD – **wAMD** – **DME** – **RVO** • Diabetic Retinopathy • Vitreomacular Adhesion • Cystoid Macular Edema (CME) • Detached Retina • Posterior Uveitis

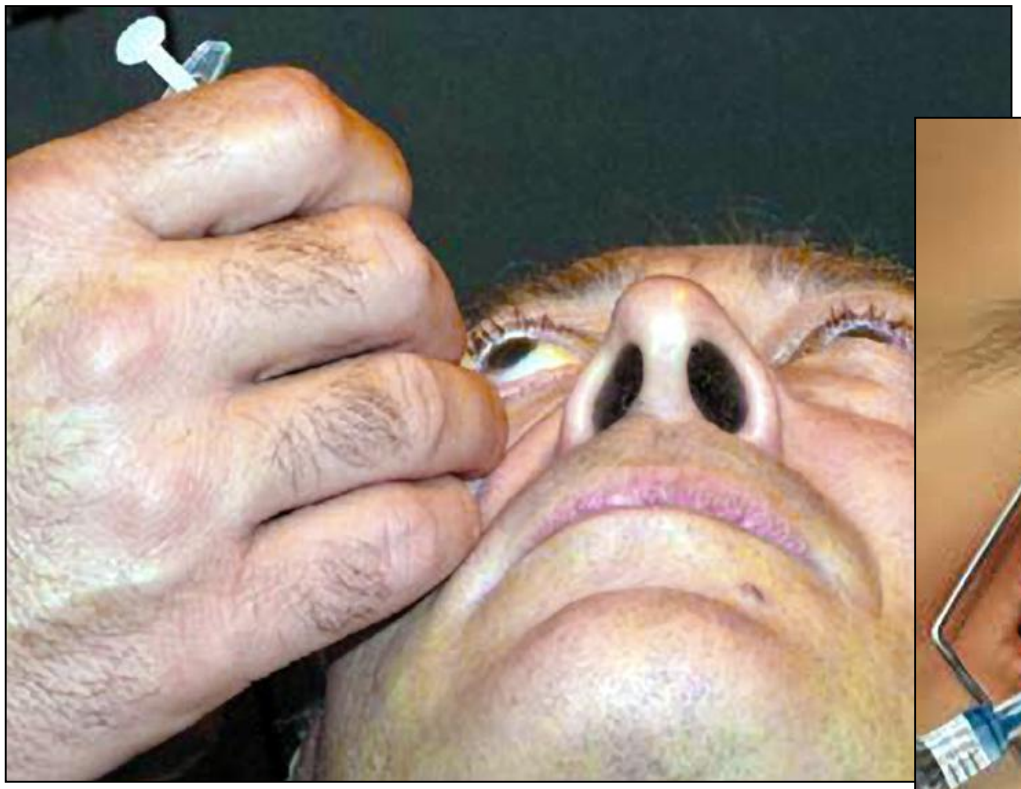


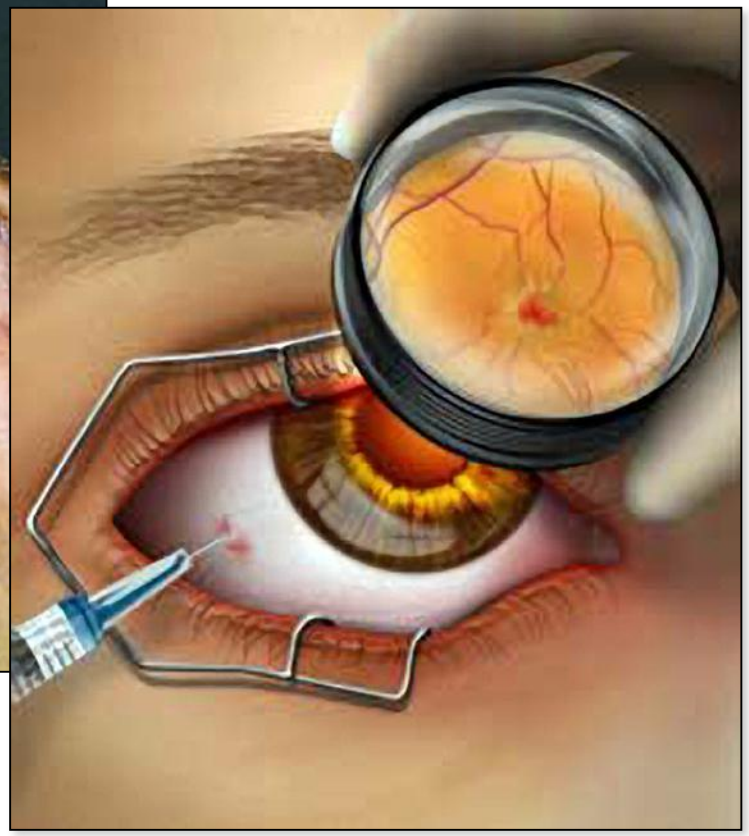
Source: National Eye Institute; team analysis

鞏膜 Sclera



睫狀體 Ciliary Body (睫狀體平坦部 pars plana)
臨床相關症狀: 玻璃體內注射- Intravitreal injection





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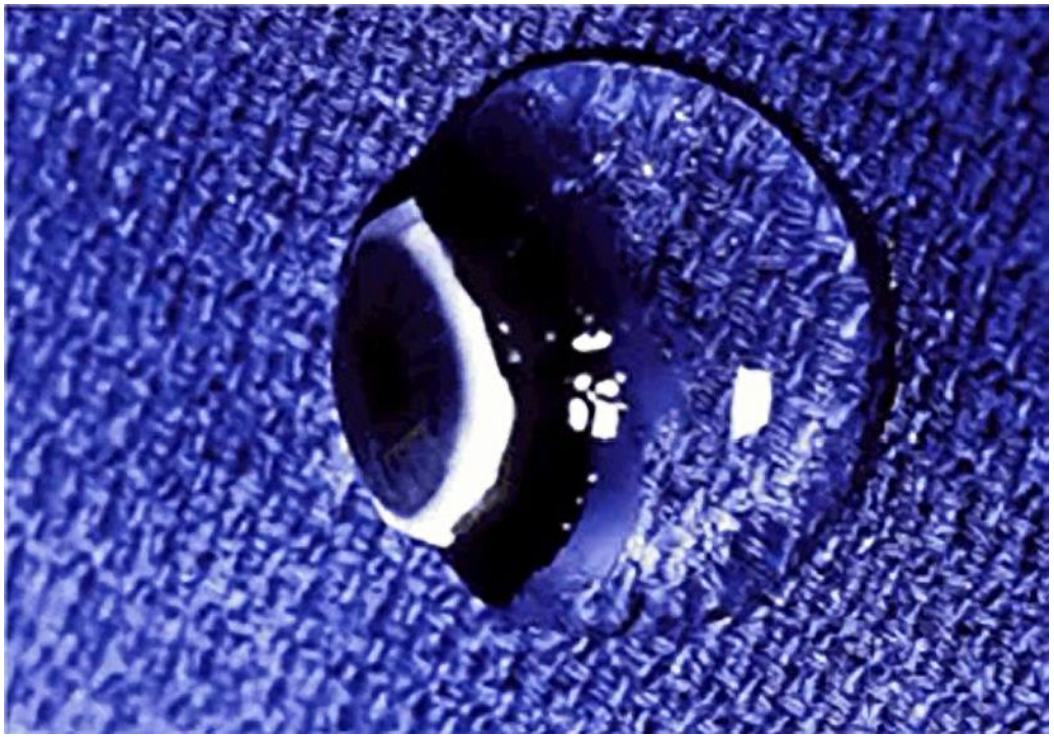
玻璃體 Vitreous



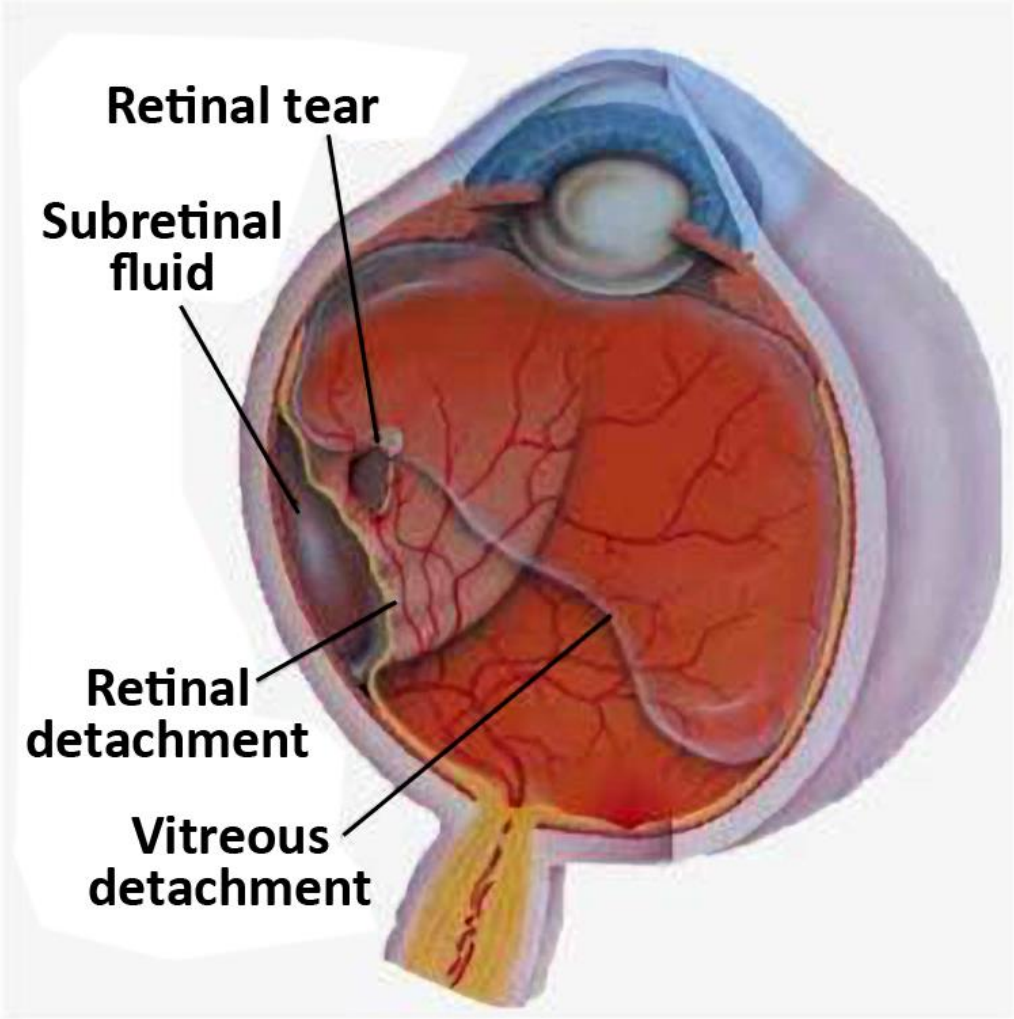
玻璃體
臨床相關症狀: 玻璃體剝離 /視網膜剝離

視網膜撕裂

視網膜下液體

視網膜剝離

玻璃體剝離



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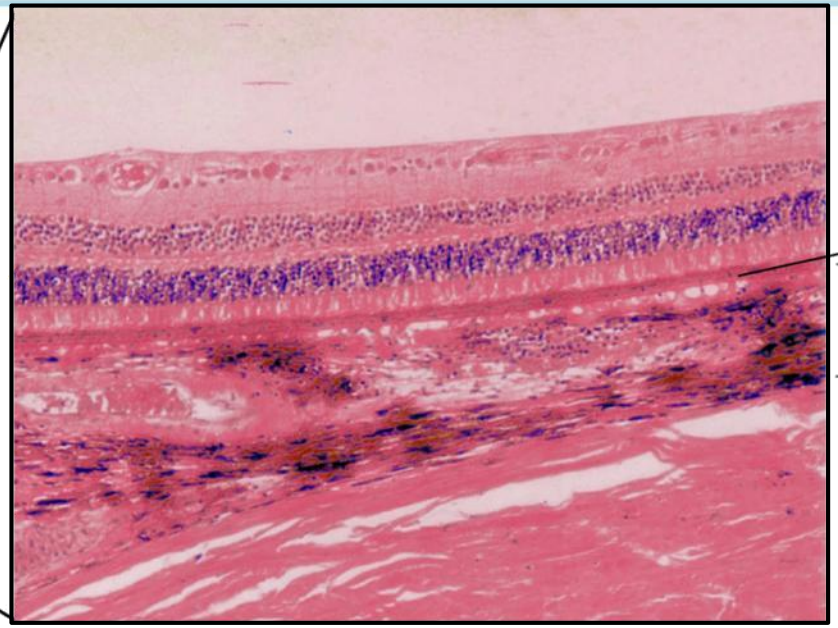
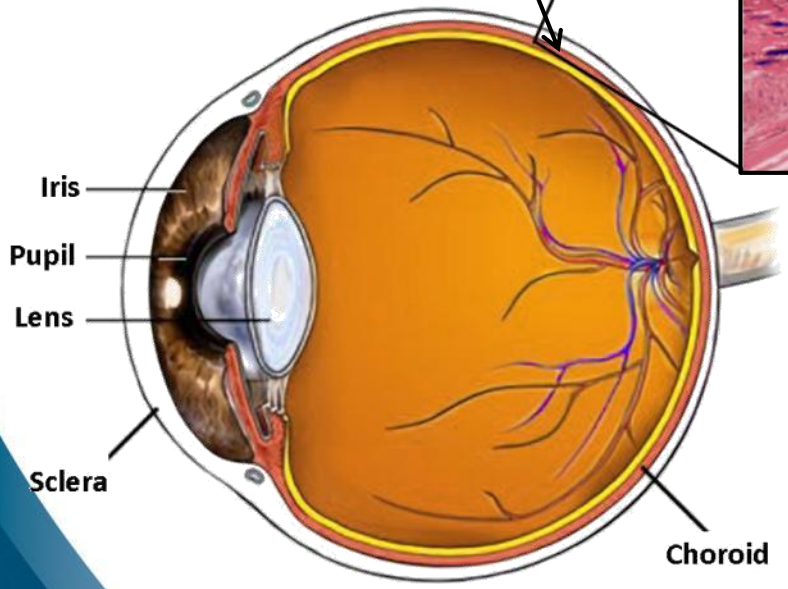
脈絡膜 Choroid



Choroid layers
脈絡膜層



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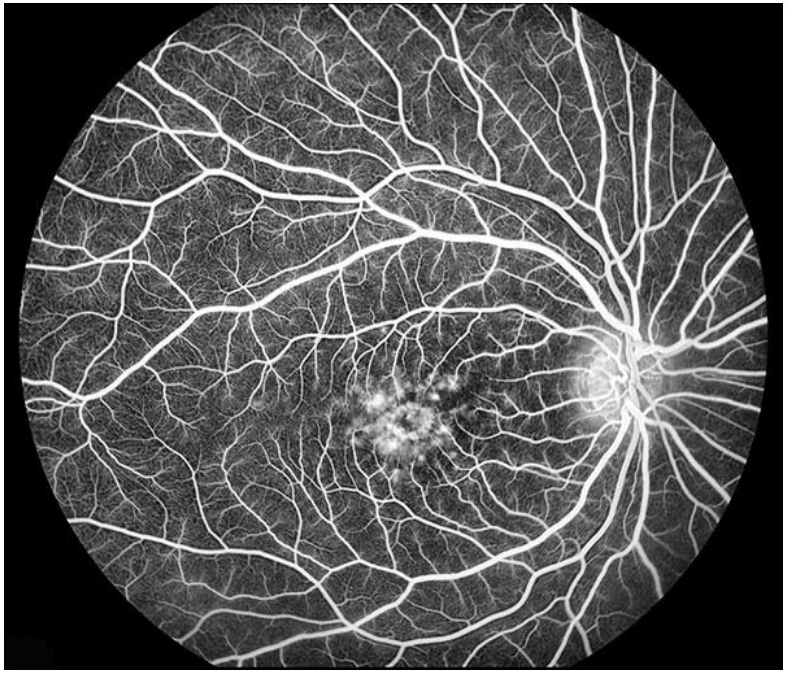
脈絡膜毛細血管 Choriocapillaris



眼科疾病- 相關的診斷及症狀
Ophthalmological Disease- Diagnosis, Symptoms, etc.

Lance Chen

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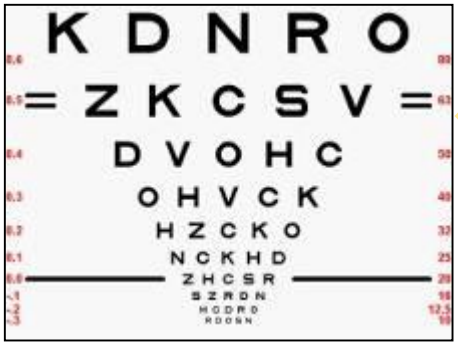
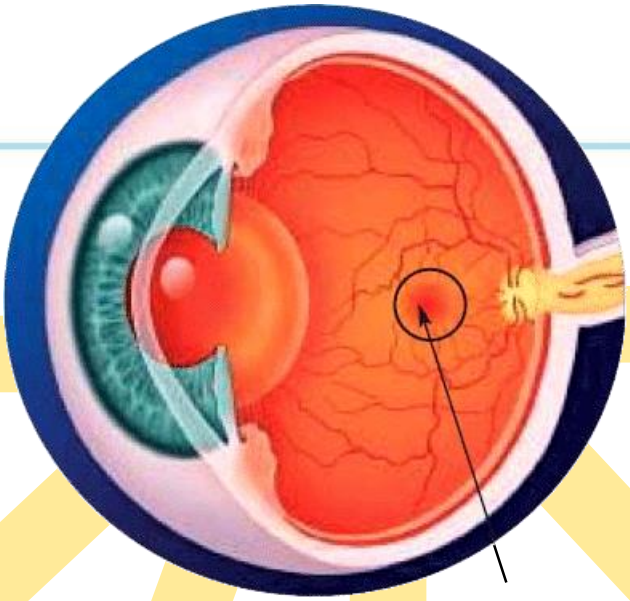
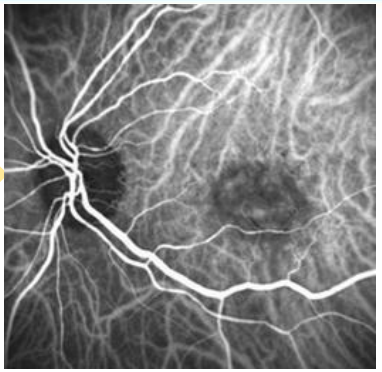
眼科相關檢驗

視力測量
Visual Acuity

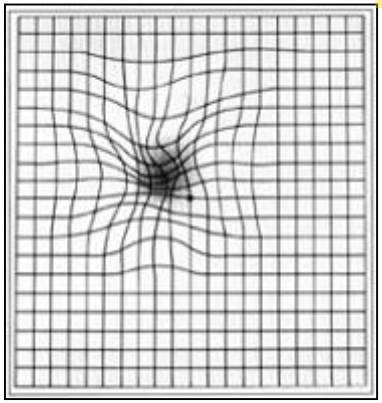




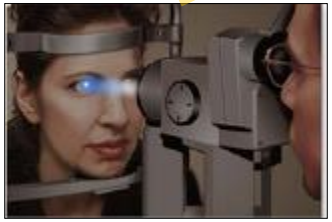
黃斑部



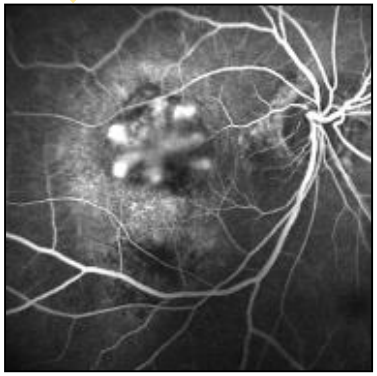
循血綠眼底血管攝影
Indocyanine green angiography



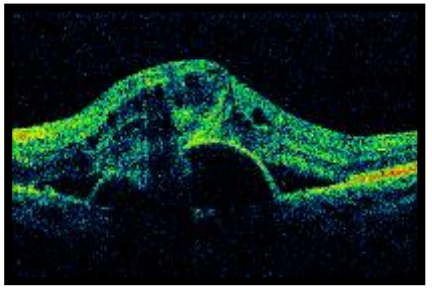
阿姆斯勒方格表
Amsler Grid



視網膜檢查



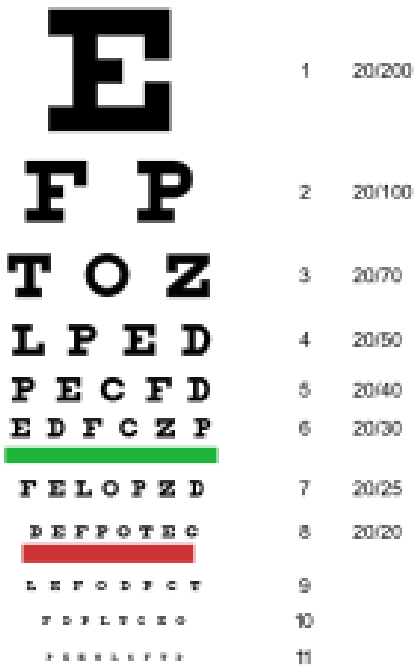
螢光血管造影
Fluorescein angiography



光學同調斷層掃描術
Optical Coherence Tomography (OCT)

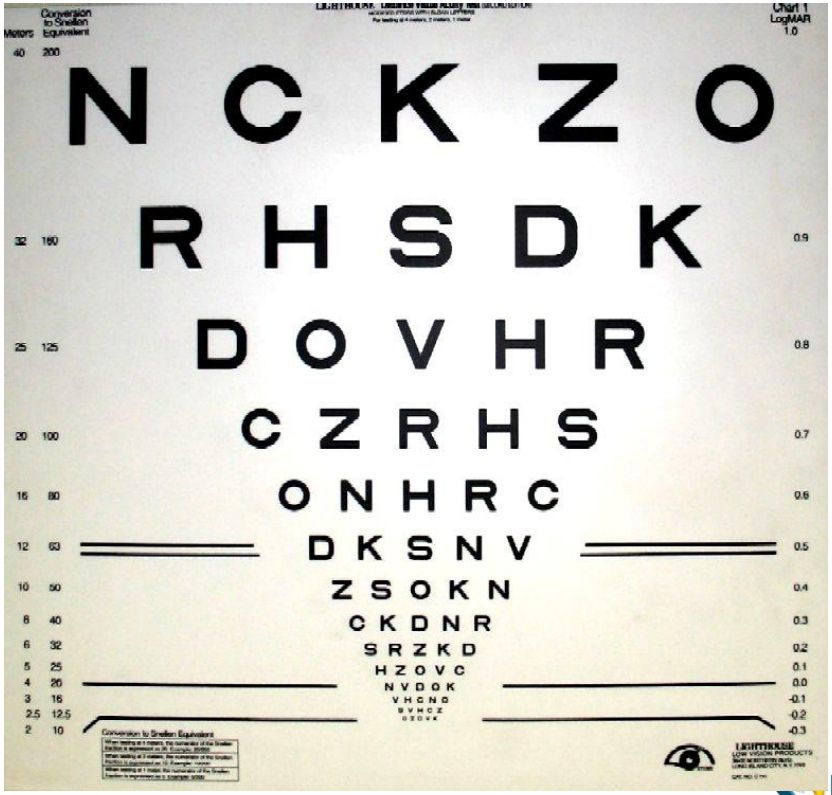
視力測量 Visual Acuity (VA)

Snellen acuity



ETDRS letter score

ETDRS, Early Treatment Diabetic Retinopathy Study



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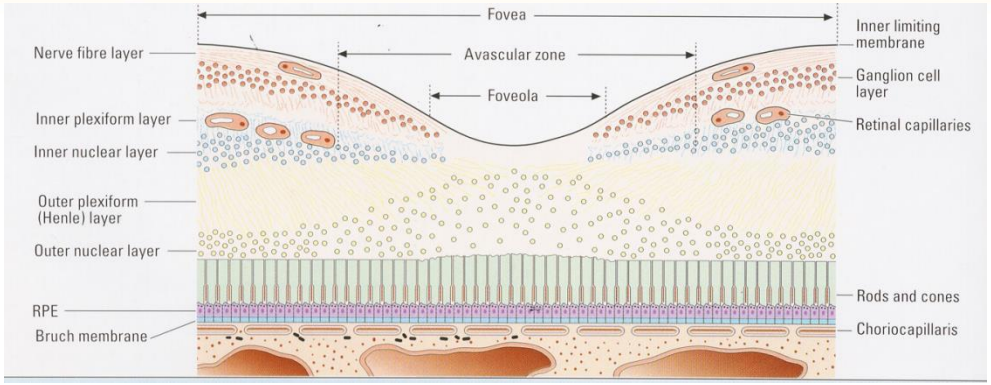
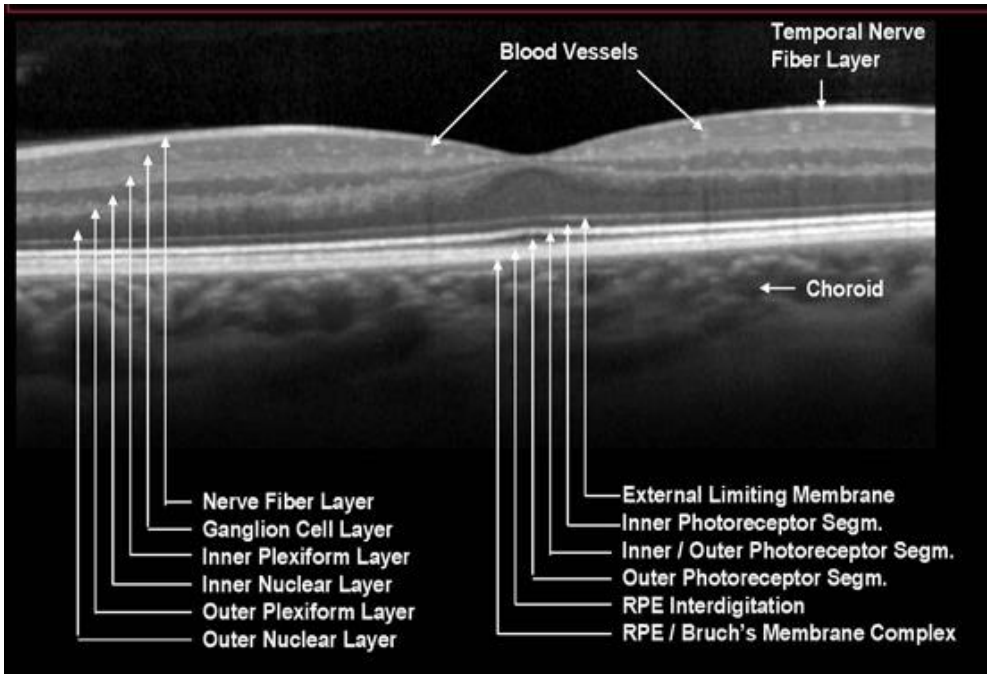
光學同調斷層掃描術
Optical Coherence Tomography (OCT)





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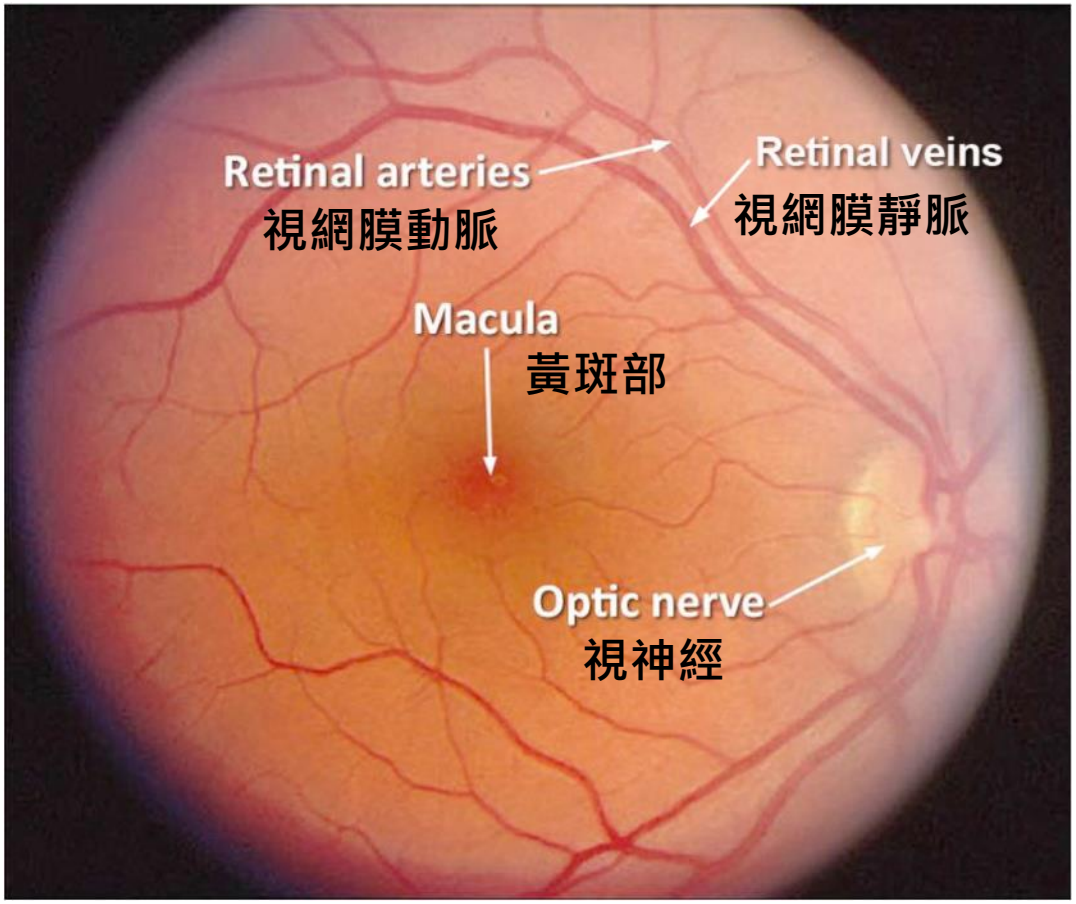
醫師通常使用
間接眼底鏡 - Indirect Ophthalmoscope
來觀察視網膜



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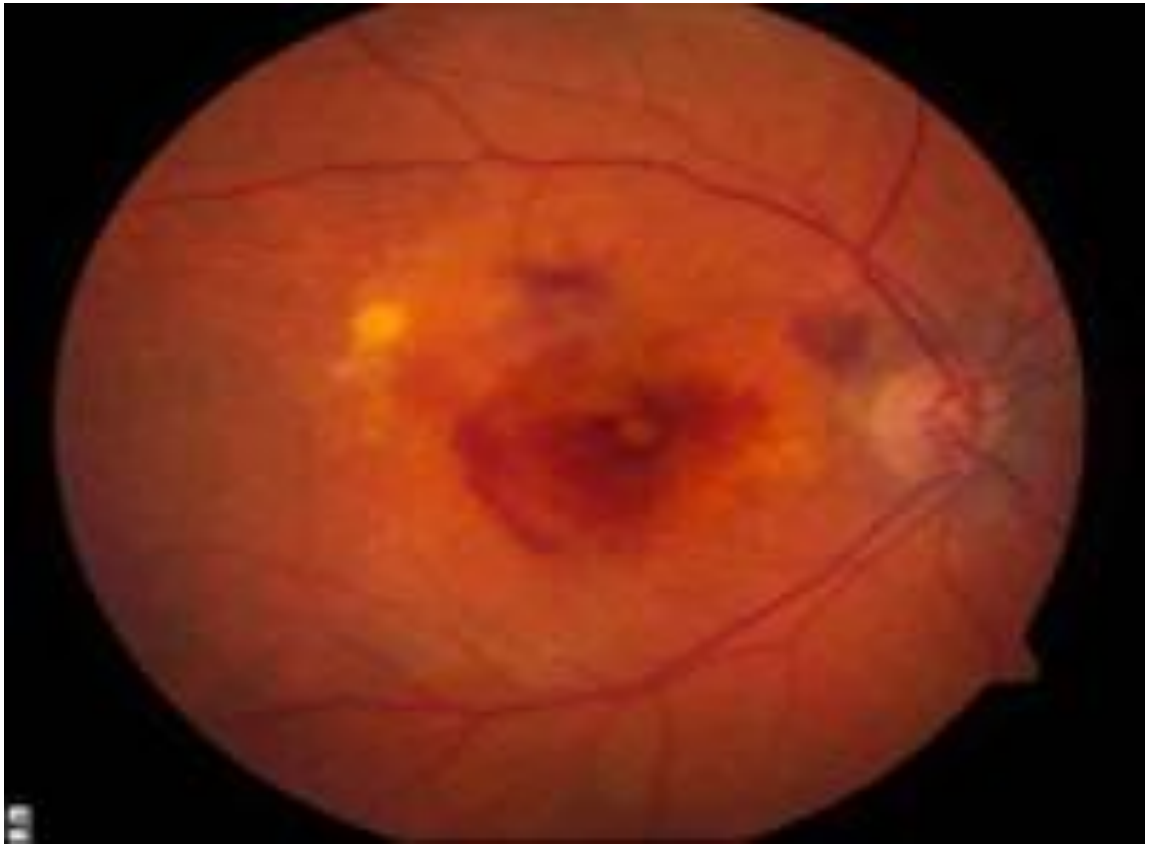
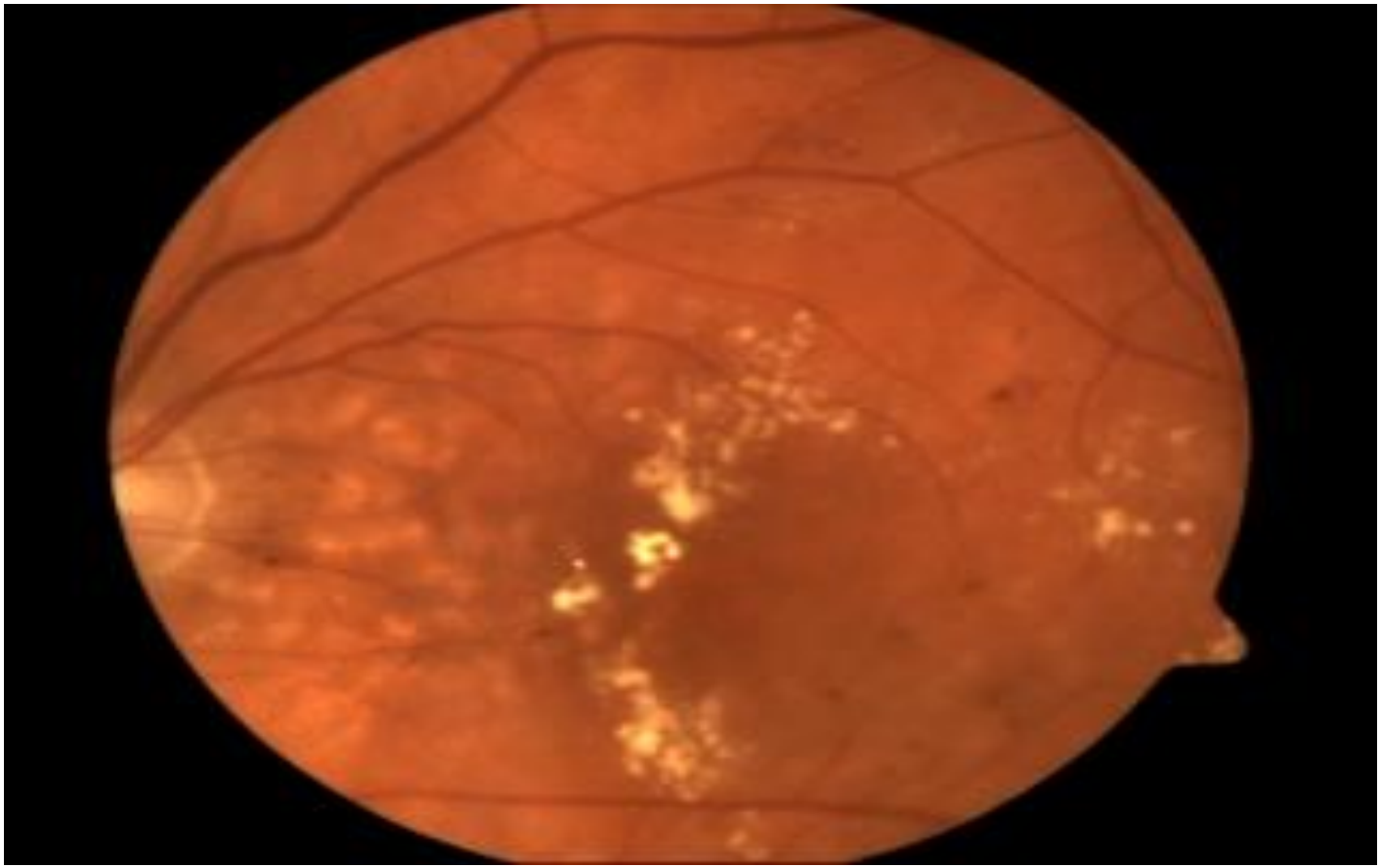
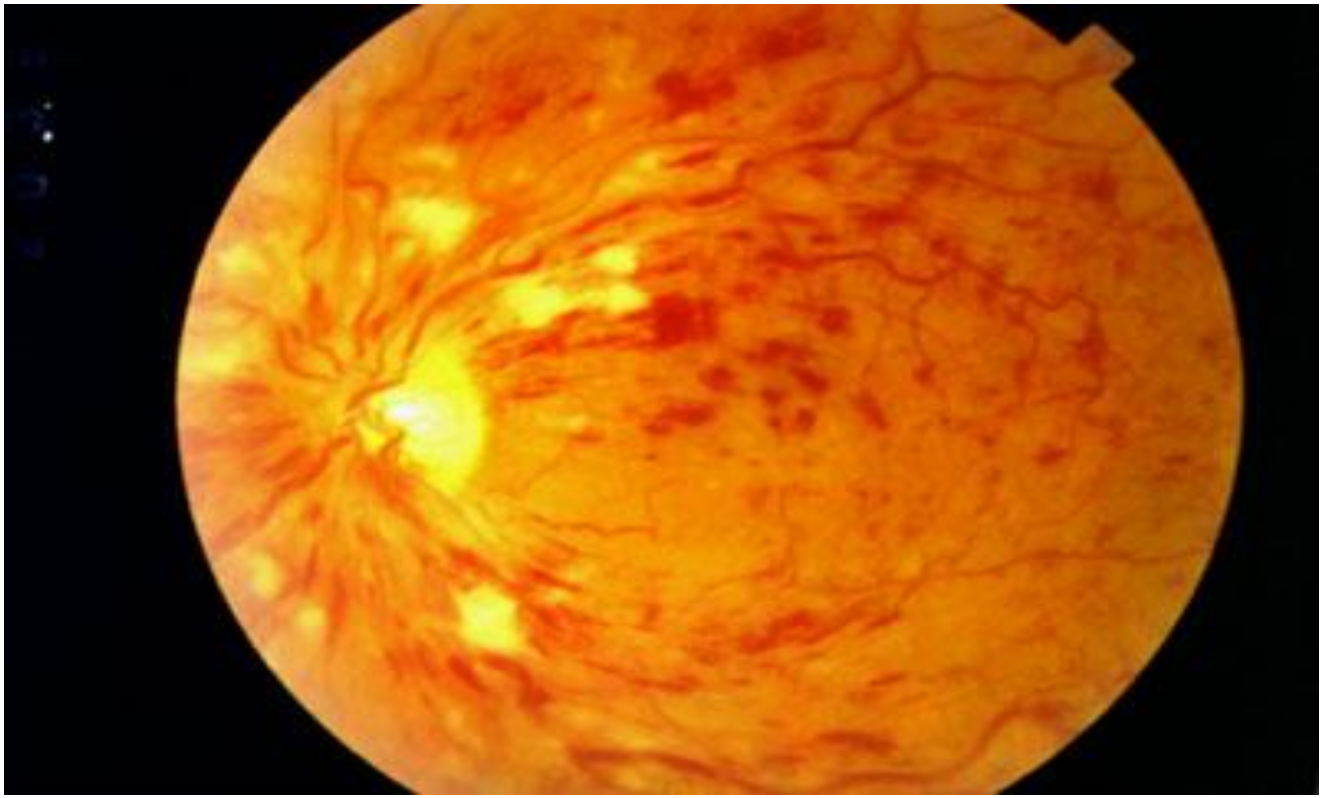
濕性(新生血管) 老年性黃斑部病變
Wet (Neovascular) AMD



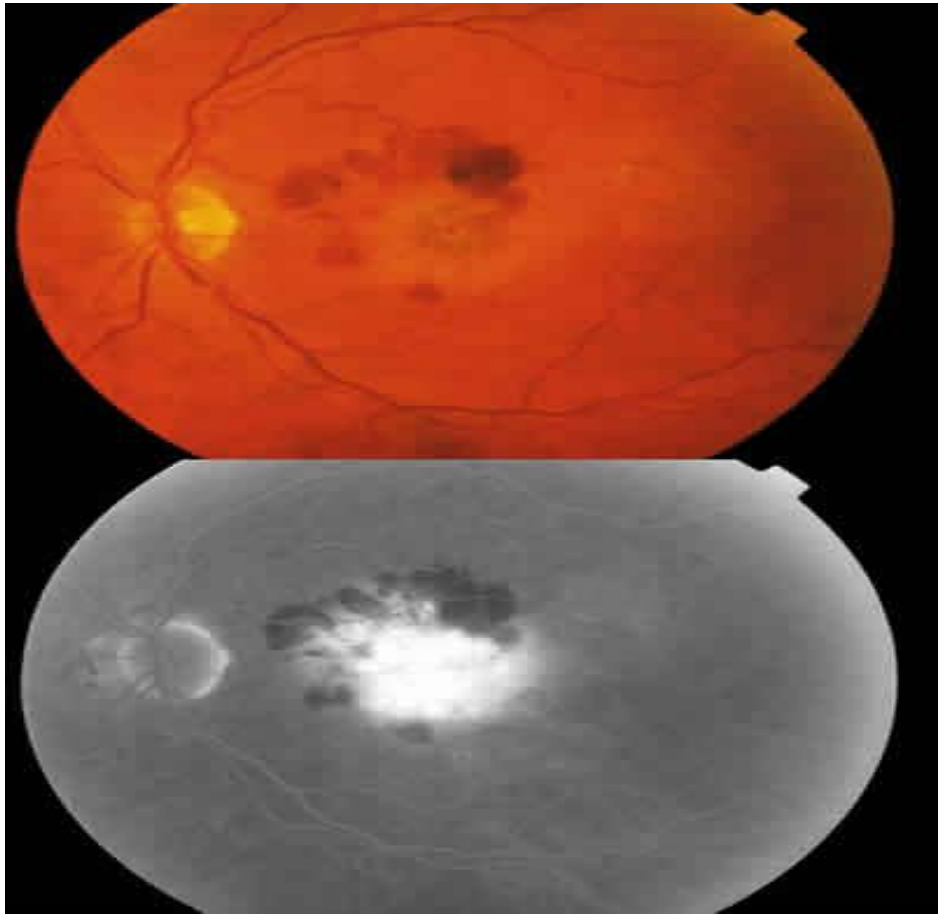
糖尿病黄斑部水腫
Diabetic Macular Edema: DME



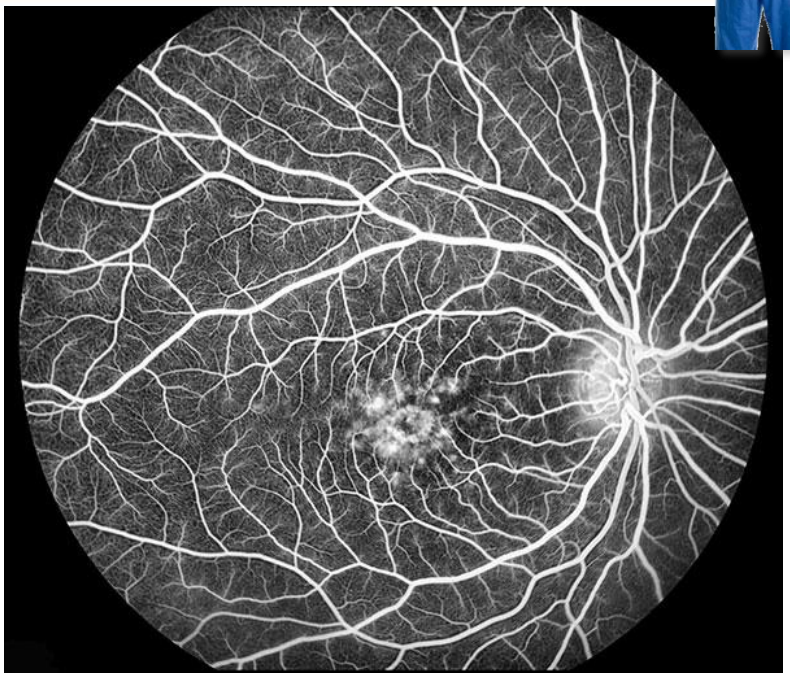
視網膜中央靜脈阻塞
Central Retinal Vein Occlusion (CRVO)



近視引起之脈絡膜新生血管
Myopic CNV



脈絡膜毛細血管 Choriocapillaris
臨床相關症狀:螢光血管造影 Fluorescein Angiography



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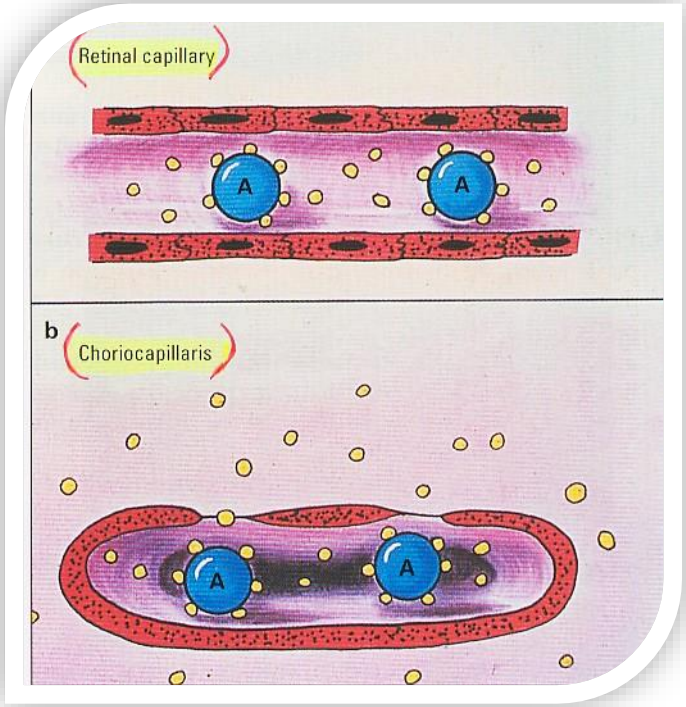
FAG vs. ICGA

- 螢光血管造影

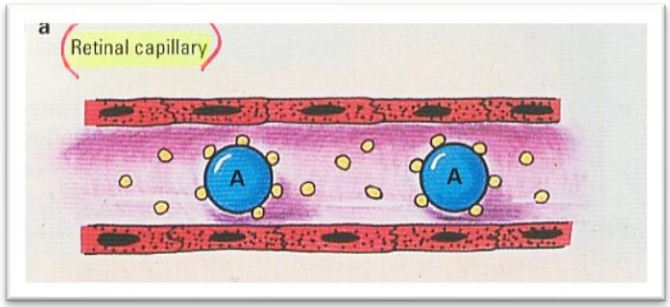
  Fluorescein angiography (FAG)

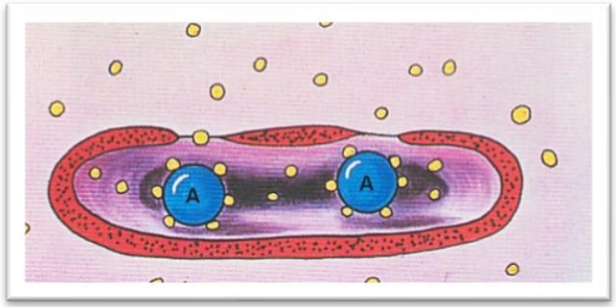
- 循血綠眼底血管攝影

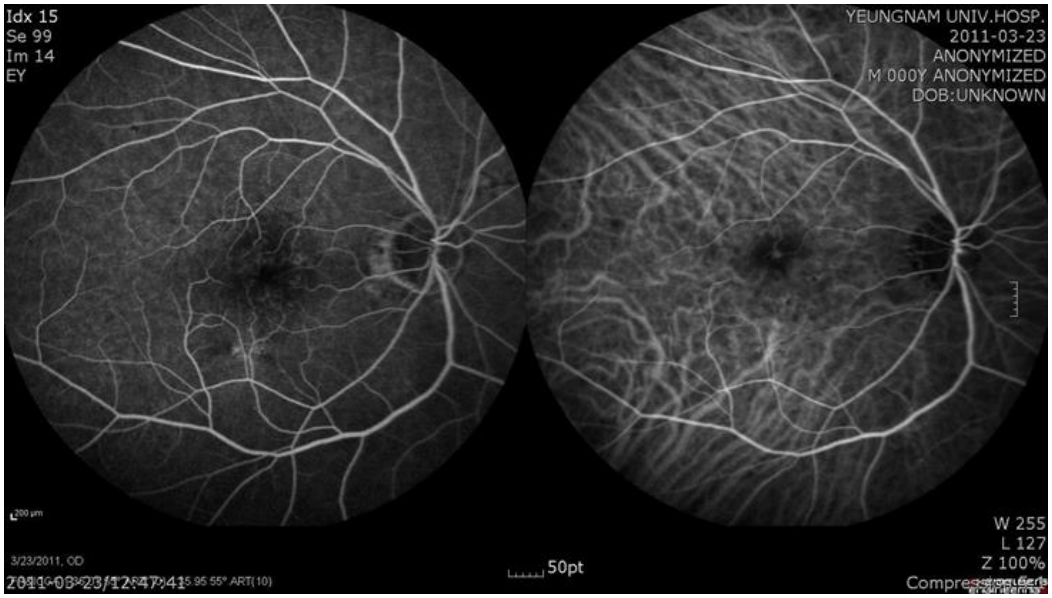
  Indocyanine green angiography (ICGA)



FAG vs. ICGA







螢光血管造影
Fluorescein angiography (FAG)

FLUORESCEIN ANGIOGRAPHY

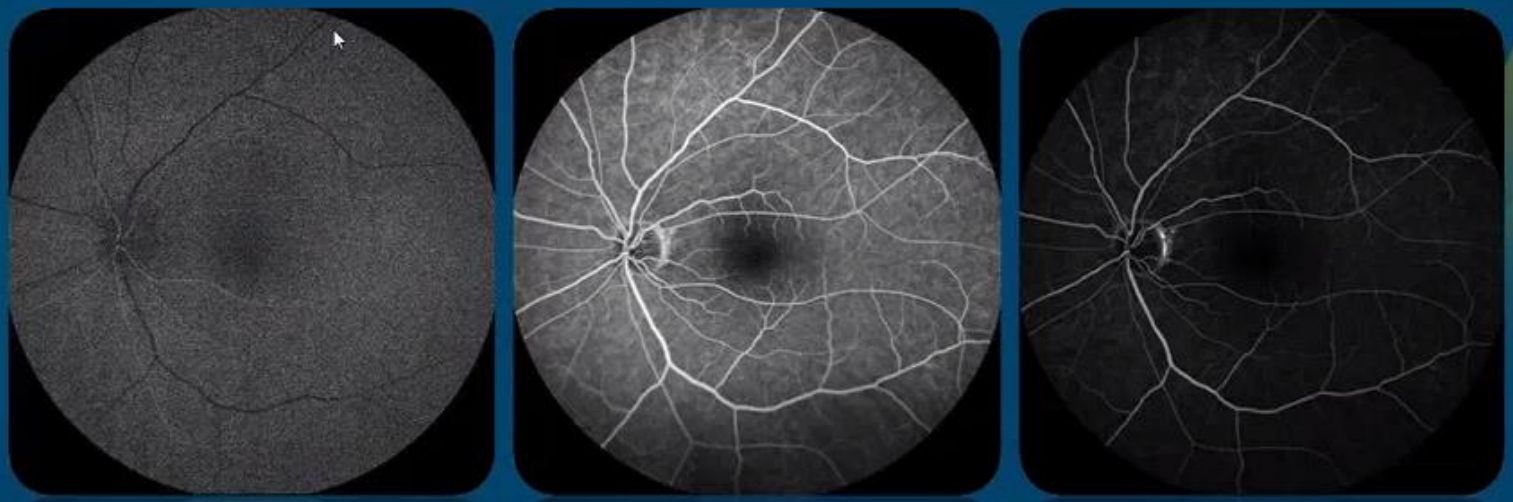
- FA uses a fundus camera or scanning laser ophthalmoscope equipped with exciter and barrier filters to capture the fluorescence in the retinal vasculature
- No X-ray radiation is used in the procedure
- Fluorescein is injected into a vein (typically in the arm or hand) and the retinal vessel circulation is imaged over time
- The camera captures the fluorescence of the dye in the retinal vasculature
- Fluorescein is a dye first synthesized by Adolf Baeyer in 1871

Images courtesy Darrin Landry

FA, fluorescein angiography.

螢光血管造影
Fluorescein angiography (FAG)

FLUORESCEIN ANGIOGRAPHY: STAGES OF FA IN A NORMAL RETINA



Early (15–30 seconds) | Mid (3–5 minutes) | Late (5–10 minutes)

FA, fluorescein angiography.

Images courtesy Dardin Landry

循血線眼底血管攝影
Indocyanine green angiography (ICGA)

INDOCYANINE GREEN ANGIOGRAPHY

- ICG angiography is much like FA in that a dye is injected into a vein and imaged with the aid of special filters
- ICG, however, is a larger molecule dye that binds to plasma protein. This means that the dye does not leak from choroidal vessels, which are fenestrated and normally leak fluorescein dye
- ICG is also excited by a longer infrared wavelength of light. This allows imaging through the RPE and into the choroid

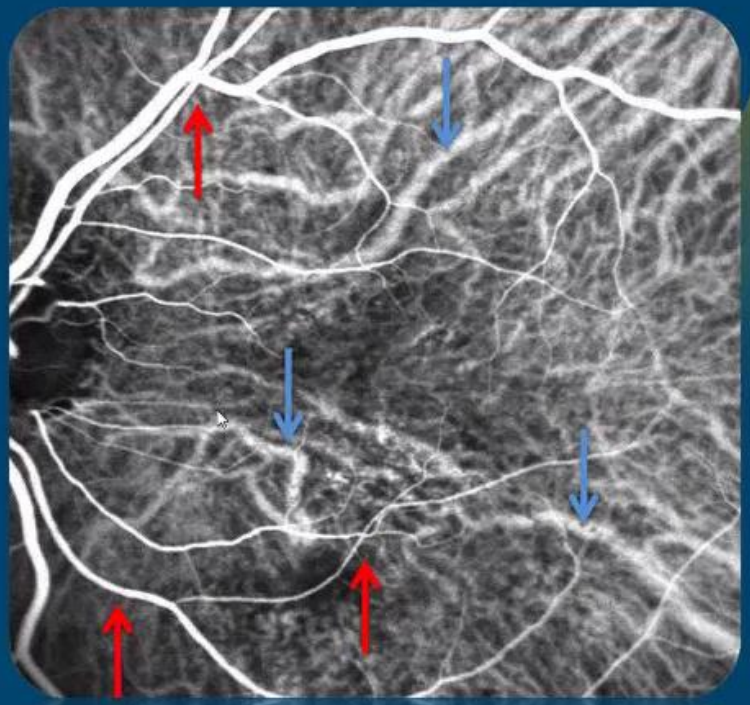
Image courtesy Darrin Landry

FA, fluorescein angiography; ICG, indocyanine green angiography; RPE, retinal pigment epithelium.

循血綠眼底血管攝影
Indocyanine green angiography (ICGA)

INDOCYANINE GREEN ANGIOGRAPHY: NORMAL RETINAL AND CHOROIDAL VESSELS

- ICG dye allows for visualization of both retinal (red arrows) and choroidal (blue arrows) vessels



ICG, indocyanine green.

Image courtesy Darrin Landry

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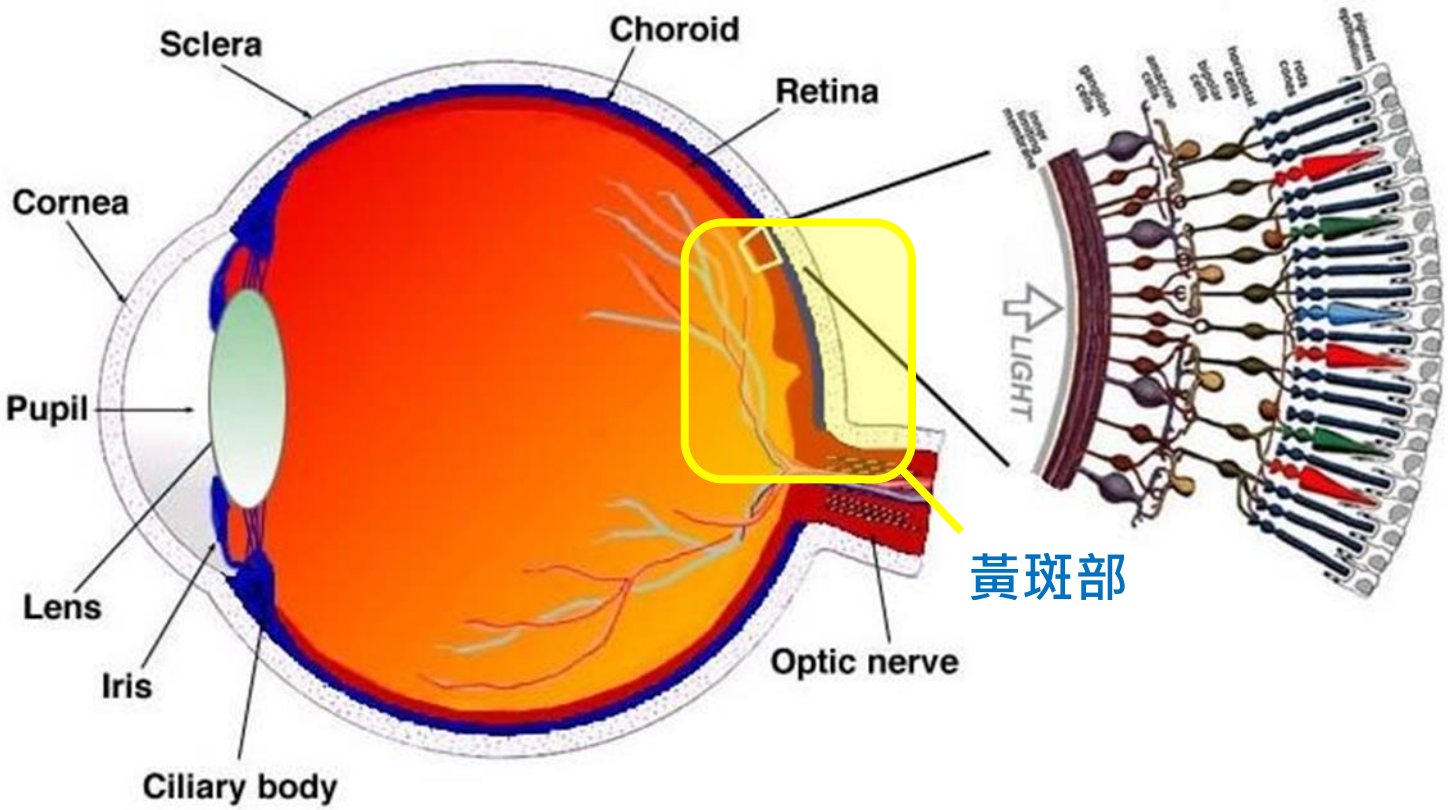
實際上病患每次回診做的檢查...

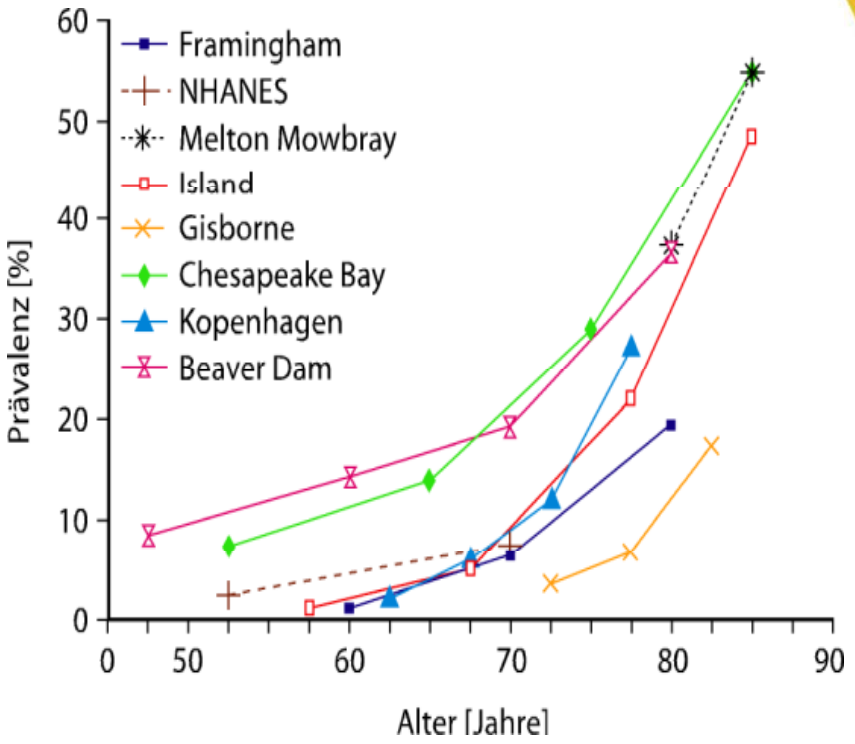
- 初診:
  - FAG+ (選擇性做ICGA) (侵入性檢查)
  - VA
  - OCT
  - Fundus
- 複診:
  - 每個月做OCT, Fundus
  - VA

AGE-RELATED MACULAR DEGENERATION
老年性黃斑部病變

黃斑部對於視網膜中央視力具有重要的影響



老年性黃斑部病變
Age-related Macular Degeneration (AMD)



老年性黃斑部病變是西方國家 50 歲以上老年人主要引起嚴重視力喪失的主因，而且疾病的好發率會隨著年紀的遞增而快速增加。

老年性黃斑部病變: 既定與可能的危險因子

既定的危險因子	可能的危險因子
年紀 (大於六十歲)	女性
有家族病史	淺色虹膜
吸菸	具有心血管疾病
低量攝取或血液中抗氧化維他命及鋅含量不足	

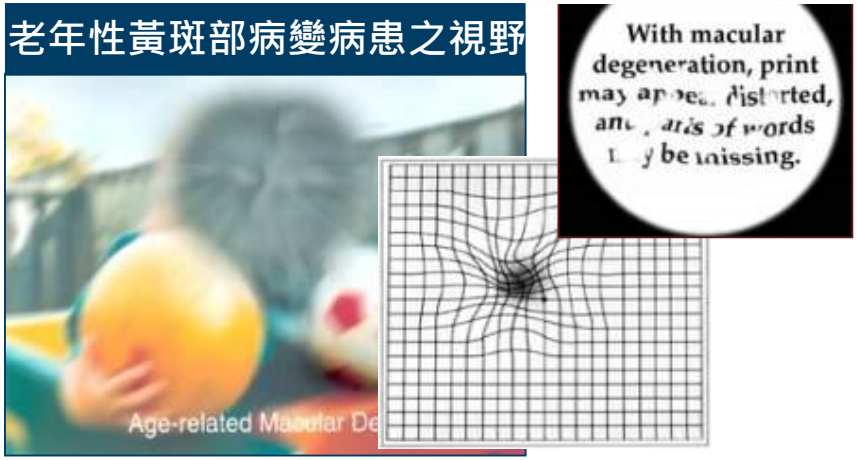
老年性黃斑部病變不僅造成視力損失的負擔
也造成病患自理能力的喪失

一般民眾之視野

老年性黃斑部病變開始症狀

- 視力模糊，視野扭曲
- 直線彎曲
- 物體大小或形狀扭曲變形
- 中心視野變暗

老年性黃斑部病變病患之視野

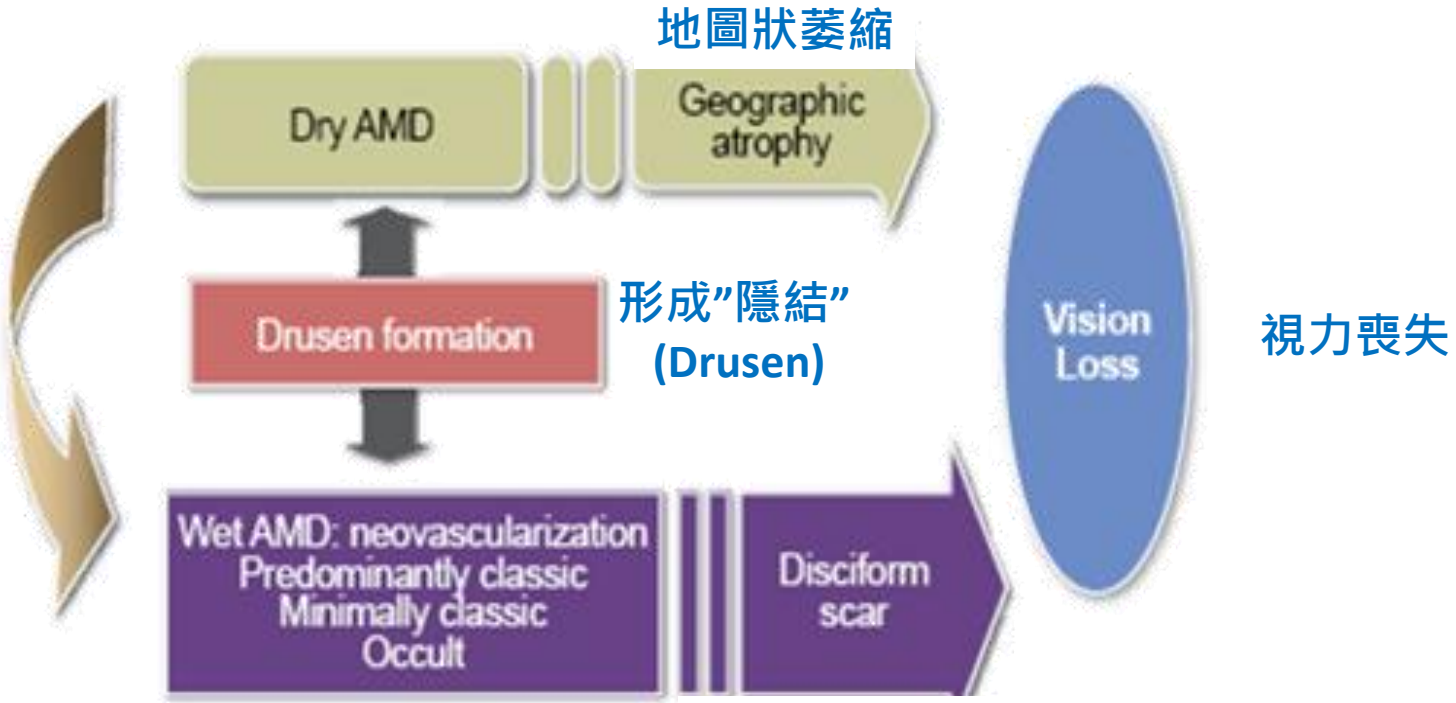


濕性老年性黃斑部病變所造成之影響

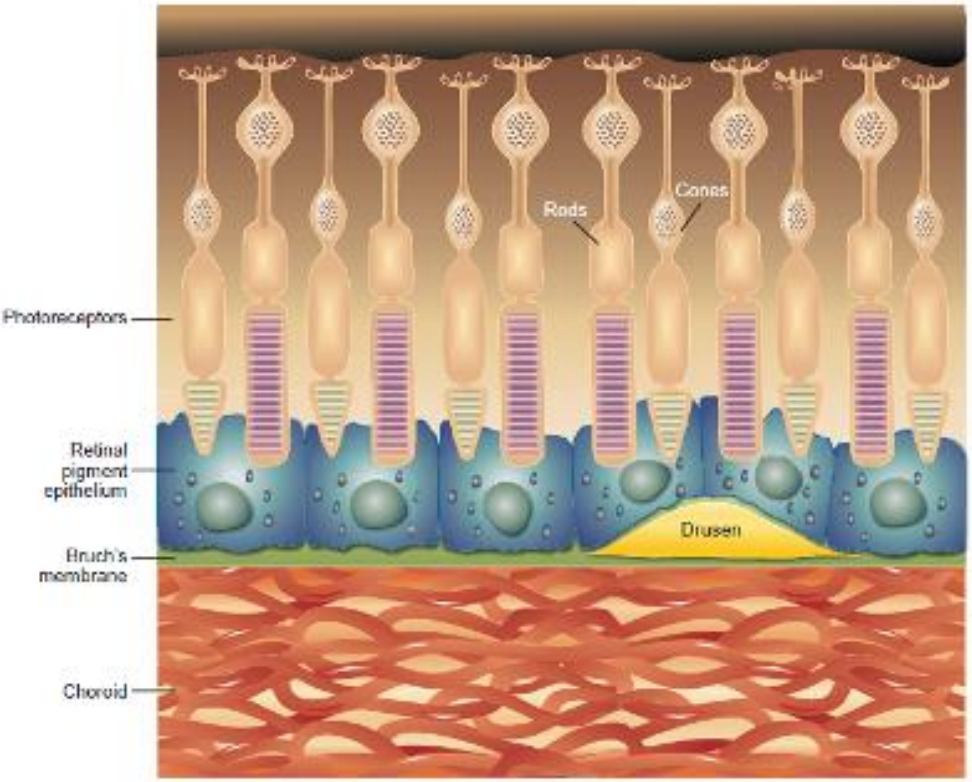
- 日常生活活動受到影響　(開車，閱讀，煮飯等）依賴性變高，自理能力逐漸喪失
- 病患與家庭心理負擔增加
- 家庭與健保系統經濟負擔增加

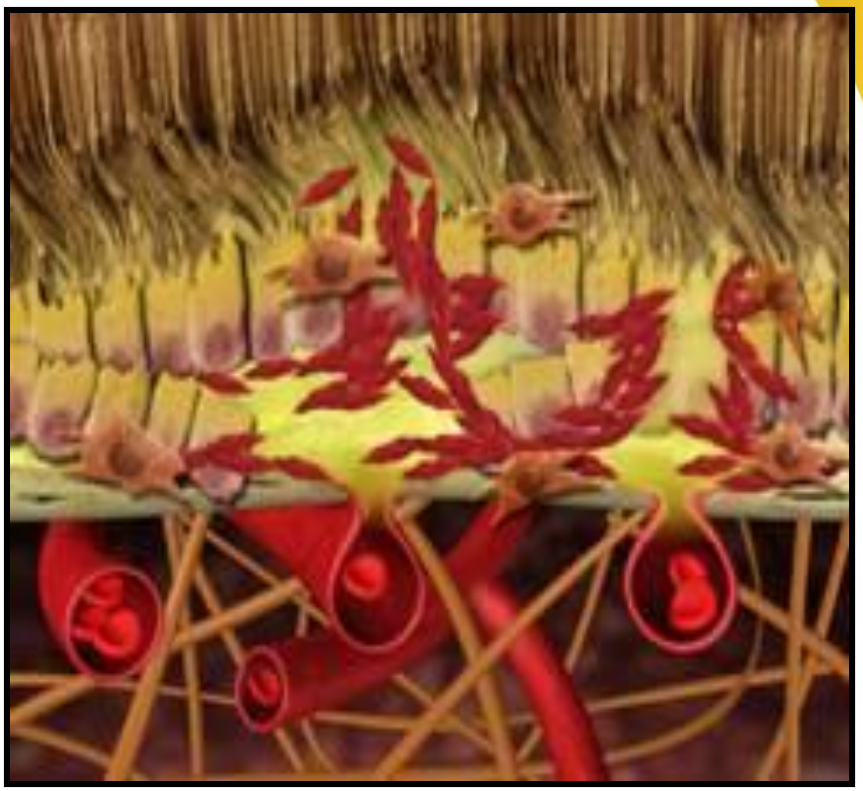
老年性黃斑部病變分成兩種:“乾性”與“濕性”

- 人類隨著年紀增長，眼睛黃斑部的細胞逐漸地退化: 這種現象稱為“老年性黃斑部病變”(AMD)
  - 患有此疾病的病患的中央視力會急速且顯著地退化。
    - 老年性黃斑部病變分成兩種:“乾性”與“濕性”

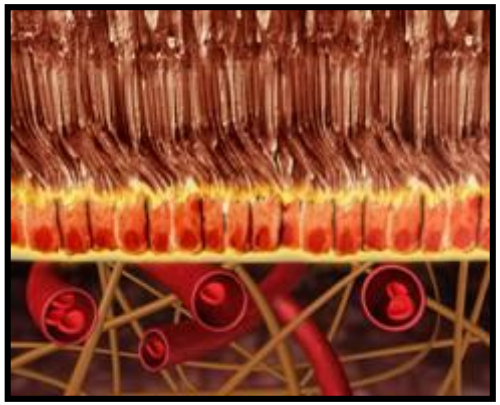


乾性老年性黃斑部病變　　濕性老年性黃斑部病變

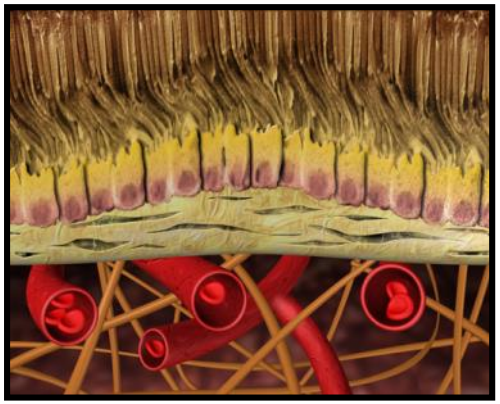




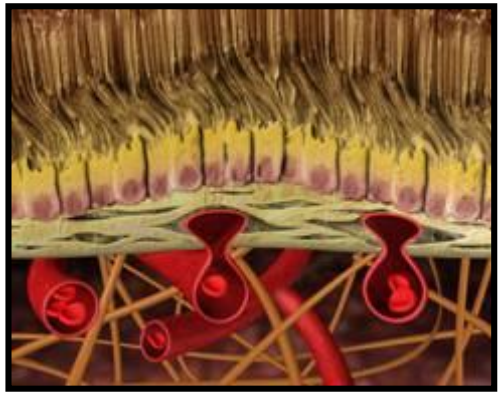
濕性老年性黃斑部病變的病程發展



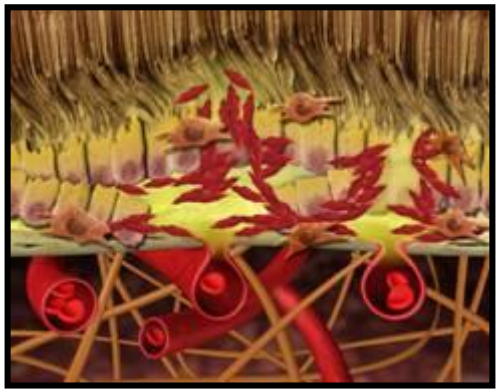
一般視網膜



視網膜增厚，
隱結(Drusen = 老廢產物) 產生

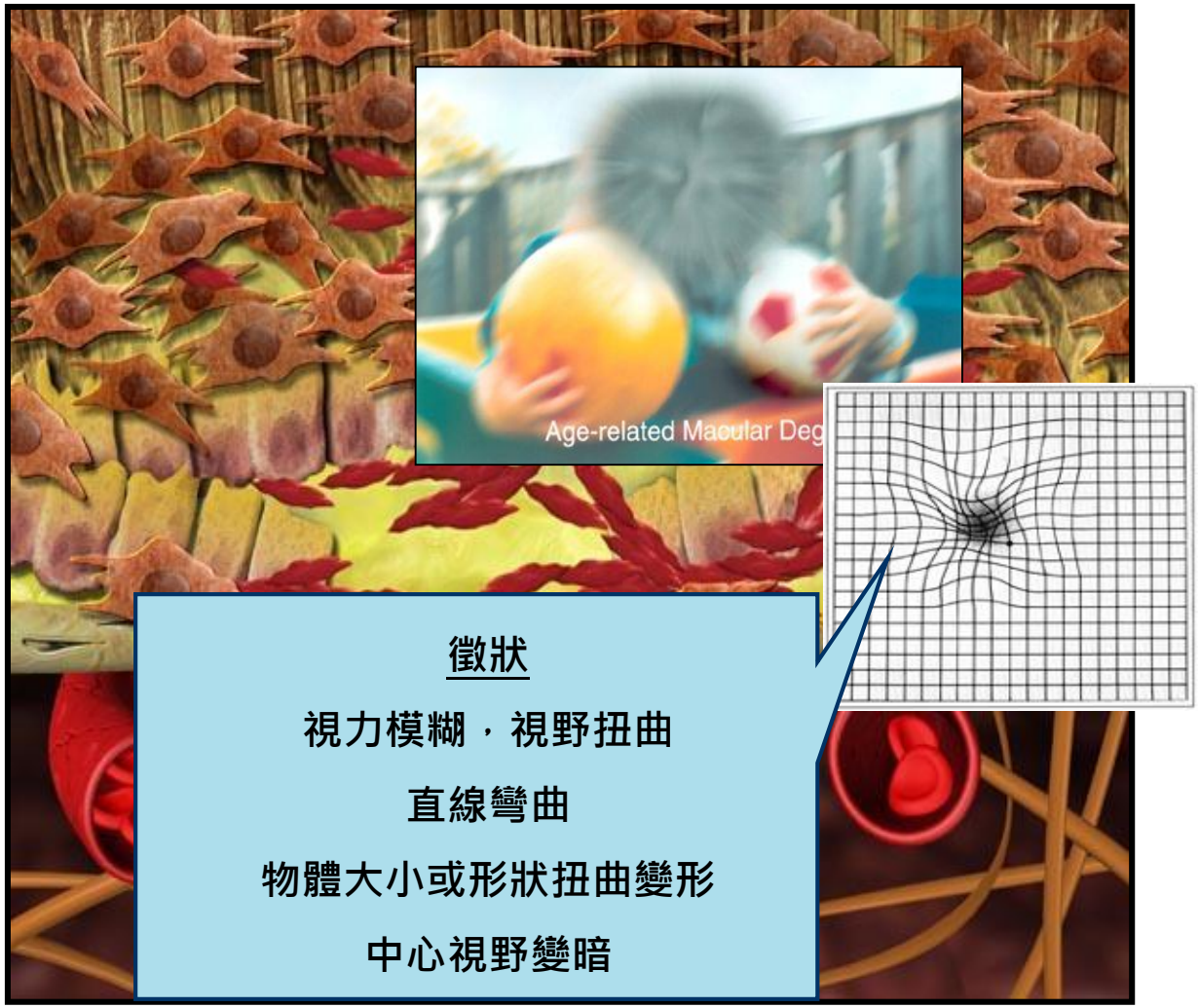


新生不正常血管穿越膜後
以提供更多的氧氣與養分



新生血管血液與液體滲漏

結痂與視力喪失



進一步診斷評估……

- 視力測量

  Visual Acuity (VA)

- 光學同調斷層掃描術

  Optical Coherence Tomography (OCT)

- 螢光血管造影

  Fluorescein angiography (FAG)

- 循血綠眼底血管攝影

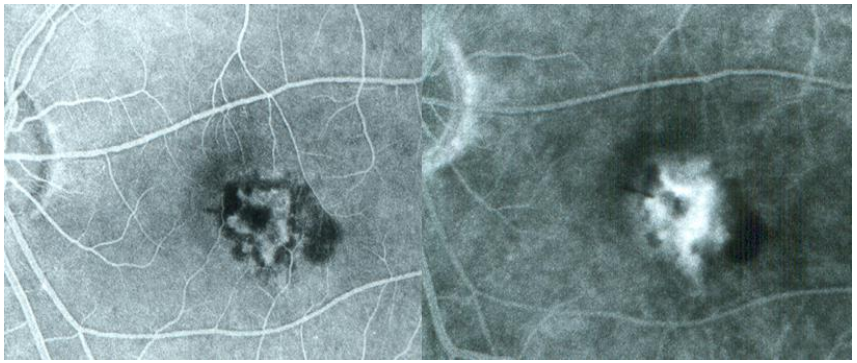
  Indocyanine green angiography (ICGA)

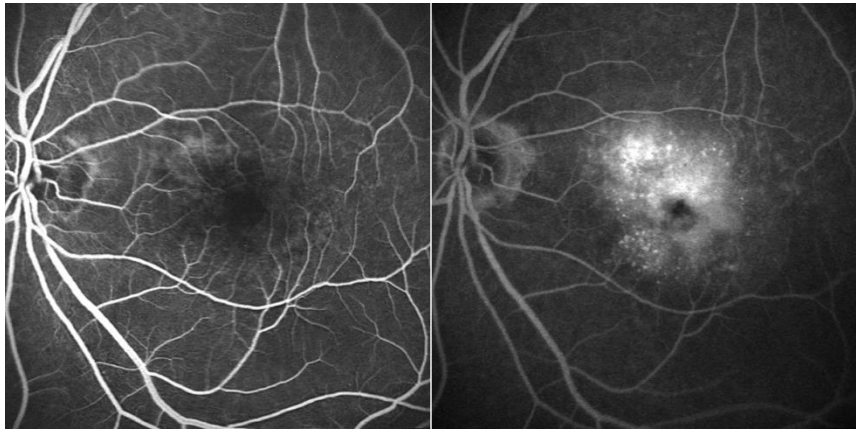
脈絡膜新生血管(CNV)的分類

- 可藉由

螢光血管造影FAG 分類成

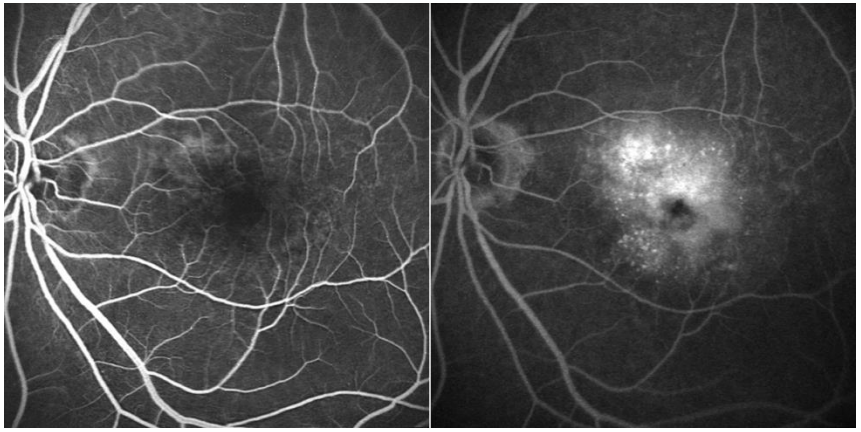
- 典型 (classic) CNV
- 潛隱 (occult) CNV

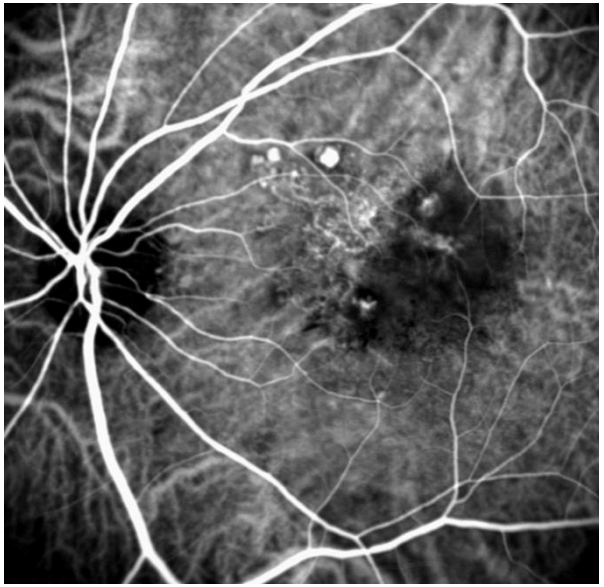




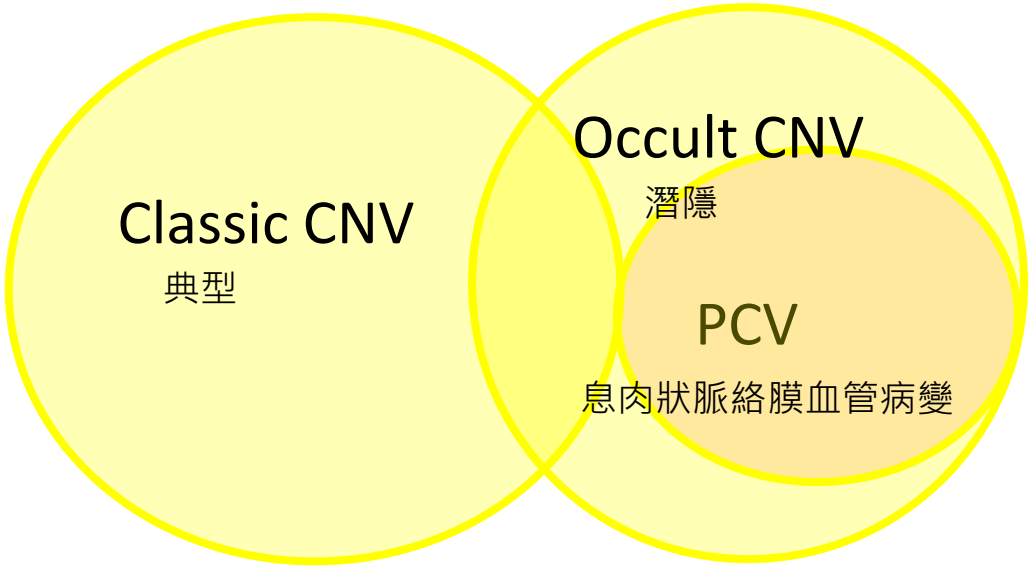
循血綠眼底血管攝影
Indocyanine green angiography (ICGA)
可分化出潛隱性(occult)脈絡膜新生血管(CNV)

- 藉由 ICGA
  - 部份的 Occult CNV was 可以被細分辨別為 息肉狀脈絡膜血管病變 (Polypoidal Choroidal Vasculophthy, PCV)

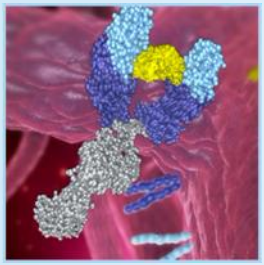




老年性黃斑部病變組合



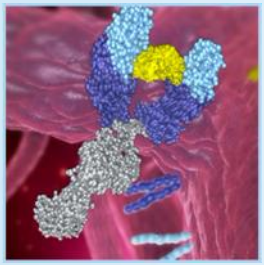




DME disease background

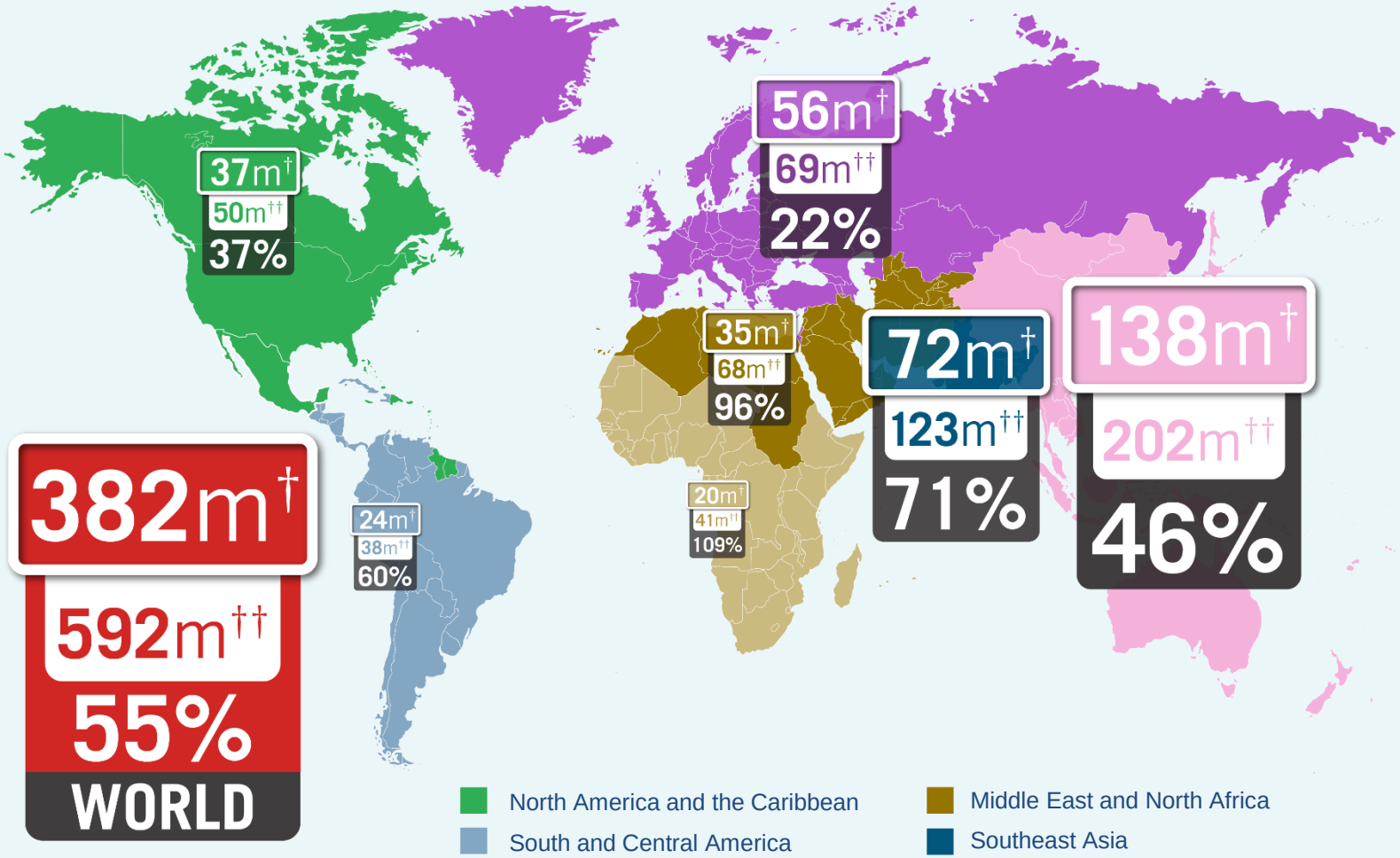
Alfie Chen, PhD
Sr. MSL of Ophthalmology





Diabetes and Diabetic Macular Edema (DME)

Global burden of diabetes



† Prevalence in 2013 (millions)
†† Projected prevalence in 2035 (millions)
Projected increase from 2013 to 2035 (%)

International Diabetes Federation. IDF Diabetes Atlas: 6th Edition. 2013.

Major complications of diabetes

Microvascular complications

Retinopathy

A leading cause of blindness in working-age populations[1]

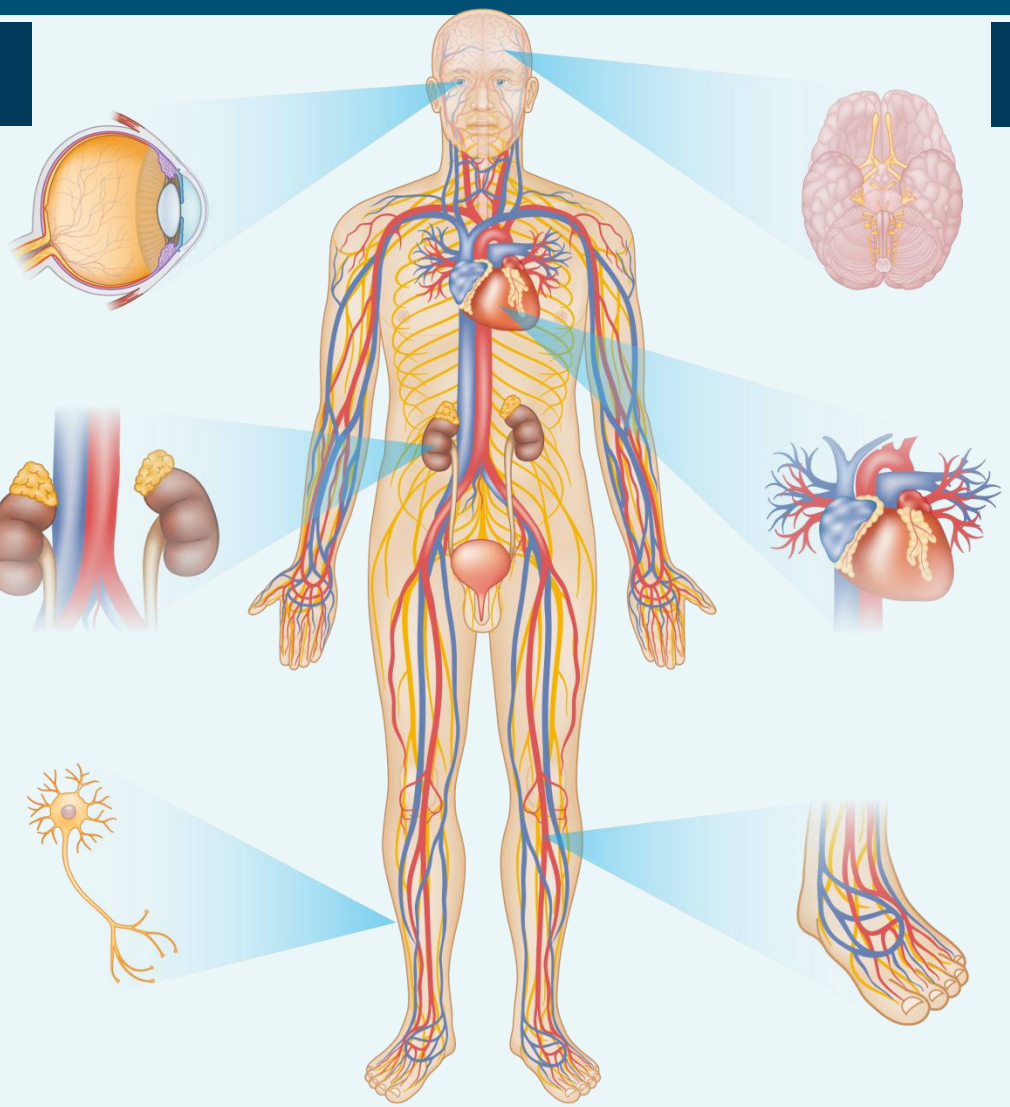
Nephropathy

Responsible for > 40% of new cases of kidney failure[2]

Neuropathy

Mild-to-severe nervous system damage present in 60–70% of patients[2]

*2004 values



Macrovascular complications

Cerebrovascular disease

Cited on 16% of diabetes-related death certificates (patients aged ≥ 65 years)*[2]

Heart disease

Cited on 68% of diabetes-related death certificates (patients aged ≥ 65 years)*[2]

Peripheral vascular disease

Occurs in ~8% of patients with diagnosed diabetes[3]

Leading cause of non-traumatic lower extremity amputations[2]

1. Ciulla TA, et al. *Diabetes Care.* 2003;26(9):2653–2664; 2. CDC. National Diabetes Fact Sheet, 2011. www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf. Accessed June 19, 2014. 3. Gregg EW, et al. *Diabetes Res Clin Pract.* 2007;77(3):485–488.

Risk factors for diabetic retinopathy

Key risk factors[1,2]

- Poorly controlled diabetes
- Chronic hyperglycemia
- Dyslipidemia
- Hypertension
- High body mass index
- Low levels of physical activity
- Insulin resistance

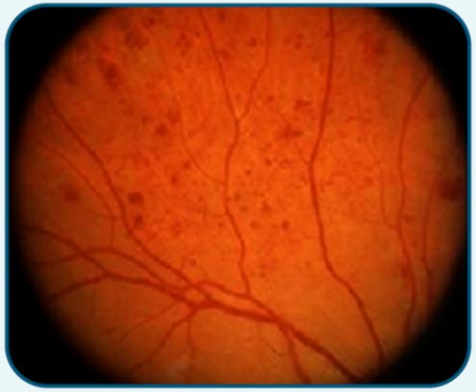
Other possible risk factors[1,3]

- Sleep apnoea; non-alcoholic fatty liver disease; levels of serum prolactin, serum adiponectin, and serum homocysteine; age; renal disease; pregnancy

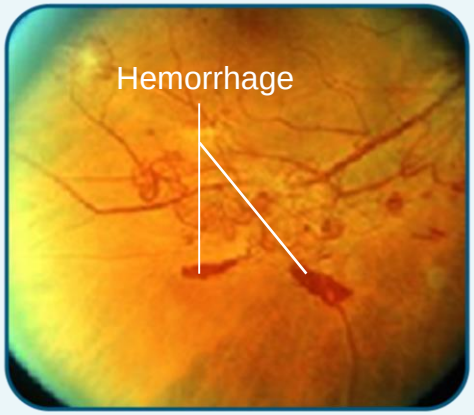
1. Antonetti D, et al. *N Engl J Med.* 2012;366(13):1227–1239; 2. Klein R, Klein BEK. *Retina.* Ryan S, et al, eds. Elsevier 2013;
3. Shaya FT, Aljawadi M. *Clin Ophthalmol.* 2007;1(3):259–265.

Diabetic retinopathy: An overview

- By the second decade after diagnosis, diabetic retinopathy (DR) affects almost all patients with T1DM and approximately 60% of those with T2DM[1]
  - Non-proliferative and proliferative forms
  - Proliferative disease characterized by retinal angiogenesis secondary to ischemia
- Macular edema can develop at any stage of DR (but also may not occur)[2]



Non-proliferative DR



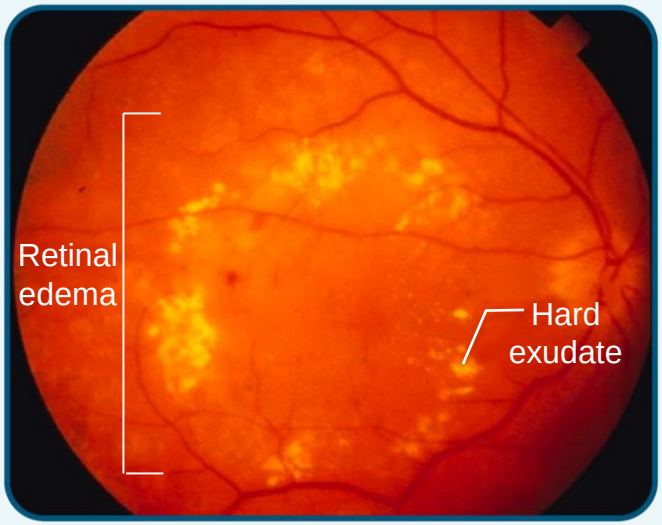
Proliferative DR

1. Shaya FT, Aljawadi M. *Clin Ophthalmol.* 2007;1(3):259–265; 2. Ciulla TA, et al. *Diabetes Care.* 2003;26(9):2653–2664; 3. Wilkinson CP, et al. *Ophthalmology.* 2003;110(9):1677–1682.

Understanding DME in the context of diabetes

What is DME?

- A microvascular complication of diabetes that is associated with diabetic retinopathy[1]
  - Diabetic retinopathy is a common complication of diabetes[2]
- The leading cause of moderate-to-severe vision loss in patients with diabetes[3]
- A leading cause of blindness in working-age populations in most developed countries[4]
- Clinically significant macular edema (CSME) is the form of DME that is considered to be most vision-threatening[3]



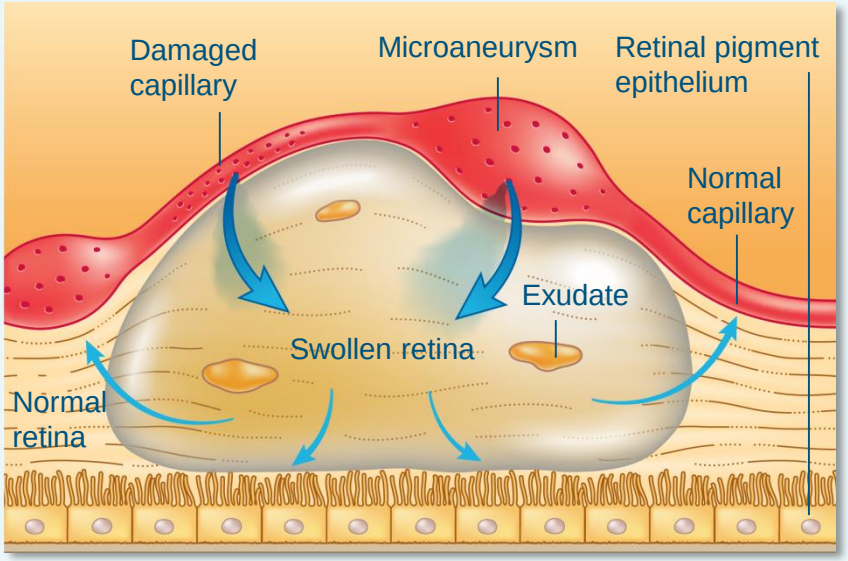
Diabetic macular edema

Image courtesy of Dr Anne-Katrin Sjølie.

1. Lobo C, et al. *Optical Coherence Tomography*. Berlin Heidelberg: Springer-Verlag; 2012; 2. Fowler MJ. *Clinical Diabetes.* 2008;26(2): 77–82; 3. International Diabetes Federation. Diabetes & blindness due to DME Q&A. www.idf.org/sites/default/files/Toolkit%2520Q%2526A_FINAL.pdf. Accessed June 19, 2014. Accessed June 4, 2014; 4. Ciulla TA, et al. *Diabetes Care*. 2003;26(9):2653–2664.

DME: An overview

- DME is the leading cause of moderate-to-severe vision loss in patients with diabetes[1,2]
- The pathogenesis of DME is complex[3,4]
  - Involves several inter-related pathway processes that are initiated by sustained hyperglycemia
  - These processes culminate in increased vascular permeability and the breakdown of the blood-retina barrier
  - Fluid and proteins leak into the macula, causing the macula to swell, which in turn affects visual function



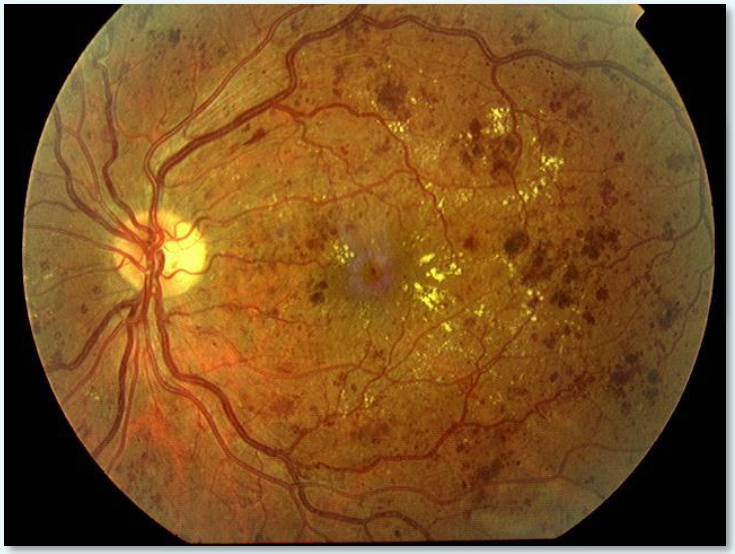
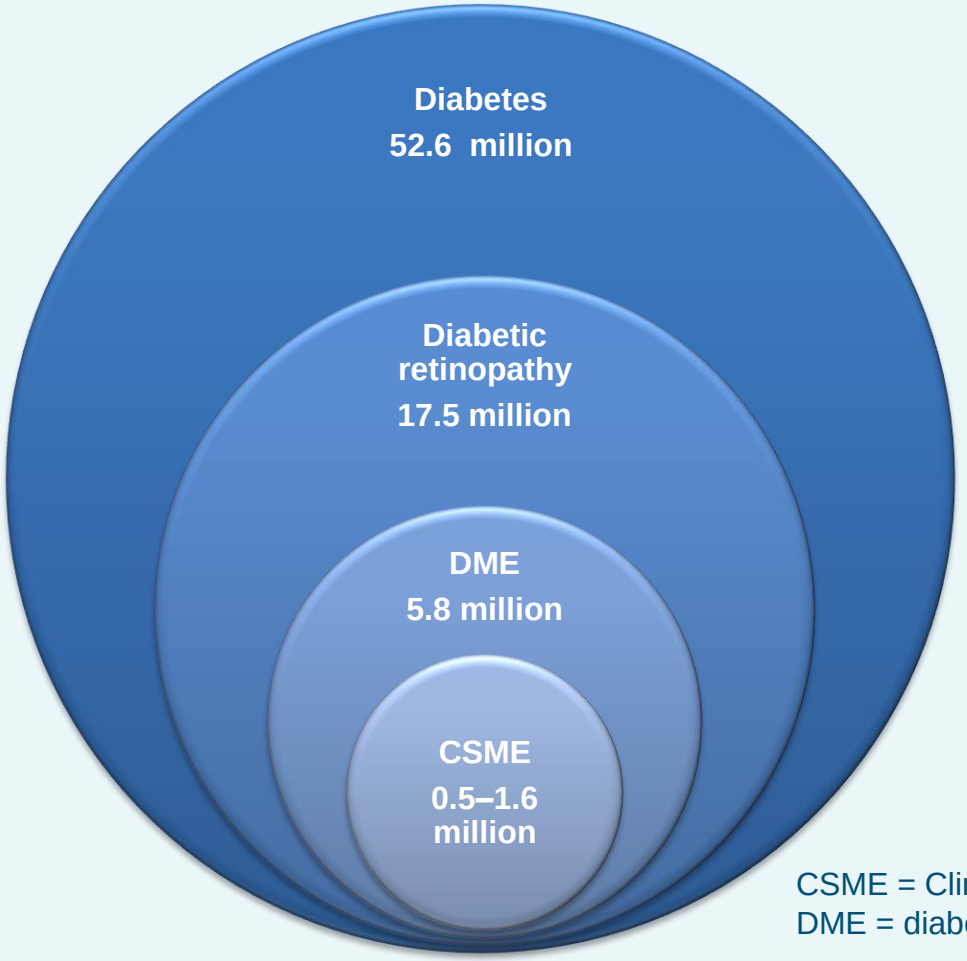


Image courtesy of Dr Alfredo Garcia Layana.

1. Ciulla TA, et al. *Diabetes Care* 2003;26(9):2653–2664; 2. International Diabetes Federation. Diabetes and Blindness due to DME. 2011. http://www.idf.org/sites/default/files/idf-europe/IDF%20Toolkit_Backgrounder_FINAL.pdf. Accessed June 6, 2014; 3. Lotery AJ. *European Ophthalmic Rev.* 2012;6(4):236–241; 4. Kleinman ME, et al. *Ophthalmologica.* 2010;224(Suppl 1):16–24.

Diabetic retinopathy and DME: Important complications that can lead to vision loss

Prevalence rates in Europe in 2011 (millions; extrapolated estimates)[1-3]



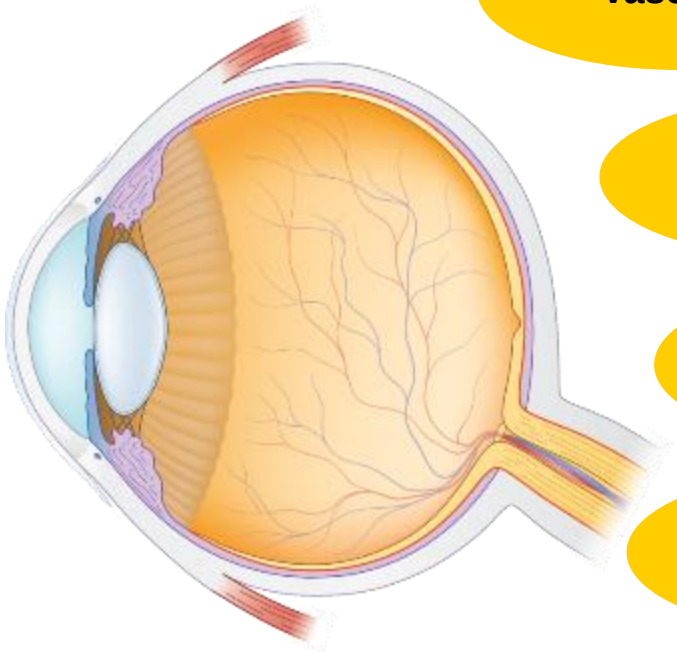
One-third rule:

- Approximately 1/3 of people with diabetes have diabetic retinopathy
- About 1/3 of people with diabetic retinopathy have DME, and 1/3 of these patients have CSME

CSME = Clinically significantly macular edema;
DME = diabetic macular edema.

1. International Diabetes Federation. IDF Diabetes Atlas: 5th Edition. 2011; 2. International Diabetes Federation. IDF Diabetes Atlas: 6th Edition. 2013; 3. IDF Europe. www.idf.org/sites/default/files/idf-europe/IDF%20Toolkit_Backgrounder_FINAL.pdf. Accessed June 4, 2014.

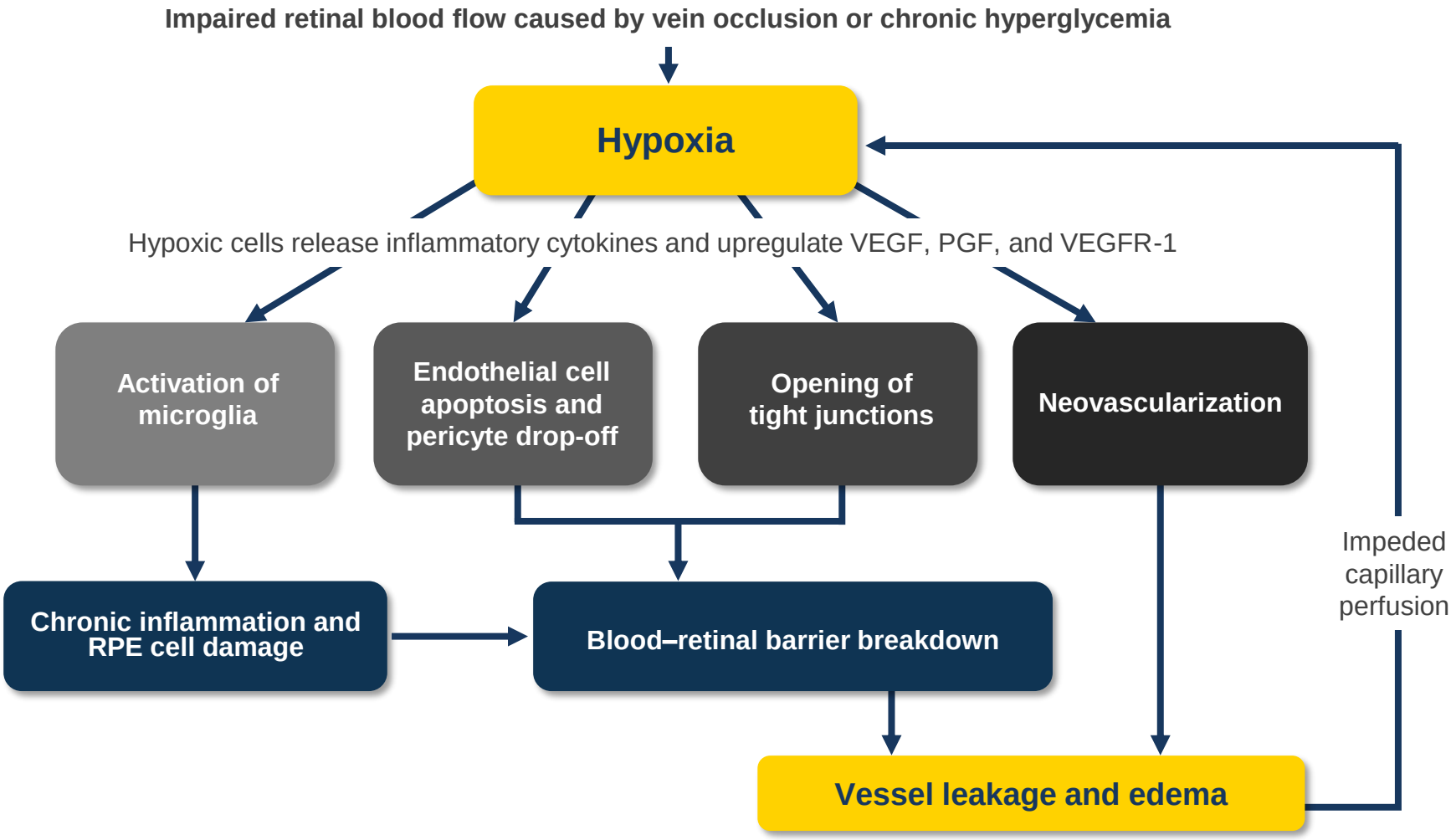
The spectrum of retinal disease



- **Vascular** — e.g. diabetic retinopathy, DME, RVO
- **Degenerative** — e.g. AMD
- **Genetic** — e.g. retinitis pigmentosa, macular dystrophies
- **Malignant** — e.g. retinoblastoma, melanoma
- **Inflammation and infections** — e.g. sarcoidosis, uveitis, HIV-associated infections

AMD, age-related macular degeneration; DME, diabetic macular edema; HIV, human immunodeficiency virus; RVO, retinal vein occlusion.

Multiple complex factors contribute to the development of retinal vascular disease

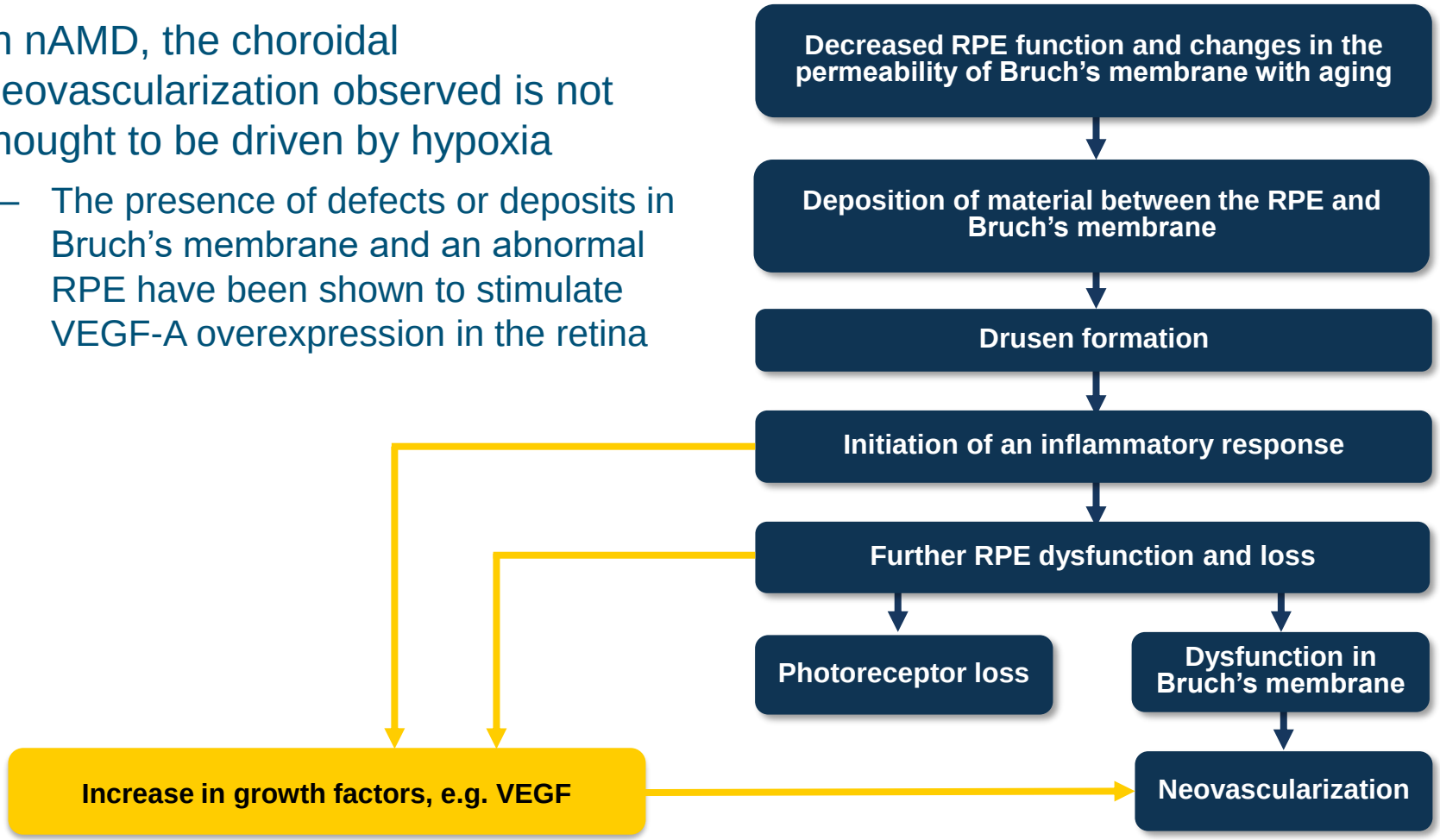


PGF, placental growth factor; RPE, retinal pigment epithelium; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Whitcup SM *et al*. *Int J Inflam* 2013; 2013: 724648. Joussen AM *et al. Mol Vis* 2009; 15: 1418–1428.

Neovascularization in nAMD is not driven primarily by hypoxia

- In nAMD, the choroidal neovascularization observed is not thought to be driven by hypoxia
  - The presence of defects or deposits in Bruch's membrane and an abnormal RPE have been shown to stimulate VEGF-A overexpression in the retina



nAMD, neovascular age-related macular degeneration; RPE, retinal pigment epithelium; VEGF, vascular endothelial growth factor.

Campochiaro PA. *J Mol Med (Berl)* 2013; 91 (3): 311–321. Kauppinen A *et al*. *Cell Mol Life Sci* 2016; 73 (9): 1765–1786.

The role of VEGF and PGF in retinal vascular disease

PGF, placental growth factor; VEGF, vascular endothelial growth factor.

VEGF-A and PGF act together through VEGF receptors

VEGF-A (VEGF)

- Acts via VEGFR-1 and VEGFR-2[1]
- Initiates normal angiogenesis and plays a critical role in pathological angiogenesis

PGF

- Binds to VEGFR-1
- Shown to be pro-angiogenic
- Can synergize with VEGF-A in VEGFR-1 activation[1]

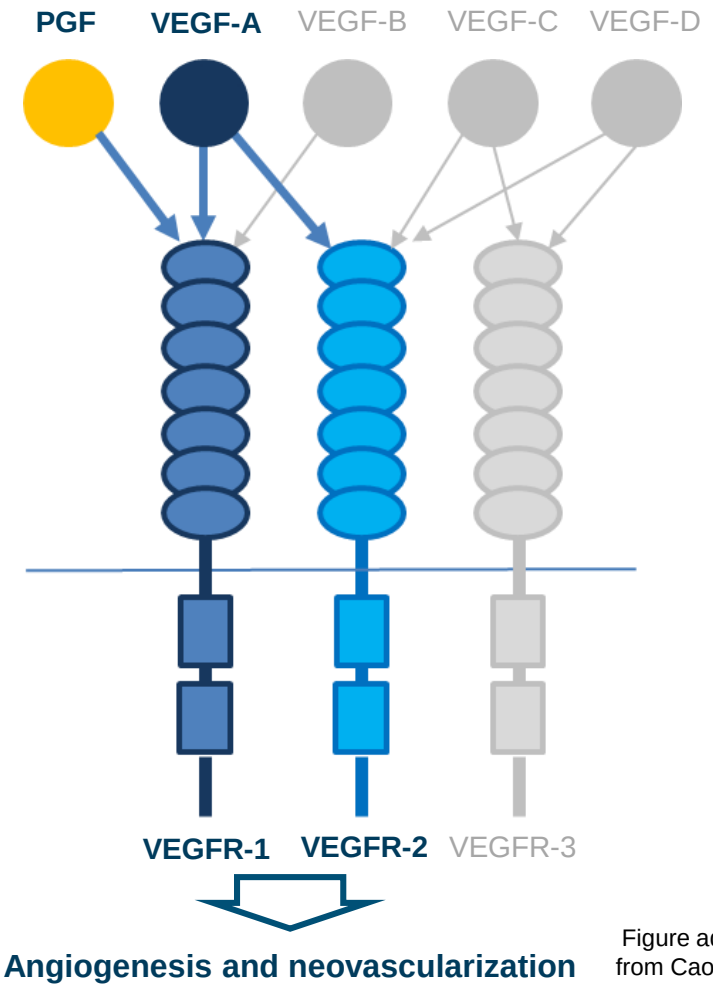


Figure adapted from Cao 2009[2]

PGF, placental growth factor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

1. Bayer Pharma AG. EYLEA – summary of product characteristics; August 2016. 2. Cao Y. *Sci Signal* 2009; 2 (59): re1. 3. Sawano A *et al. Blood* 2001; 97 (3): 785–791.

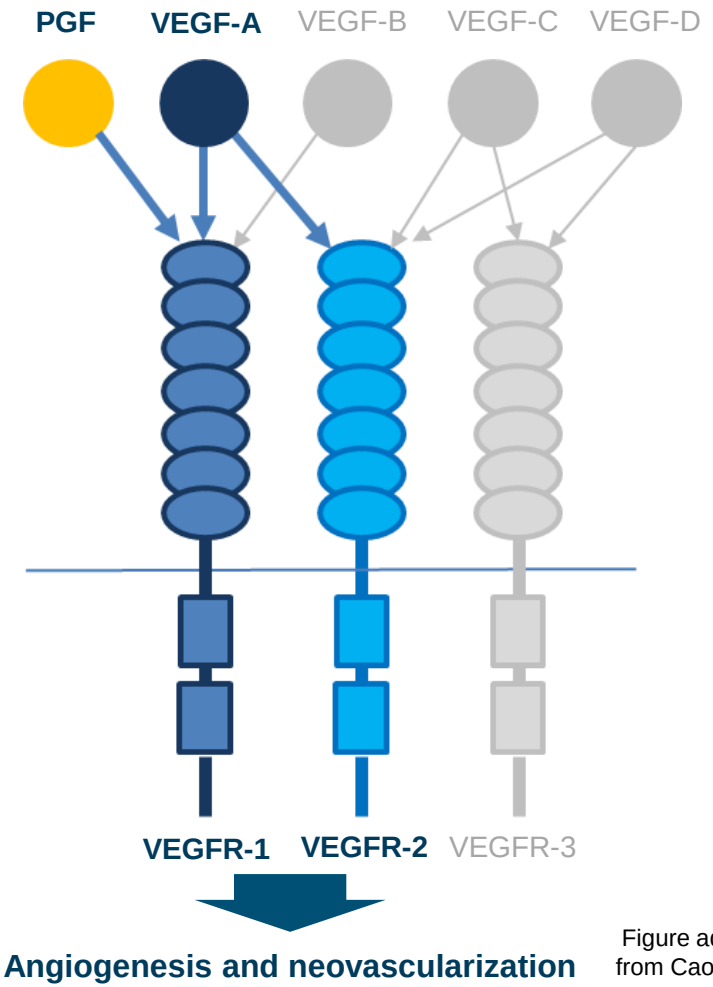
VEGF-A and PGF act together through VEGF receptors

Angiogenesis

•Excessive activation of VEGFR-1 and VEGFR-2 can result in pathological neovascularization and excessive vascular permeability, leading to macular edema[1]

Inflammation

•Human monocytes/macrophages and murine microglial cells have been shown to express VEGFR-1, but not VEGFR-2[3]



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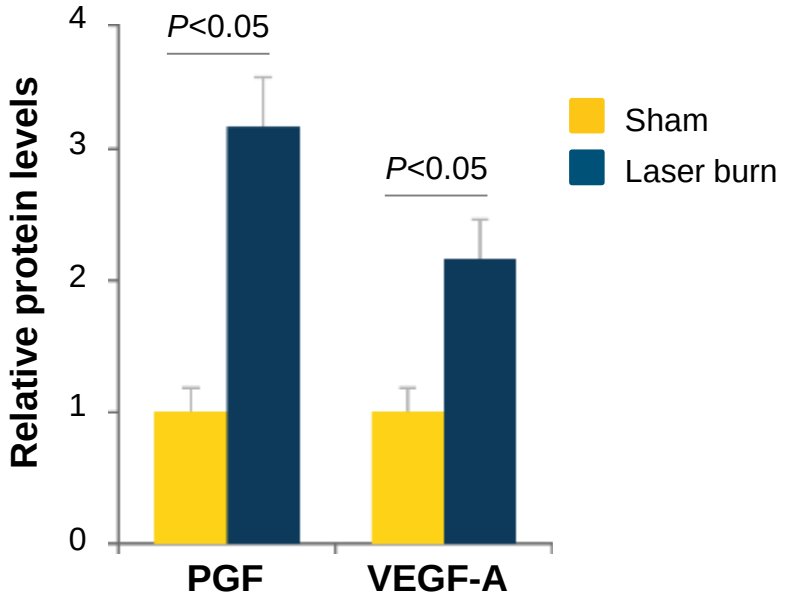
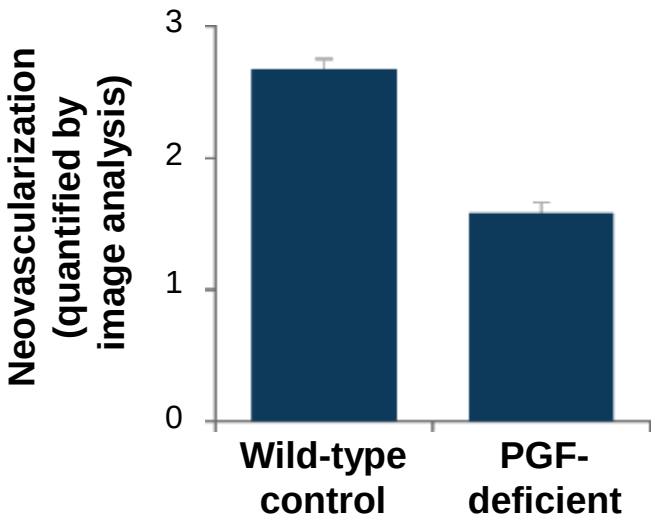
VEGF-A and PGF are upregulated in mouse retinas with experimentally-induced CNV

- In mouse models, laser burn–induced CNV was associated with significantly elevated levels of VEGF-A and PGF, compared with sham[1]
- Mice lacking PGF developed significantly reduced laser-induced CNV compared with wild-type controls ($P<0.001$)[2]

Expression of VEGF-A and PGF



Laser-induced neovascularization in mouse retinas

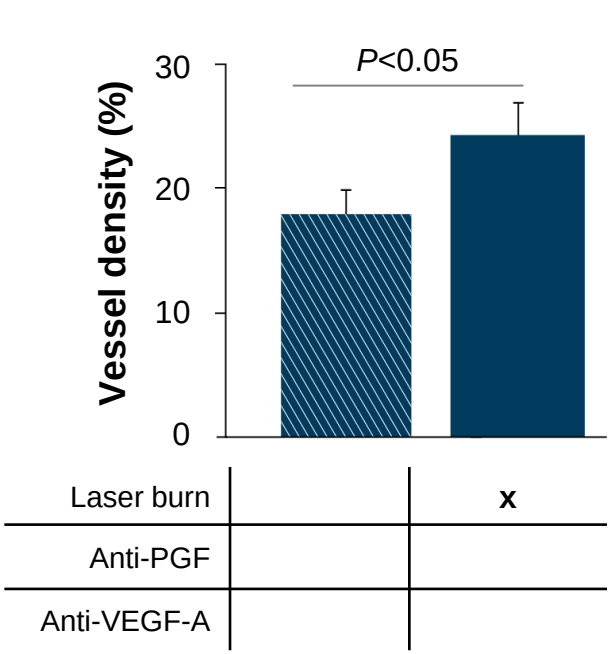


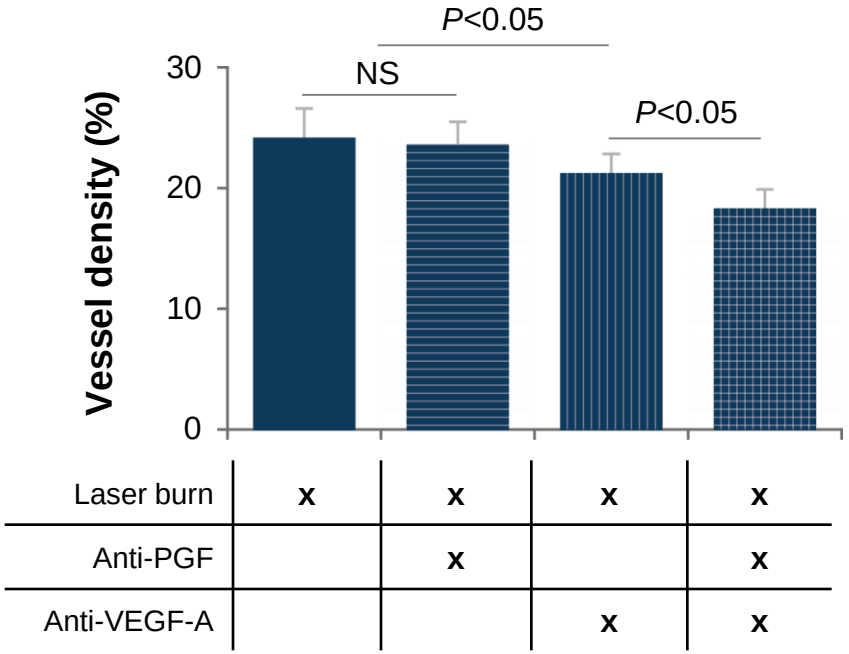
CNV, choroidal neovascularization; PGF, placental growth factor; VEGF, vascular endothelial growth factor.

1. Huo X *et al. Cell Physiol Biochem* 2015; 35 (5): 1787–1796. 2. Rakic JM *et al. Invest Ophthalmol Vis Sci* 2003; 44 (7): 3186–3193.

Inhibiting VEGF and PGF is more effective than inhibiting VEGF alone

Retinal density in CNV mouse model





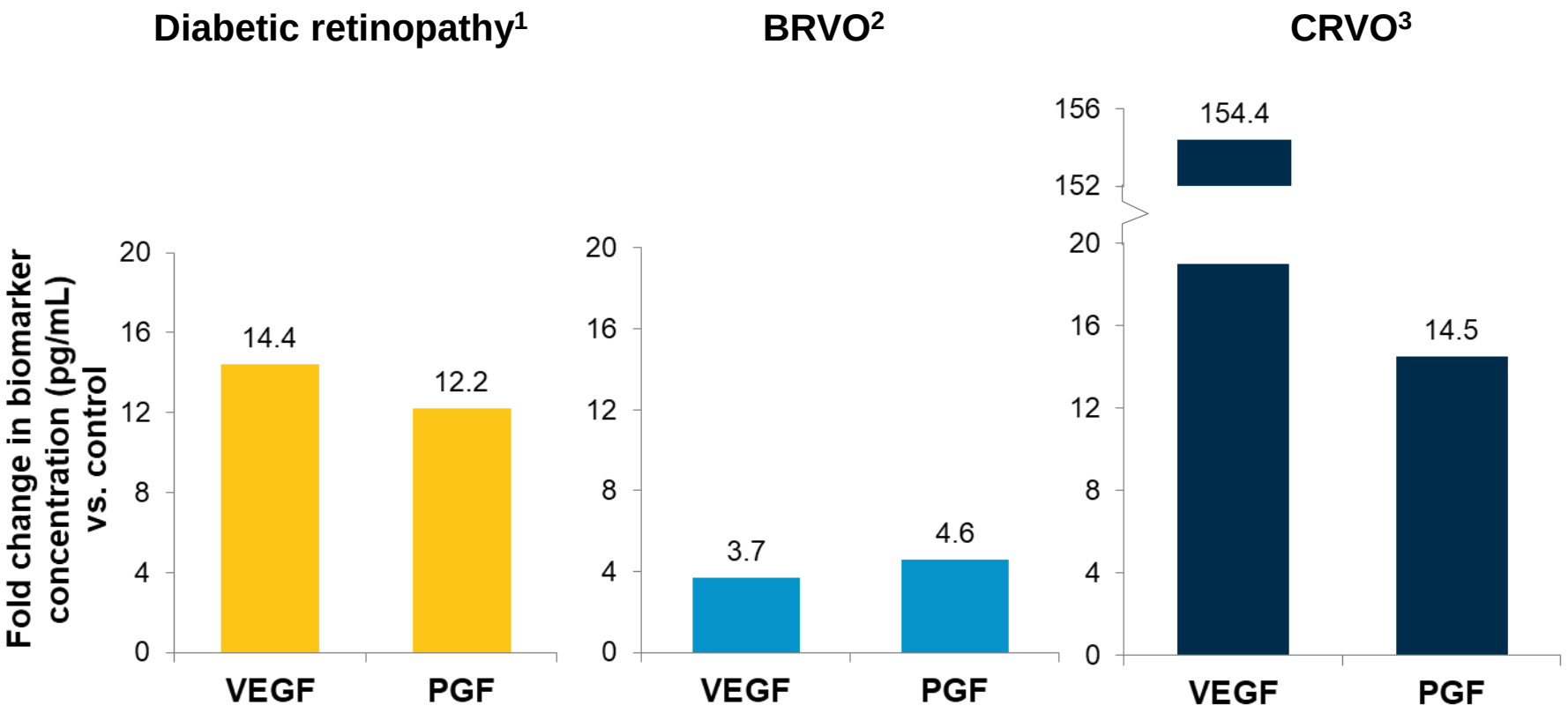
- Inhibition of VEGF-A, but not PGF, significantly reduced increases in vessel density induced by laser burn
- Co-inhibition of VEGF-A and PGF further reduced vessel density compared with inhibition of VEGF-A alone

Adapted from Huo *et al*. 2015

CNV, choroidal neovascularization; NS, not statistically significant; PGF, placental growth factor; VEGF, vascular endothelial growth factor.

Huo X *et al. Cell Physiol Biochem* 2015; 35 (5): 1787–1796.

Retinal vascular disease is associated with increased levels of VEGF and PGF, compared with controls

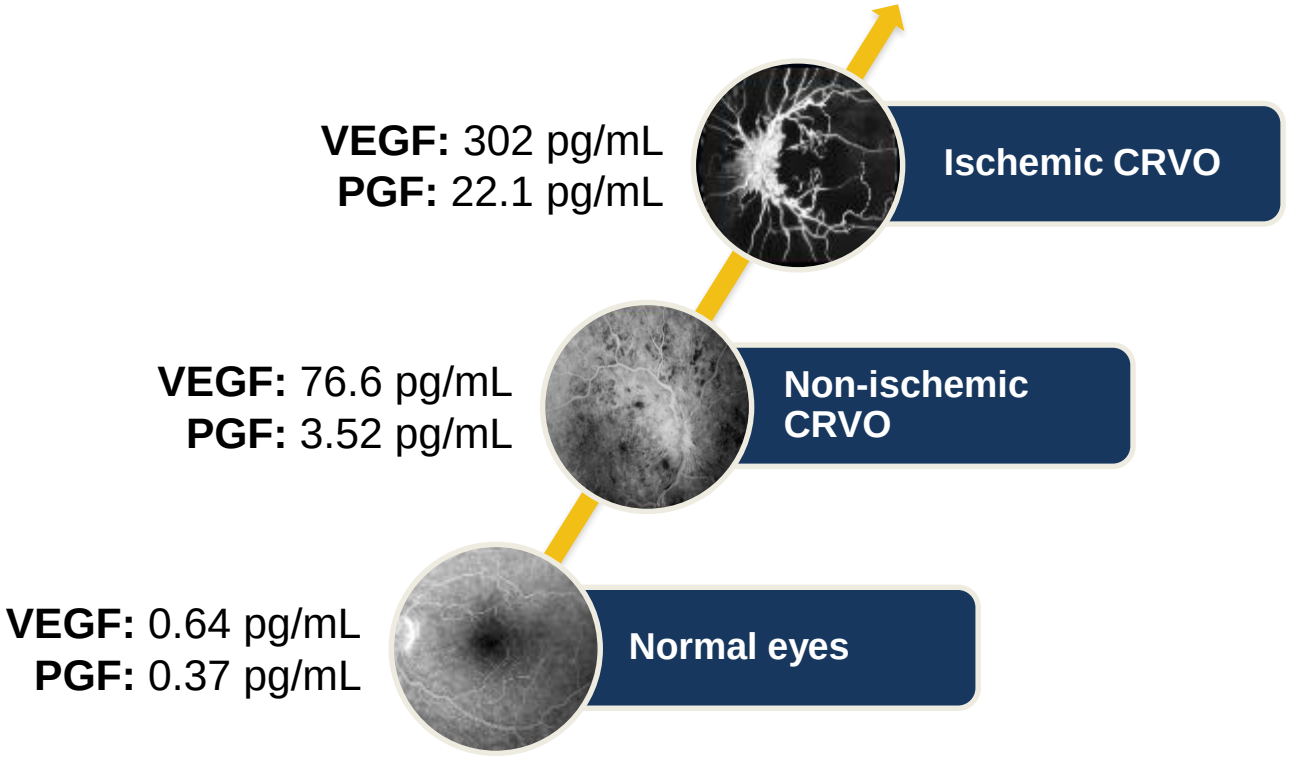


BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; PGF, placental growth factor; VEGF, vascular endothelial growth factor.

1. Kovacs K *et al. Invest Ophthalmol Vis Sci* 2015; 56 (11): 6523–6530. 2. Noma H *et al. Invest Ophthalmol Vis Sci* 2014; 55 (6): 3878–3885. 3. Noma H *et al. Invest Ophthalmol Vis Sci* 2015; 56 (2): 1122–1128.

The severity of ischemia correlates with levels of VEGF-A and PGF

- Aqueous VEGF and PGF levels are significantly increased in ischemic compared with non-ischemic retinal diseases, such as CRVO



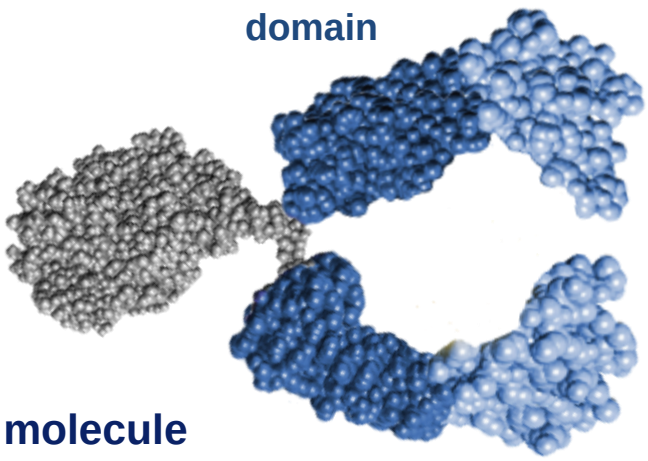
CRVO, central retinal vein occlusion; PGF, placental growth factor; VEGF, vascular endothelial growth factor.

Noma H *et al. Invest Ophthalmol Vis Sci* 2015; 56 (2): 1122–1128.

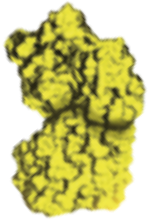
Aflibercept was specifically designed for high-affinity binding to VEGF and PGF[1]

- Aflibercept is a fusion protein for intravitreal injection that ‘traps’ VEGF-A and PGF molecules

Incorporates domains from two VEGF receptors for tight binding on both sides of VEGF and PGF, preventing interactions with other molecules[2]



Aflibercept molecule
Aflibercept–VEGF complex



VEGF dimer

Aflibercept binds more tightly to VEGF than the native VEGF receptors[2]

Fc, fragment, crystallizable; IgG, immunoglobulin G; PGF, placental growth factor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

1. Papadopoulos N *et al. Angiogenesis* 2012; 15 (2): 171–185. 2 Bayer Pharma AG. EYLEA – summary of product characteristics; August 2016.

Aflibercept: Relative VEGF-A binding affinity *in vitro*

- Kd: equilibrium dissociation constant. Lower value = tighter binding

	Aflibercept	VEGFR-1	Ranibizumab	Bevacizumab*	VEGFR-2
Kd (VEGF-A_{165})	**0.49 pM**	9.3 pM	**46 pM**	**58 pM**	88.8 pM

Highest binding affinity — **Lowest** binding affinity

- The affinity of aflibercept for VEGF-A is much greater than that of VEGFR-1 or VEGFR-2
- Aflibercept's affinity for VEGF-A is approximately 100x that of ranibizumab

*Bevacizumab is not licensed for intravitreal use.
VEGF, vascular endothelial growth factor; VEGF-A_{165}, VEGF-A 165 amino acid splice variant; VEGFR, vascular endothelial growth factor receptor.
Papadopoulos N *et al*. *Angiogenesis* 2012; 15 (2): 171–185.

Anti-angiogenic inhibition of VEGF-A and PGF *in vitro*

- IC_{50}: half maximal inhibitory concentration. Lower value = more potent inhibition

More potent inhibition

Less potent inhibition

	VEGFR-1 cell line			VEGFR-2 cell line	
	IC_{50} at 20 pM $VEGF\text{-}A_{121}$	IC_{50} at 20 pM $VEGF\text{-}A_{165}$	IC_{50} at 20 pM mPGF-2	IC_{50} at 20 pM $VEGF\text{-}A_{121}$	IC_{50} at 20 pM $VEGF\text{-}A_{165}$
Aflibercept	**15 pM**	**16 pM**	**104 pM**	**16 pM**	**26 pM**
Ranibizumab	**675 pM**	**1,140 pM**	**No activity**	**576 pM**	**845 pM**
Bevacizumab*	854 pM	1,476 pM	No activity	630 pM	1,323 pM

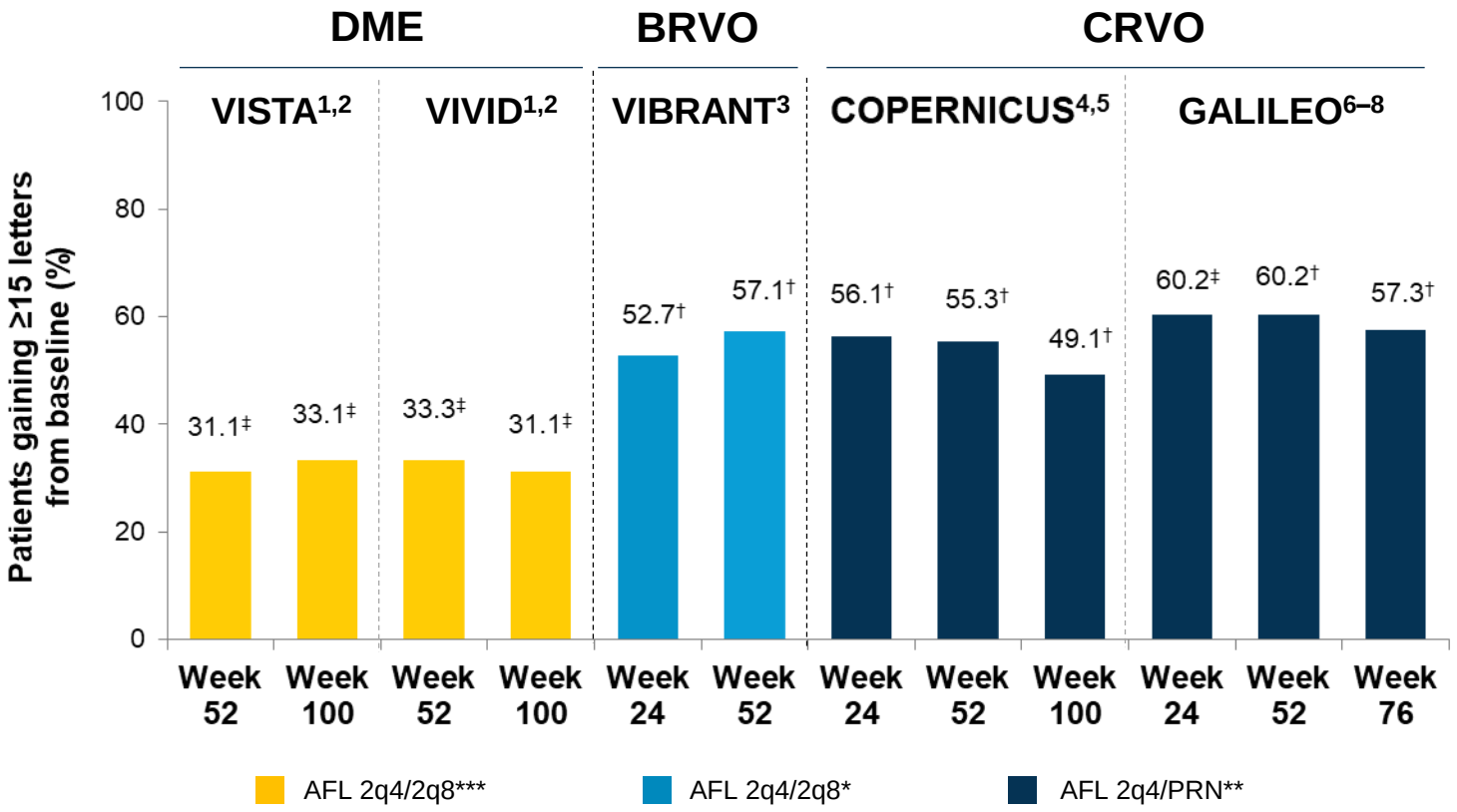
- Aflibercept, ranibizumab and bevacizumab inhibit all VEGF-A isoforms
  - Aflibercept blocks VEGF-induced activation of VEGFR-1/-2 with 71 times greater potency than ranibizumab
- Unlike ranibizumab and bevacizumab, aflibercept also inhibits the activity of PGF

*Bevacizumab is not licensed for intravitreal use.

PGF, placental growth factor; VEGF, vascular endothelial growth factor; $VEGF\text{-}A_{121}$, VEGF-A 121 amino acid splice variant; $VEGF\text{-}A_{165}$, VEGF-A 165 amino acid splice variant; VEGFR, vascular endothelial growth factor receptor.

Papadopoulos N *et al*. *Angiogenesis* 2012; 15 (2): 171–185.

The majority of aflibercept-treated patients had significant VA gains from baseline, which were maintained up to 100 weeks



*AFL 3 x 2q4 then 2q8. **AFL PRN from Week 24 onwards. ***AFL 2q8 after 5 monthly doses. †$P \leq 0.001$ vs. control. ‡$P \leq 0.0001$ vs. control. 2q4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks; AFL, aflibercept; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; DME, diabetic macular edema; PRN, *pro re nata* (as needed); VA, visual acuity.

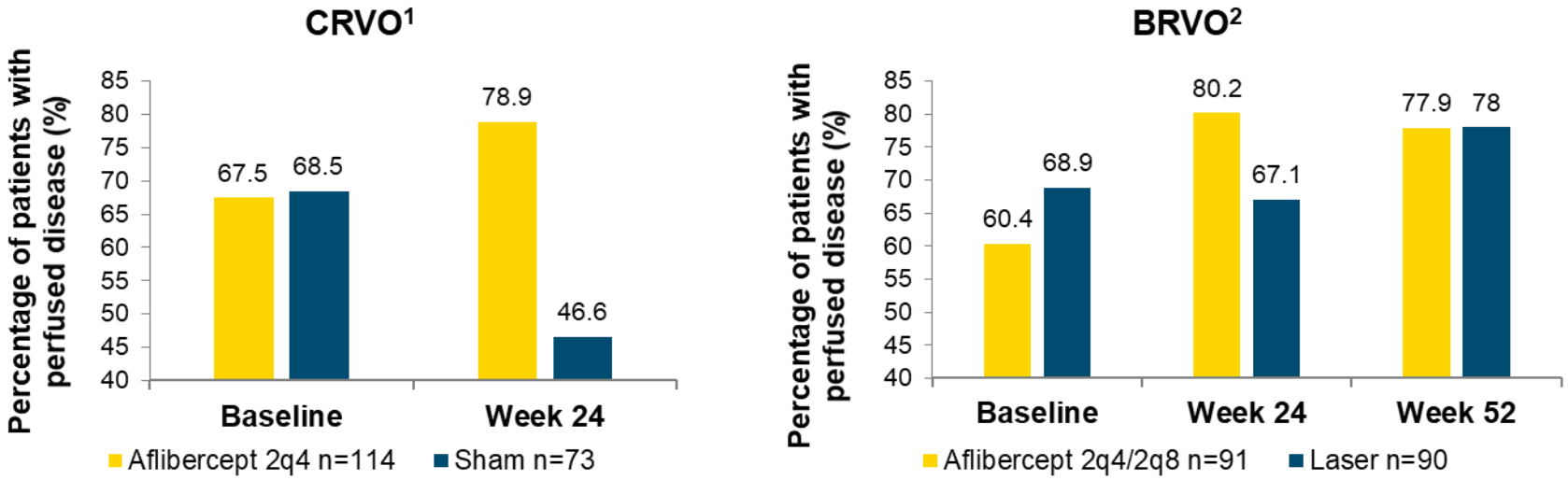
Please note that this information is from separate, independent studies and therefore should be carefully interpreted.

1. Korobelnik J-F *et al. Ophthalmology* 2014; 121 (11): 2247–2254. 2. Brown DM *et al. Ophthalmology* 2015; 122 (10): 2044–2052. 3. Lloyd Clark W *et al. Ophthalmology* 2016; 123 (2): 330–336. 4. Brown DM *et al. Am J Ophthalmol* 2013; 155 (3): 429–437.e7. 5. Heier JS *et al. Ophthalmology* 2014; 121 (7): 1414–1420.e1. 6. Holz FG *et al. Br J Ophthalmol* 2013; 97 (3): 278–284. 7. Korobelnik J-F *et al. Ophthalmology* 2014; 121 (1): 202–208. 8. Ogura Y *et al. Am J Ophthalmol* 2014; 158 (5): 1032–1038.

Aflibercept increased the percentage of RVO patients with a perfused retina

- The percentage of perfused* patients increased with aflibercept and was largely maintained to Week 52
  - In CRVO, perfusion improved with aflibercept, yet worsened with sham
  - In BRVO, the percentage of perfused patients in the laser arm remained relatively stable and increased after aflibercept rescue treatment became available (from Week 24)

Percentage of patients with perfused disease



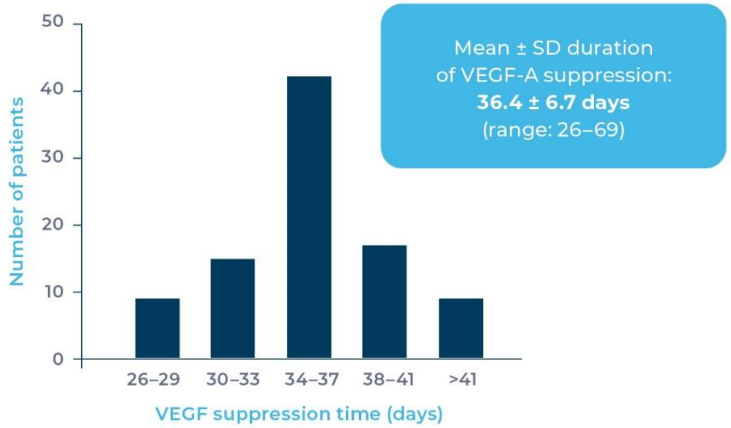
*Fewer than 10 disc areas of non-perfusion.
CRVO perfusion data from COPERNICUS; BRVO perfusion data from VIBRANT.
2q4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; RVO, retinal vein occlusion.
Boyer D *et al. Ophthalmology* 2012; 119 (5): 1024–1032. Lloyd Clark W *et al. Ophthalmology* 2016; 123 (2): 330–336.

The durability of aflibercept

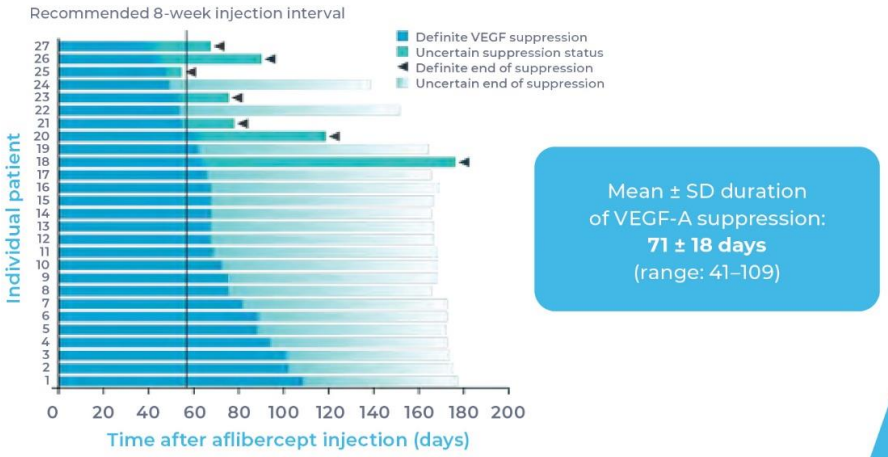
PK/PD modelling can provide robust estimates of clinical results

- Stewart and Rosenfeld estimated that the intravitreal biological activity of aflibercept 0.5–4 mg at 73–87 days equals that of ranibizumab 0.5 mg at 30 days[1]
- PK/PD modeling was confirmed by clinical studies in nAMD showing a mean VEGF-A suppression time of 36.4 days[2] and 71 days[3] with ranibizumab 0.5 mg and aflibercept 2 mg, respectively

Distribution of VEGF-A suppression in the aqueous humor by ranibizumab in patients with nAMD*,2



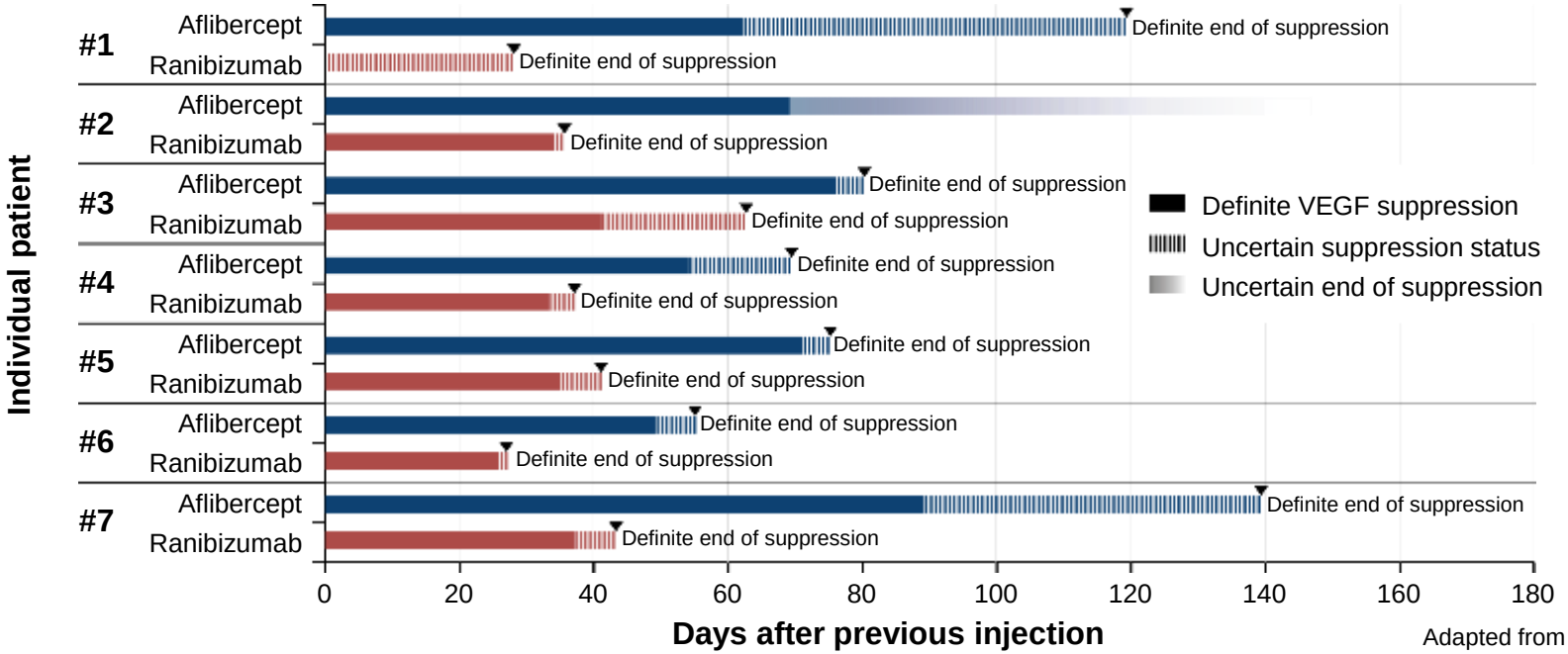
VEGF-A suppression in the aqueous humor by aflibercept in individual patients with nAMD†,3



*83 eyes of 83 patients with nAMD received 3 initial monthly doses of ranibizumab 0.5 mg and were monitored monthly thereafter. Recurrences were retreated with series of 3 consecutive, monthly ranibizumab 0.5 mg injections. A total of 859 aqueous humor specimens were taken and VEGF-A levels were measured. †27 eyes of 27 patients with nAMD received 3 initial monthly doses of aflibercept 2 mg and were monitored monthly thereafter. Recurrences were treated with additional aflibercept injections on a PRN regimen driven by morphologic findings on SD-OCT. Duration of complete suppression, as well as the end of suppression whenever definable. LLOQ, lower limit of quantification; nAMD, neovascular age-related macular degeneration; SD, standard deviation; SD-OCT, spectral domain optical coherence tomography; VEGF, vascular endothelial growth factor. **References:** 1. Stewart MW et al. *Br J Ophthalmol* 2008; 92 (5): 667–8. 2. Muether PS et al. *Am J Ophthalmol*. 2013; 156 (5): 989–993.e2. 3. Fauser S et al. *Am J Ophthalmol* 2014; 158 (3): 532–536.

Aflibercept was shown to have a VEGF suppression time twice as long as ranibizumab in nAMD

- Fauser *et al.* prospectively studied 7 eyes of 7 patients with long-standing persistent activity under ranibizumab therapy who were switched to aflibercept*
- Mean duration of VEGF-A suppression: **34 ± 5 days for ranibizumab** and **67 ± 14 days for aflibercept (*P*<0.001)**



Adapted from Fauser *et al.* 2016

*Aqueous samples obtained immediately prior to injection; LLD 4 pg/mL VEGF-A.
LLD, lower limit of detection; nAMD, neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor.
Fauser S *et al. Br J Ophthalmol* 2016; 100 (11): 1494–1498.