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Characterization of macular neovascularization subtypes in age-related macular degeneration to optimize treatment outcomes

The Vision Academy is a group of over 100 international ophthalmology experts who provide guidance for best clinical practice through their collective expertise in areas of controversy or with insufficient conclusive evidence.

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MNV, macular neovascularization.

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Objectives

To describe and define MNV subtypes in nAMD

To provide recommendations on tailoring treatments to the different MNV subtypes

- The Vision Academy provides ophthalmic specialists with a forum to share existing skills and knowledge, build best practice, and lead the wider community in the drive toward optimized, compassionate patient care
- Through their collective expertise, the Vision Academy seeks to provide guidance for best clinical practice in the management of retinal disease, particularly in areas with insufficient or inconclusive evidence

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QUESTION

Do different types of MNV result in different patient outcomes?

MNV, macular neovascularization; nAMD, neovascular age-related macular degeneration.

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Background

Neovascular subtypes

- Since AMD was first described, many efforts have been made to classify its pathology and the different types of **macular neovascularization** (MNV)[1-3]
- Recent developments in imaging techniques have allowed for a more precise definition of MNV localization[4]

Old classification system

Angiographic-based subtypes
(use of FA imaging)

- Occult
- Classic
- Mixed
- RAP

New classification system

Anatomic-based subtypes
(use of FA, ICGA, and SD-OCT imaging)

- Type 1
- Type 2
- Mixed
- Type 3

RECOMMENDATION

AMD, age-related macular degeneration; FA, fluorescein angiography; ICGA, indocyanine green angiography; RAP, retinal angiomatous proliferation; SD-OCT, spectral-domain optical coherence tomography.

1. Spaide RF *et al*. *Ophthalmology* 2020; 127 (5): 616–636; 2. Gass JD. *Trans Am Ophthalmol Soc* 1994; 92: 91–111; 3. Grossniklaus HE, Gass JD. *Am J Ophthalmol* 1998; 126 (1): 59–69; 4. Freund KB *et al*. *Retina* 2010; 30 (9): 1333–1349.

MNV subtypes on multimodal imaging

- When the following examinations are interpreted together, the intra- and inter-observer agreement for the definition of neovascular subtypes is higher:[1]
  - Fluorescein angiography
  - Indocyanine green angiography
  - Spectral-domain / swept-source OCT
- Ideally, they should therefore be **used in conjunction** to determine the MNV subtype
- The **three subtypes** of MNV are characterized through **multimodal imaging**[2-4]
- A clearly defined classification of MNV can help **predict functional and anatomical outcomes** after treatment and could help with patient management[5]

MNV, macular neovascularization; OCT, optical coherence tomography.

1. Ravera V *et al*. *Retina* 2019; 39 (2): 281–287; 2. Freund KB *et al*. *Retina* 2010; 30 (9): 1333–1349; 3. Jung JJ *et al*. *Am J Ophthalmol* 2014; 158 (4): 769–779.e2; 4. Spaide RF *et al*. *Ophthalmology* 2020; 127 (5): 616–636; 5. Mathis T et al. Eye 2022; https://doi.org/10.1038/s41433-022-02231-y.

Classification of MNV subtypes

MNV subtype	Known as	Characterized by	FA imaging shows	ICGA imaging shows	SD-OCT imaging shows	Variants
Type 1	Occult neovascularization	The presence of MNV beneath the RPE layer[1,2]	Poorly defined leakage[1,2]	A late hyperfluorescent plaque that represents the neovascular network[1,2]	PED with no disruption of the RPE layer[1,2]	• PCV[3] • Treatment-naïve, quiescent (i.e., non-exudative)[4]
Type 2	Classic neovascularization	The presence of MNV of choroidal origin in the neuroretina, having broken through the RPE layer[1]	A well-defined neovascular membrane defined by intense leakage that increases over time[1,2]	Less important but can reveal a sub-RPE part of MNV, defining MNV as a mixed lesion with both type 1 and type 2 components[1]	Disruption of the RPE–Bruch's membrane complex and localization of the neovessels above the RPE layer[1,3]	Mixed (1/2) subtype[3,6]
Type 3	Retinal angiomatous proliferation (RAP)	An anomalous vascular complex originating in neuroretinal layers[1]	Early focal leakage close to retinal vessels[1,2]	Late hyperfluorescent hot spot[5]	Information on the stage of the disease[7,8]	Stages 1–3[7,8]

FA, fluorescein angiography; ICGA, indocyanine green angiography; MNV, macular neovascularization; PCV, polypoidal choroidal vasculopathy; PED, pigment epithelial detachment; RPE, retinal pigment epithelial; SD-OCT, spectral-domain optical coherence tomography.

1. Mathis T *et al*. *Eye* 2022; https://doi.org/10.1038/s41433-022-02231-y; 2. Spaide RF *et al*. *Ophthalmology* 2020; 127 (5): 616–636; 3. Freund KB *et al*. *Retina* 2010; 30 (9): 1333–1349; 4. Querques G *et al*. *Eur J Ophthalmol* 2021; 31 (6): 3164–3176; 5. Fernández M *et al*. https://amdbook.org/content/diagnostic-usefulness-indocyanine-green-angiography-icga-age-related-macular-degeneration-am. Accessed October 2022; 6. Levine ES *et al*. *Int J Retina Vitreous* 2020; 6: 39; 7. Kim JH *et al*. *Retina* 2018; 38 (12): 2356–2362; 8. Su D *et al*. *Retina* 2016; 36 (Suppl 1): S40–S49.

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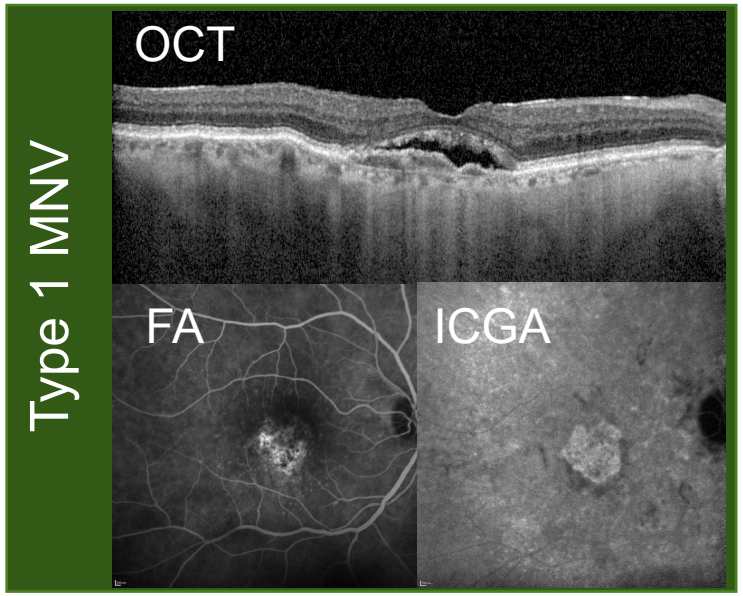
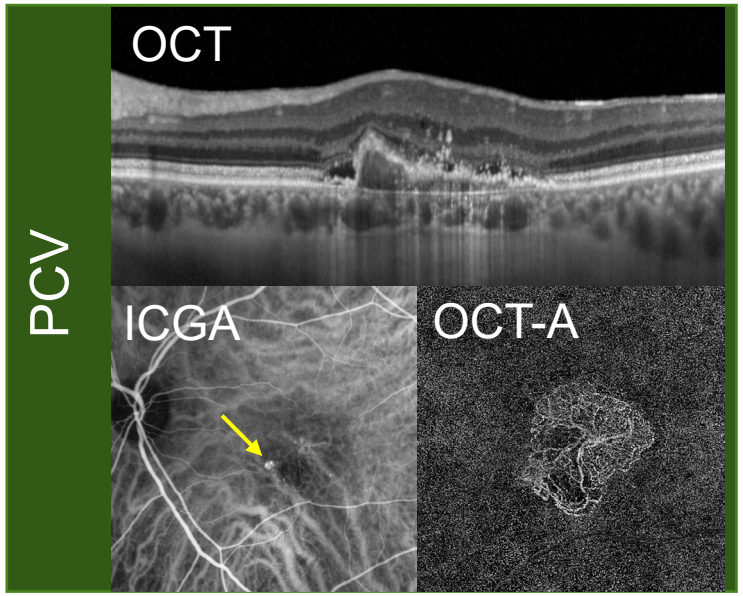
Type 1 (occult) MNV

MNV subtype	Known as	Characterized by	FA imaging shows	ICGA imaging shows	SD-OCT imaging shows	Variants
Type 1	Occult neovascularization	The presence of MNV beneath the RPE layer[1,2]	Poorly defined leakage[1,2]	A late hyperfluorescent plaque that represents the neovascular network[1,2]	PED with no disruption of the RPE layer[1,2]	• PCV[3] • Treatment-naïve, quiescent (i.e., non-exudative)[4]





Images courtesy of Dr. Thibaud Mathis.

FA, fluorescein angiography; ICGA, indocyanine green angiography; MNV, macular neovascularization; OCT, optical coherence tomography; OCT-A, optical coherence tomography angiography; PCV, polypoidal choroidal vasculopathy; PED, pigment epithelial detachment; RPE, retinal pigment epithelial; SD-OCT, spectral-domain optical coherence tomography.

1. Mathis T *et al*. *Eye* 2022; https://doi.org/10.1038/s41433-022-02231-y; 2. Spaide RF *et al*. *Ophthalmology* 2020; 127 (5): 616–636; 3. Freund KB *et al*. *Retina* 2010; 30 (9): 1333–1349; 4. Querques G *et al*. *Eur J Ophthalmol* 2021; 31 (6): 3164–3176.

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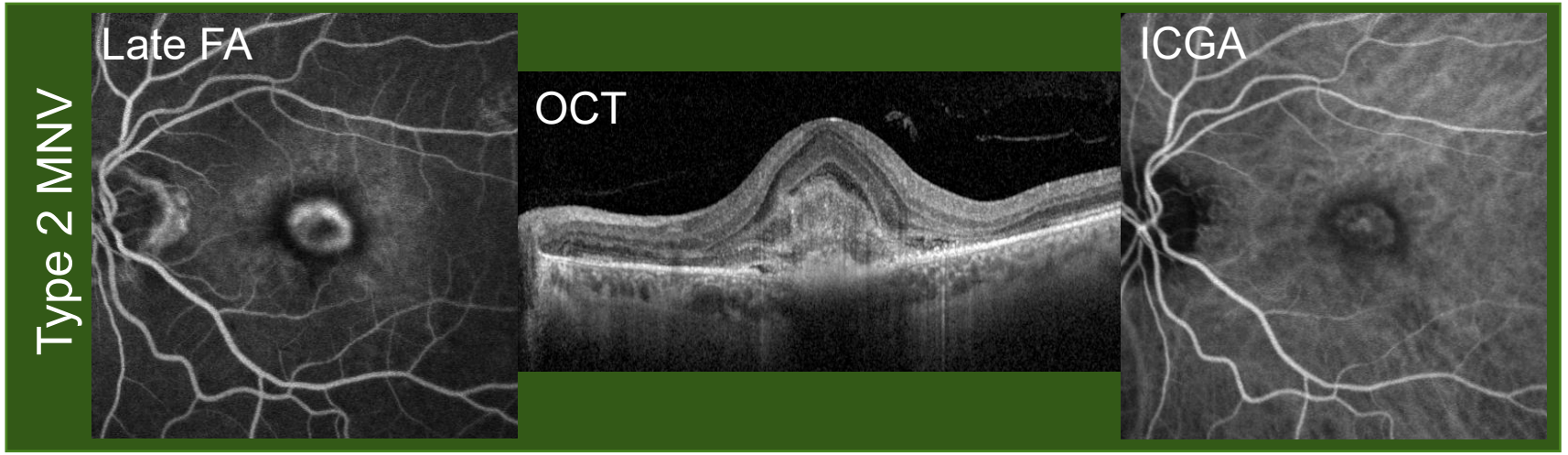
Type 2 (classic) MNV

MNV subtype	Known as	Characterized by	FA imaging shows	ICGA imaging shows	SD-OCT imaging shows	Variants
Type 2	Classic neovascularization	The presence of MNV of choroidal origin in the neuroretina, having broken through the RPE layer[1]	A well-defined neovascular membrane defined by intense leakage that increases over time[1,2]	Less important but can reveal a sub-RPE part of MNV, defining MNV as a mixed lesion with both type 1 and type 2 components[3]	Disruption of the RPE–Bruch's membrane complex and localization of the neovessels above the RPE layer[1,4]	Mixed (1/2) subtype[4,5]



Images courtesy of Dr. Thibaud Mathis.
FA, fluorescein angiography; ICGA, indocyanine green angiography; MNV, macular neovascularization; OCT, optical coherence tomography; RPE, retinal pigment epithelial; SD-OCT, spectral-domain optical coherence tomography.

1. Mathis T *et al*. *Eye* 2022; https://doi.org/10.1038/s41433-022-02231-y; 2. Spaide RF *et al*. *Ophthalmology* 2020; 127 (5): 616–636; 3. Fernández M *et al*. https://amdbook.org/content/diagnostic-usefulness-indocyanine-green-angiography-icga-age-related-macular-degeneration-am. Accessed October 2022; 4. Freund KB *et al*. *Retina* 2010; 30 (9): 1333–1349; 5. Levine ES *et al*. *Int J Retina Vitreous* 2020; 6: 39.

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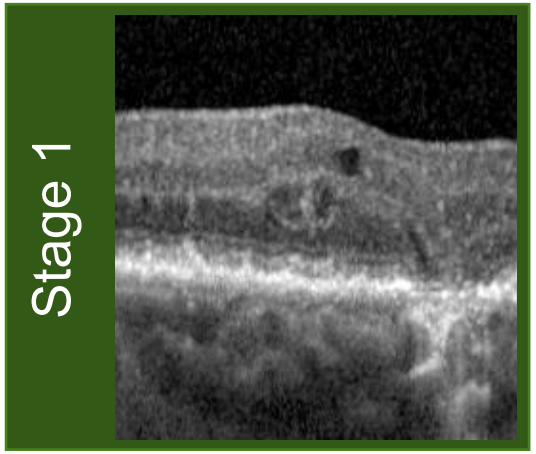
Type 3 (RAP) MNV

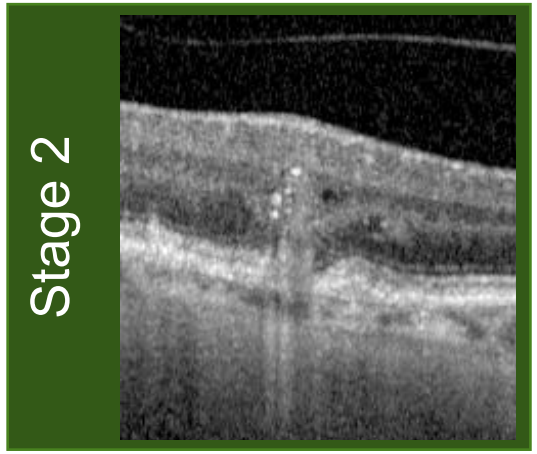
MNV subtype	Known as	Characterized by	FA imaging shows	ICGA imaging shows	SD-OCT imaging shows	Variants
Type 3	Retinal angiomatous proliferation (RAP)	An anomalous vascular complex originating in neuroretinal layers[1]	Early focal leakage close to retinal vessels[1,2]	Late hyperfluorescent hot spot[3]	Information on stage of the disease[4,5]	Stages 1–3[4,5]

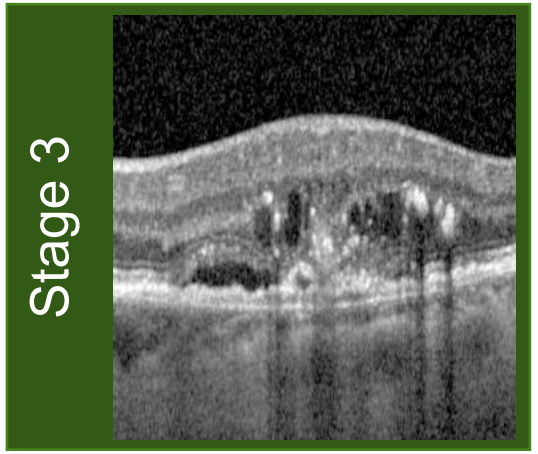
Stage 1 involves an intraretinal hyperreflective lesion in front of a PED, associated with mild cystoid macular edema without outer-retinal alterations[5]

Stage 2 involves an outer-retinal alteration with RPE disruption and an increase in the hyperreflective lesion, in addition to the intraretinal edema[5]

Stage 3 is defined by intraretinal hyperreflective lesions that extend through the RPE to vascularize the PED[5]







Images courtesy of Dr. Thibaud Mathis.
FA, fluorescein angiography; ICGA, indocyanine green angiography; MNV, macular neovascularization; PED, pigment epithelial detachment; RAP, retinal angiomatous proliferation; RPE, retinal pigment epithelium / epithelial; SD-OCT, spectral-domain optical coherence tomography.
1. Mathis T *et al*. *Eye* 2022; https://doi.org/10.1038/s41433-022-02231-y; 2. Spaide RF *et al*. *Ophthalmology* 2020; 127 (5): 616–636; 3. Fernández M *et al*. https://amdbook.org/content/diagnostic-usefulness-indocyanine-green-angiography-icga-age-related-macular-degeneration-am. Accessed October 2022; 4. Kim JH *et al*. *Retina* 2018; 38 (12): 2356–2362; 5. Su D *et al*. *Retina* 2016; 36 (Suppl 1): S40–S49.

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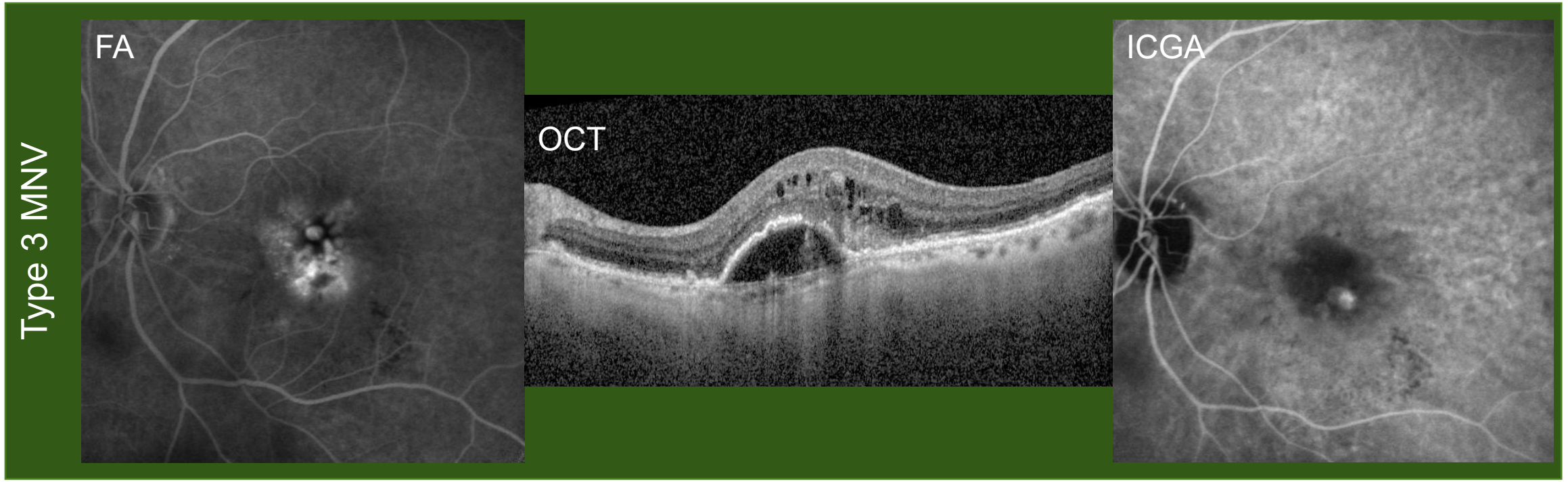
Type 3 (RAP) MNV



Images courtesy of Dr. Thibaud Mathis.
FA, fluorescein angiography; ICGA, indocyanine green angiography; MNV, macular neovascularization; OCT, optical coherence tomography; RAP, retinal angiomatous proliferation.

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Treatment outcomes may depend on the MNV subtype

MNV, macular neovascularization.

Classification of MNV subtypes: Why does it matter?

Accurately assessing MNV subtypes can provide information on expected prognosis and aid in optimizing treatment

A clearly defined classification of MNV can predict functional and anatomical outcomes after treatment

Treatment regimens should be individualized to each patient, according to MNV subtype

?

CHALLENGE REQUIRING VISION ACADEMY GUIDANCE

How should nAMD treatment be tailored according to MNV subtype?

RECOMMENDATION

MNV, macular neovascularization; nAMD, neovascular age-related macular degeneration.

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Natural history of MNV differs according to subtype

- Patients with certain MNV subtypes may experience worse visual outcomes if left untreated

Best VA	Intermediate VA	Worst VA
Type 1 MNV	**Type 2 MNV**	**Type 3 (stage 3) MNV**
• ~50% of patients have VA loss of ≥2 or 3 lines at 1 year (n=372)[1] • Median VA loss of 1.9 lines (no blood, n=12) to 2.8 lines (with blood, n=9) at 9–12 months[2] • Mean VA loss of 3 lines at 2 years (n=238)[3]	• ~55% of patients have VA loss of ≥3 lines at 1 year (n=207)[4] • Mean VA loss of ~4 lines at 2 years (n=112)[5]	• 69% of eyes <20/200 (n=16)[6] • 36% legally blind at 1 year[6] • Mean VA loss of 6 lines at 1 year[6] • Higher risk of fellow-eye involvement than with type 1 or type 2 MNV[7]

- MNV subtypes need to be carefully characterized so study data can be correctly interpreted, especially as lesions can progress over time from one choroidal neovascularization subtype to another[8]

MNV, macular neovascularization; n, number of eyes; VA, visual acuity.

1. Polito A *et al*. *Ann Acad Med Singap* 2006; 35 (3): 145–150; 2. Stevens TS *et al*. *Arch Ophthalmol* 1997; 115 (3): 345–350; 3. Rosenfeld PJ *et al*. *N Engl J Med* 2006; 355 (14): 1419–1431; 4. TAP Study Group. *Arch Ophthalmol* 1999; 117 (10): 1329–1345; 5. Macular Photocoagulation Study Group. *Arch Ophthalmol* 1991; 109 (9): 1232–1241; 6. Viola F *et al*. *Retina* 2009; 29 (6): 732–739; 7. Bochicchio S *et al*. *Ophthalmol Retina* 2019; 3 (1): 27–31; 8. Schneider U *et al*. *Acta Ophthalmol Scand* 2005; 83 (2): 141–147.

MNV subtype can affect mean number of injections during anti-VEGF treatment

- In a retrospective cohort study, patients with newly diagnosed, treatment-naïve nAMD were followed consecutively for 6 years during T&E treatment. The number of injections varied between different MNV subtypes

	Mean number of injections per year					
MNV subtype[a]	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6**
Type 1	9.4	8.2	8.6	8.6	8.5	9.1
Type 2	8.3	6	7.8	7.8	8.1	8.2
Type 3	8.7	8	7.5	8.1	7.8	8.4
Multiple lesion types	8.8	7.3	7.4	6.8	7.9	7

[a]MNV subtype classified using fluorescein angiography and optical coherence tomography.
MNV, macular neovascularization; nAMD, neovascular age-related macular degeneration; T&E, treat-and-extend; VEGF, vascular endothelial growth factor.
Mrejen S *et al*. *J Clin Med* 2015; 4 (7): 1380–1402.

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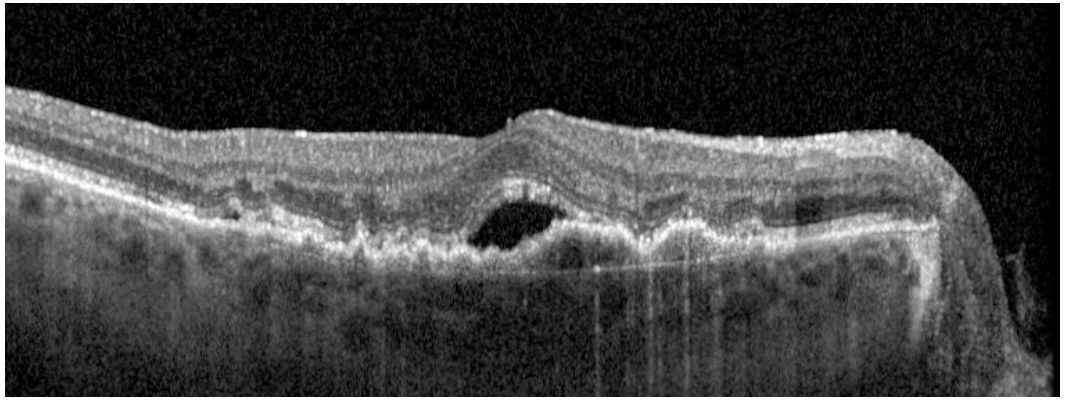
Treatment outcomes and type 1 MNV

- **More anti-VEGF injections** are required to treat type 1 lesions since large mature vessels are often present and may produce recalcitrant or persistent subretinal exudation[1]
- Eyes with type 1 MNV are **more likely to maintain vision over time** than eyes with other lesion subtypes despite more frequent injections in a T&E regimen (~8–9 per year in a 4- to 5-year follow-up)[2]
- The **risk of developing GA is 4.3–7.7 times lower** in type 1 MNV than in other lesion subtypes[3]
  - Progression of GA is reduced in both treatment-naïve, quiescent and formerly exudative type 1 MNV[3,4]
- In a T&E regimen, **tolerating some SRF** (which is a major finding in patients with type 1 MNV) has been reported to achieve similar VA, with fewer injections, compared with treatments aiming to resolve SRF entirely[5]

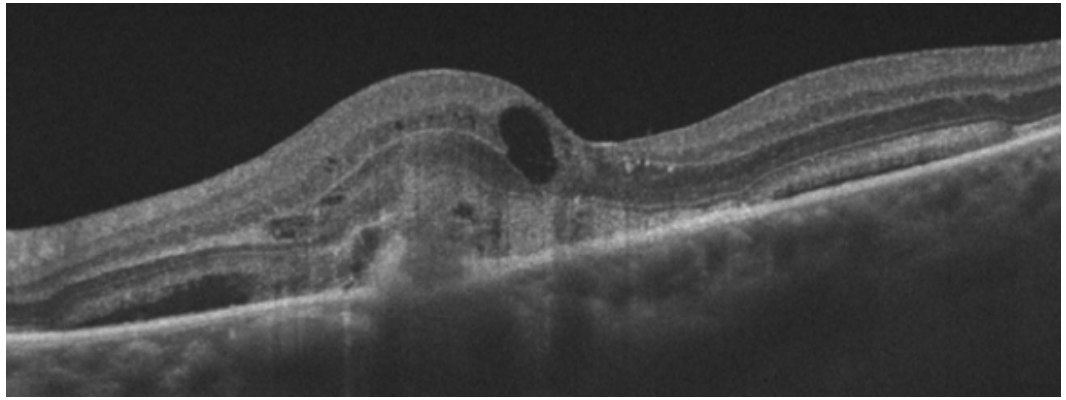


GA, geographic atrophy; MNV, macular neovascularization; SRF, subretinal fluid; T&E, treat-and-extend; VA, visual acuity; VEGF, vascular endothelial growth factor.

1. Mathis T *et al*. *Eye* 2022; https://doi.org/10.1038/s41433-022-02231-y; 2. Mrejen S *et al*. *J Clin Med* 2015; 4 (7): 1380–1402; 3. Xu L *et al*. *Retina* 2015; 35 (2): 176–186; 4. Pfau M *et al*. *Ophthalmol Retina* 2020; 4 (3): 238–248; 5. Guymer RH *et al*. *Ophthalmology* 2019; 126 (5): 723–734.

Treatment outcomes and type 2 MNV

- Eyes with type 2 MNV are associated with more **fibrotic scars**, a major risk factor for poor visual outcomes after treatment[1,2]
  - A *post hoc* analysis of the CATT study found that type 2 lesions had a 4.5-fold higher risk of developing a fibrotic scar than type 1 lesions ($p<0.001$)[3]
- Type 2 lesions typically **respond more quickly to anti-VEGF therapy** than type 1 lesions[4]
  - This quicker response may be due to the small lesion size and localization of the MNV complex above the RPE cell layer[4]
- Type 2 lesions generally **require fewer injections** than other MNV subtypes[5]



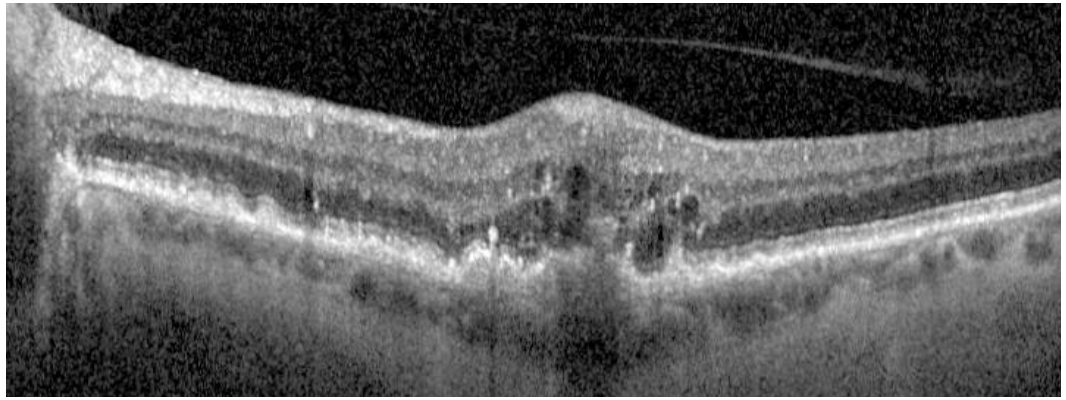
CATT, Comparison of Age-related Macular Degeneration Treatments Trials; MNV, macular neovascularization; RPE, retinal pigment epithelial; VEGF, vascular endothelial growth factor.

1. TAP Study Group. *Arch Ophthalmol* 1999; 117 (10): 1329–1345; 2. Cohen SY *et al*. *Retina* 2012; 32 (8): 1480–1485; 3. Daniel E *et al*. *Ophthalmology* 2018; 125 (7): 1037–1046; 4. Invernizzi A *et al*. *Am J Ophthalmol* 2019; 204: 105–112; 5. Mrejen S *et al*. *J Clin Med* 2015; 4 (7): 1380–1402.

Treatment outcomes and type 3 MNV

- Eyes with early type 3 MNV are more **prone to responding to anti-VEGF therapy** and demonstrate relatively good short-term visual outcomes in response to treatment[1]
  - The small size and intraretinal localization of the neovascularization likely result in better exposure to treatment[1]
- Type 3 lesions have a **high occurrence of GA** compared with types 1 and 2, with up to 86% of patients developing atrophy during follow-up,[2,3] and their location induces the accumulation of IRF[1]
- Type 3 lesions are more associated with fellow-eye involvement than types 1 and 2[4]
- **Fewer injections** are required if the lesions are treated at an earlier stage[5]
- When using an OCT-based classification method, visual outcomes are worse in stage 3 than in stage 2[6]

Retinal angiomatous proliferation (RAP) → Type 3



GA, geographic atrophy; IRF, intraretinal fluid; MNV, macular neovascularization; OCT, optical coherence tomography; VEGF, vascular endothelial growth factor.

1. Invernizzi A *et al*. *Br J Ophthalmol* 2019; 103 (9): 1337–1341; 2. Baek J *et al*. *Invest Ophthalmol Vis Sci* 2016; 57 (3): 1500–1505; 3. McBain VA *et al*. *Retina* 2011; 31 (6): 1043–1052; 4. Bochicchio S *et al*. *Ophthalmol Retina* 2019; 3 (1): 27–31; 5. Park YG, Roh Y-J. *BMC Ophthalmol* 2015; 15: 182; 6. Kim JH *et al*. *Retina* 2018; 38 (12): 2356–2362.

What is the risk of fellow-eye involvement?

- Involvement of the fellow eye varies between MNV subtypes
  - Type 3 lesions have a higher risk of being associated with pathology in the fellow eye[1]

	Proportion of patients receiving treatment in the fellow eye in follow-up years			
MNV subtype[a]	**Year 1**	**Year 2**	**Year 3**	**Year 4**
CNV (n=202)[b]	1%	2%	8%	17%
RAP (n=29)[b]	0%	10%	38%	68%

- In patients diagnosed with unilateral RAP lesions, the form of neovascularization that develops in the fellow eye is generally also RAP[2]
- Treating early-stage RAP appears to result in fewer recurrences and better visual outcomes compared with treating later stages[3]

Due to the variation in published results, it is not clear from the literature whether the rate of recurrence is higher in eyes with type 3 lesions

[a]Only patients affected by CNV (classic or occult lesions) or RAP were enrolled in the analysis; [b]n=number of eyes.
CNV, choroidal neovascularization; MNV, macular neovascularization; RAP, retinal angiomatous proliferation.
1. Bochicchio S *et al*. *Ophthalmol Retina* 2019; 3 (1): 27–31; 2. Gross NE *et al*. *Retina* 2005; 25 (6): 713–718; 3. Park YG, Roh Y-J. *BMC Ophthalmol* 2015; 15: 182.

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Clinical challenges

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Clinical challenges requiring guidance

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Classifying subtypes

- What is the best way to characterize the different MNV subtypes?

Treatment

- How should patients be managed according to MNV subtype?

Management

- Is there a clear resource to guide management?

MNV, macular neovascularization.

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Vision Academy recommendations

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BACK TO NEOVASCULAR SUBTYPES

Multimodal imaging is recommended

Multimodal imaging tools should be used in conjunction to accurately classify the lesion as type 1, 2, or 3 or mixed MNV[1,2]

- Imaging modalities should ideally include:
  - Fluorescein angiography
  - Indocyanine green angiography
  - OCT
- The role of OCT-A in making distinctions between the different neovascular subtypes is yet to be clarified – it can help in detecting neovessels when they are not clearly visible on classic examinations but cannot characterize the MNV subtype on its own[3,4]

Lesions can be classified as type 1, 2, or 3 or mixed MNV using multimodal imaging

General consensus

MNV, macular neovascularization; OCT, optical coherence tomography; OCT-A, optical coherence tomography angiography.

1. Freund KB *et al*. *Retina* 2010; 30 (9): 1333–1349; 2. Jung JJ *et al*. *Am J Ophthalmol* 2014; 158 (4): 769–779.e2; 3. Farecki M-L *et al*. *Graefes Arch Clin Exp Ophthalmol* 2017; 255 (5): 913–921; 4. Nakano Y *et al*. *PLoS One* 2019; 14 (4): e0216304.

BACK TO CHALLENGES
BACK TO MNV SUBTYPES

Treating type 1 MNV

An individualized T&E regimen should be used for type 1 MNV

- Type 1 lesions usually require more anti-VEGF injections, but eyes are more likely to maintain vision over time[1,2]
- Type 1 lesions have better outcomes than type 2 or 3 lesions and can be stable for months or years if left untreated[3,4]
- To reduce the burden in patients with type 1 MNV, an individualized T&E regimen should be used
  - Where T&E is not feasible due to resource or organizational constraints, a fixed-dose regimen could be proposed depending on the observed time to recurrence
- Prolonged treatment and observation periods are necessary to avoid the development of PCV and related complications

An individualized T&E regimen is recommended with extended treatment and observation periods

General consensus

MNV, macular neovascularization; PCV, polypoidal choroidal vasculopathy; T&E, treat-and-extend; VEGF, vascular endothelial growth factor.

1. Chae B *et al. Invest Ophthalmol Vis Sci* 2015; 56 (9): 5040–5047; 2. Mrejen S *et al. J Clin Med* 2015; 4 (7): 1380–1402; 3. Polito A *et al. Ann Acad Med Singap* 2006; 35 (3): 145–150; 4. Stevens TS *et al. Arch Ophthalmol* 1997; 115 (3): 345–350.

BACK TO CHALLENGES

Treating type 2 MNV

Type 2 lesions should be treated according to treatment duration

- First 2 years:
  - An intense T&E regimen should be used, extending beyond q12w if possible
- After the first 2 years:
  - The T&E regimen can be pursued
  - Purely type 2 lesions can be managed with careful and frequently monitored PRN treatment (after at least three consecutive q12w intervals without disease reactivation)

Studies have shown that type 2 lesions are more prone to the development of fibrotic scars, which are a risk factor for poor visual outcomes[1-3]

General consensus

MNV, macular neovascularization; PRN, *pro re nata* (as needed); q12w, every 12 weeks; T&E, treat-and-extend.

1. Daniel E *et al*. *Ophthalmology* 2018; 125 (7): 1037–1046; 2. Cohen SY *et al*. *Retina* 2012; 32 (8): 1480–1485; 3. Mrejen S *et al*. *J Clin Med* 2015; 4 (7): 1380–1402.

BACK TO CHALLENGES

Treating mixed lesions

Mixed lesions (with both type 1 and type 2 components) should be treated proactively

- First 2 years:
  - Mixed lesions, with both type 1 and type 2 components, can be monitored using an intense T&E regimen
- After the first 2 years:
  - Mixed lesions can be managed on a case-by-case basis with T&E or careful and frequently monitored PRN treatment (after at least three consecutive q12w intervals without disease reactivation)

General consensus

PRN, *pro re nata* (as needed); q12w, every 12 weeks; T&E, treat-and-extend.

BACK TO CHALLENGES

Treating type 3 MNV

Patients with type 3 MNV should be treated according to the stage of the lesion

- Type 3, stage 1:
  - Patients stable after three initial treatment doses can be kept on a strict (monthly) PRN regimen with contralateral eye checks
  - Patients with non-stable or relapsing MNV can be switched to a proactive (T&E or fixed[a]) regimen
- Type 3, stage 2 or 3:
  - A proactive (T&E or fixed[a]) regimen should be applied

Type 3 lesions tend to be very responsive to anti-VEGF therapy, and treating them early leads to better visual outcomes with fewer recurrences and injections

The occurrence of GA in type 3 lesions is higher than in other lesion types, and the fellow eye frequently develops neovascular complications and should therefore be closely monitored[1,2]

General consensus

[a]**Fixed should not be the treatment regimen of choice but can be used in some instances where T&E is not feasible due to resource or organizational constraints.**
GA, geographic atrophy; MNV, macular neovascularization; PRN, *pro re nata* (as needed); T&E, treat-and-extend; VEGF, vascular endothelial growth factor.
1. Baek J *et al*. *Invest Ophthalmol Vis Sci* 2016; 57 (3): 1500–1505; 2. McBain VA *et al*. *Retina* 2011; 31 (6): 1043–1052.

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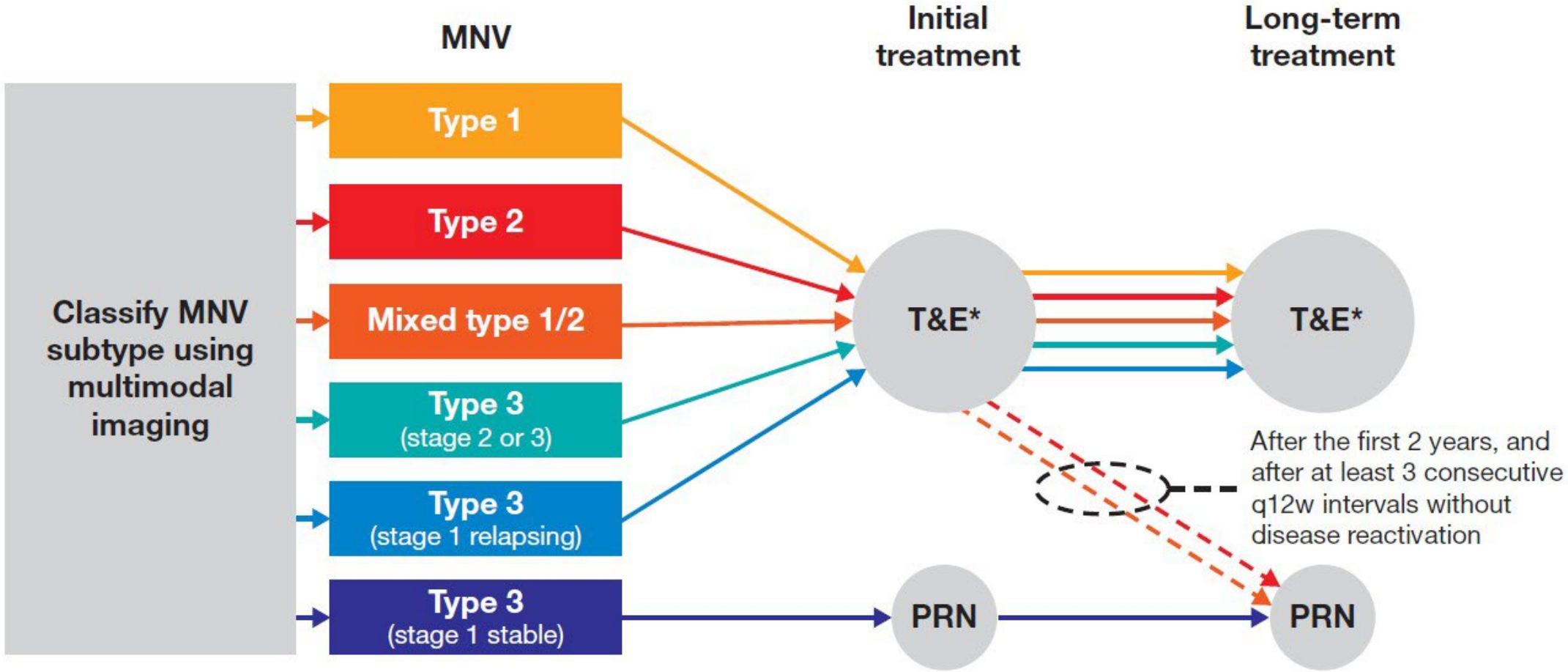
Algorithm on how to tailor the treatment regimen according to MNV subtype



***Fixed should not be the treatment regimen of choice but can be used in some instances where T&E is not feasible due to resource or organizational constraints.**

Mathis T *et al*. *Eye* 2022; https://doi.org/10.1038/s41433-022-02231-y.

MNV, macular neovascularization; PRN, *pro re nata* (as needed); q12w, every 12 weeks; T&E, treat-and-extend.

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Vision Academy recommendations on the characterization of MNV subtypes

- Multimodal imaging, ideally including fluorescein angiography, indocyanine green angiography, and OCT, should be used to accurately classify the lesion as type 1, 2, or 3 or mixed MNV
- Patients with type 1 (occult) MNV should be treated with an individualized T&E regimen to reduce patient burden. These patients should benefit from an extended treatment and observation period to avoid the development of PCV and other related complications
- Patients with type 2 (classic) MNV should be treated with an intensive T&E regimen in the first 2 years to rapidly dry the retina and reduce the risk of developing fibrotic scars. This can be followed by a reduced number of injections after the second year: the T&E regimen can be pursued, purely type 2 lesions can be managed with PRN treatment, and mixed lesions should be maintained on a proactive treatment regimen
- Patients with mixed lesions (with both type 1 and type 2 components) should be treated with an intensive T&E regimen in the first 2 years. Management should then occur on a case-by-case basis, with T&E or careful and frequently monitored PRN treatment (after at least three consecutive q12w intervals without disease reactivation)
- Patients with type 3 (RAP) MNV should be treated according to stage of the lesion: patients with type 3, stage 1 lesions, having reached stability after three loading doses, can be kept on a strict (monthly) PRN regimen with contralateral eye checks. Patients with non-stable or relapsing MNV may be switched to a proactive (T&E or fixed[a]) regimen. Patients with type 3, stage 2 or 3 lesions should be treated with a proactive (T&E or fixed[a]) regimen

[a]**Fixed should not be the treatment regimen of choice but can be used in some instances where T&E is not feasible due to resource or organizational constraints.**
MNV, macular neovascularization; OCT, optical coherence tomography; PCV, polypoidal choroidal vasculopathy; PRN, *pro re rata* (as needed); q12w, every 12 weeks; RAP, retinal angiomatous proliferation; T&E, treat-and-extend.

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Further considerations

The role of OCT-A in distinguishing between MNV subtypes needs to be clarified, but there has been some success in using this technology to define the subtype.[1,2] B-scan OCT can help to define the location and plane of MNV

Longer follow-up studies of treated patients with type 1–3 MNV are necessary to evaluate the evidence of the proposed MNV transformation under anti-VEGF therapy, to evaluate the proposed anti-angiogenic effect of anti-VEGF therapy additional to the anti-permeability effect, and to define specific endpoints of MNV transformation

Further studies are needed to determine the correlation of MNV type and additional visually relevant changes such as PR death and RPE atrophy by analyzing whether eyes with type 3 lesions at high risk of GA might be more safely managed with a PRN regimen, which MNV leads to more RPE atrophy and PR death, and whether these factors can be predicted in order to develop additional therapies

Due to the evolving treatment paradigms for PCV, this vascular abnormality should be considered, especially when the initial imaging is not typical of other MNV subtypes or when treatment outcomes are not as expected

GA, geographic atrophy; MNV, macular neovascularization; OCT, optical coherence tomography; OCT-A, optical coherence tomography angiography; PCV, polypoidal choroidal vasculopathy; PR, photoreceptor; PRN, *pro re nata* (as needed); RPE, retinal pigment epithelial; VEGF, vascular endothelial growth factor.

1. Farecki M-L *et al*. *Graefes Arch Clin Exp Ophthalmol* 2017; 255 (5): 913–921; 2. Nakano Y *et al*. *PLoS One* 2019; 14 (4): e0216304.