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Deliberations of an International Panel of Experts on OCTA Nomenclature of nAMD

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PII: S0161-6420(20)31198-2

DOI: <https://doi.org/10.1016/j.ophtha.2020.12.022>

Reference: OPHTHA 11590

To appear in: *Ophthalmology*

Received Date: 24 September 2020

Revised Date: 8 December 2020

Accepted Date: 16 December 2020

Please cite this article as: Mendonça LSM, Perrott-Reynolds R, Schwartz R, Madi HA, Cronbach N, Gendelman I, Muldrew A, Bannon F, Balaskas K, Gemmy Cheung CM, Fawzi A, Ferrara D, Freund KB, Fujimoto J, Munk MR, Querques G, Ribeiro R, Rosenfeld PJ, Sadda SR, Sahni J, Sarraf D, Spaide RF, Schmidt-Erfurth U, Souied E, Staurenghi G, Tadayoni R, Wang RK, Chakravarthy U, Waheed NK, Deliberations of an International Panel of Experts on OCTA Nomenclature of nAMD, *Ophthalmology* (2021), doi: <https://doi.org/10.1016/j.ophtha.2020.12.022>.

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Running Head: OCTA Nomenclature for Neovascular AMD

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Keywords: optical coherence tomography angiography, neovascular age macular degeneration, macular neovascularization, nomenclature.

Abbreviations: age-related macular degeneration – AMD; intraclass correlation – ICC; macular neovascularization – MNV; neovascular AMD – nAMD; optical coherence tomography – OCT; optical coherence tomography angiography – OCTA; outer retina-choriocapillaris – ORCC; polypoidal choroidal vasculopathy – PCV; retinal angiomatous proliferation – RAP.

This article contains additional online-only material. The following should appear online-only: Table S1, Table S2, Figure S1 and Figure S2.

Human subjects: This study was approved by the Institutional Review Board at Tufts Medical Center and conformed to the tenets of the Declaration of Helsinki.

Funding: *This study was partially funded by a Grant from Fight for Sight, a Research to Prevent Blindness Challenge grant made to the Department of Ophthalmology, Tufts Medical Center and by Massachusetts Lions Club Grant. Luísa S. M. Mendonça was supported with Scholarship provided by Capes Foundation, Ministry of Education of Brazil, in the scope of Capes-PrInt program, process nº 88887.369769/2019-00*

Financial disclosures: **Rhianon Perrott-Reynolds** received travel support from Allergan and honoraria from Novartis. **Roy Schwartz** received travel expenses from Allergan and is a Board member of EyeWise Diagnostics. **Konstantinos Balaskas** is a consultant for Roche and Novartis and receives speaker fees from Novartis, Bayer, Allergan, Alimera, Topcon and Heidelberg Engineering. **Chui Ming Gemmy Cheung** receives grants and speakers' fee from Bayer, Topcon, Zeiss, Novartis, Roche, Boehringer Ingelheim, Allergan. **Amani Fawzi** is a consultant for Regeneron and Boehringer Ingelheim. **Daniela Ferrara** is an employee of Genentech, South San Francisco, CA, USA. **K.B. Freund** is a consultant for Optovue, Heidelberg Engineering, Zeiss, Genentech, Novartis, and Allergan. He receives research support from Genentech/Roche. **James Fujimoto** reports research support from Topcon Corporation. Equity in Optovue. Royalties from intellectual property owned by MIT and licensed to Topcon and Optovue. **Marion R. Munk** receives grant support from Bayer and she is a consultant for Bayer, Novartis, Lumithera, Zeiss, Isarna Therapeutics and Helbling. **Giuseppe Querques** reports personal fees from Alimera Sciences (Alpharetta, Georgia, USA), personal fees from Allergan Inc (Irvine, California, USA), personal fees from Amgen (Thousand Oaks, USA), Boehringer-Ingelheim (Germany) personal fees from Heidelberg (Germany), personal fees from KBH (Chengdu, China), personal fees from LEH Pharma (London, UK), personal fees from Lumithera (Poulsbo, USA), personal fees from Novartis (Basel, Switzerland), personal fees from Bayer Shering-Pharma (Berlin, Germany), personal fees from Sandoz (Berlin, Germany), personal fees from Sifi (Catania, Italy), personal fees from Soof-Fidia (Albano, Italy), personal fees from Zeiss (Dublin, USA), outside the submitted work. **Ramiro Ribeiro** is an employee of Apellis Pharmaceuticals, Inc. **Philip J. Rosenfeld** receives research support from Carl Zeiss Meditec and Stealth BioTherapeutics, and he is a consultant for Apellis, Biogen, Boehringer-Ingelheim, Carl Zeiss Meditec, Chengdu Kanghong Biotech, EyePoint, Ocunexus Therapeutics, Ocudyne, and Unity Biotechnology. Philip Rosenfeld has equity interest in Apellis, Valitor, Verana Health, and Ocudyne. **Srinivas Sadda** is a consultant to Amgen, Allergan, Roche/Genentech, Regeneron, Novartis, Merck, 4DMT, Optos, Heidelberg Engineering, Carl Zeiss Meditec, and Centervue. He

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142 **Abstract**

143 A panel of imaging experts was assembled to review neovascular age-related macular
144 degeneration optical coherence tomography angiography descriptors published to date, and test
145 agreement on use of these terms, which was found to be low.

Optical coherence tomography angiography (OCTA) has been used to identify and characterize macular neovascularization (MNV) secondary to age-related macular degeneration (AMD).¹⁻⁴ Many studies have explored OCTA morphological features of MNV that might serve as biomarkers to assess disease activity and response to treatment.¹⁻⁶ The proliferation of studies however has resulted in an OCTA terminology that has been variable and inconsistent. To address inconsistency of nomenclature and allow harmonization, a multidisciplinary panel of retinal imaging experts with a history of relevant research contributions to the field was assembled with the purpose of reviewing published terminology and to recommend a reduced list of key terms pertinent to OCTA. The group was called UNICORN, because of its ultimate goal of generating a **UN**ified **CO**mentary of the committee of international experts on the nomenclature for **Ne**ovascular AMD in OCTA. In this report we describe the first steps, which included a review of OCTA descriptors of neovascular AMD (nAMD) published to date, and an exercise that tested agreement of these terms among retinal imaging experts.

Prior to the first UNICORN meeting, a non-systematic review of the literature was performed, using the search terms “optical coherence tomography angiography” or “OCT angiography” or “OCT-A”, AND “neovascular macular degeneration” or “neovascular age-related macular degeneration” or “neovascular AMD” or “nAMD” or “wet age-related macular degeneration” or “wet AMD” or “wet ARMD”. A dictionary of OCTA descriptors relating to the features of MNV in AMD was generated and circulated to the panel.

At the first meeting (April 2019), UNICORN group members reviewed the list of descriptive terms on MNV due to AMD culled from the literature. Morphological patterns of MNV complexes have been described by different groups with redundancies, for example “central trunk” or “feeding vessel” both of which are likely to mean the same.^{1, 2, 6} Patterns of vessel

branching (dead tree, sea-fan or tangle) and central and peripheral vascular arrangements within an MNV have also been described.^{1, 2, 6} The group identified three areas of concern: first, terms that overlapped; second, terms that are subjective and difficult to replicate in clinical practice because of the lack of a clear definition; and third, those used to describe lesion activity but without appropriate reproducibility testing.⁵ Using these 3 broad categories the panel created a consensus terminology list, removing terms that were considered weak, poorly defined or redundant (Table S1, available at <https://www.aaojournal.org>).

The need for standardization of OCTA reporting was also discussed, because current reporting practices for display of OCTA images were found to be widely variable in the literature. The panel agreed that the entire volumetric cube of the OCTA, either the 3 x 3 mm or the 6 x 6mm, depending on the size of the lesion, is essential for interpretation and diagnosis of MNV. For future publications in OCTA, the panel recommended a minimum set of images which should include the en face OCTA images showing the relevant slabs that were used for visualization of the MNV, associated OCT B-scans with flow signal overlay and segmentation lines, and en face structural OCT images.

In a preliminary exercise, in order to assess agreement of the terms identified by the panel, 23 cases with or without MNV were circulated to the UNICORN group (See cases details on Table S2, available at <https://www.aaojournal.org>). OCTA images included treatment-naïve and previously treated MNV due to AMD, polypoidal choroidal vasculopathy (PCV) and non-AMD lesions. For feasibility reasons, cases were sent to graders as static sets that included the minimum recommended set of images (Figure S1, available at <https://www.aaojournal.org>). Participants completed a form of 13 dichotomous items for each image set (Table 1, first column). Due to the unbalanced nature of data, a crossed random-effects model partitioned

variation in the data due to images, graders, and residual noise components, generating intraclass correlation coefficients (ICC). As some image sets were considered of suboptimal quality (reflecting data from real-world busy clinics), a sensitivity analysis was carried out by removing this subset of images.

Eleven participants, all experienced retina specialists, completed the grading exercise. The ICCs ranged from 0.079 to 0.550 (Table 1). All items initially showed poor agreement, except for type 1 MNV and PCV, which presented moderate agreement. On the sensitivity analysis, new ICCs ranged from 0.025 to 0.859. Lesions due to nAMD (ICC = 0.52), hyper-mature MNV (0.60) and lesions with vessel profiles at the core (0.53) showed moderate agreement, while PCV lesions showed good agreement (0.86).

Based on the findings from our preliminary exercise, the high number of items achieving only poor or moderate agreement even among retinal imaging experts highlight the difficulties in obtaining consensus and in applying morphological descriptors and subjective grading in this field. Variables such as the device used for image acquisition,⁷ employment of projection artifact removal and segmentation strategy affects MNV appearance. Because MNV lesions have varying characteristics across the different regions of the lesion, descriptive parameters analyzed in this exercise could be considered to be relative rather than absolute. Furthermore, dynamic evaluation of structural OCT with flow overlay may be better at defining MNV type than static en face OCTA images.

Our study has a number of limitations. Firstly, the small sample of images might not be representative of all features being analysed. Furthermore, experts did not have the opportunity to dynamically review images and access the volumetric cube of the OCTA. Also, training was not carried out before the grading exercise.

In conclusion, our preliminary exercise has revealed a lack of agreement on OCTA morphological descriptors. Our next steps (Figure S2, available at <https://www.aaojournal.org>) are to undertake a systematic review of OCTA and develop a consensus list of robust descriptive terms. Secondly, we will create a high-quality database of representative images illustrating key descriptors and use this to develop and validate a methodology for interpretation. This process will guide further UNICORN publications and assist in generating a standardised nomenclature. We envision that integration of reproducible OCTA morphologic patterns as exploratory endpoints into clinical trials may enhance the understanding of disease pathogenesis, activity or response to treatment.

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All images included					Sensitivity analysis			
Item	Proportion of scores that are positive (%)	ICC	#scores	iterations	Proportion of scores that are positive (%)	ICC	#scores	iterations
Central trunk present	23.4%	0.164	233	6	34.1%	0.025	122	7
Lesion border well defined	53.1%	0.476	234	16	73.4%	0.346	121	9
Lesion due to AMD	83.8%	0.465	245	21	82.0%	0.516	127	18
MNV present	92.6%	0.226	243	50	90.6%	0.201	127	50
MNV hyper-mature	23.3%	0.343	206	7	25.9%	0.604	110	32
MNV immature	31.2%	0.079	218	16	27.7%	0.179	115	10
MNV mature	58.8%	0.237	211	5	66.1%	0.373	113	9
Type 1 MNV	71.3%	0.531	231	43	77.2%	0.235	122	50
Type 2 MNV	28.9%	0.422	215	10	23.4%	0.382	113	10
Type 3 MNV	6.9%	0.303	217	50	1.9%	0.060	113	50
PCV / aneurysmal Type 1 MNV	6.7%	0.550	217	34	8.3%	0.859	114	47
Vessel profiles visible in central lesion	58.5%	0.484	236	24	76.6%	0.529	123	37
Vessel profiles visible in peripheral lesion	73.1%	0.408	235	12	84.8%	0.260	122	50

AMD – Age-related macular degeneration; ICC – intraclass correlation; MNV – Macular neovascularization; PCV – Polypoidal choroidal vasculopathy.

Table 1. Column 1 shows the items (descriptors) graded, and columns 3 and 7 show the intraclass correlation reliability measure as estimated using mixed-effects logistic model, before and after sensitivity analysis, respectively. The mean of the individual proportions for each image's non-missing scores that are graded positive, and the number of non-missing scores (# scores) for each descriptor, summed across all graders that was used in the model, are also shown. The number of iterations needed for convergence of the mixed-effects logistic model are presented in columns 5 and 9. When the probability of a positive score was either very high or very low, the model had difficulty converging. Model iterations to convergence were capped at 50.

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