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Machine Learning to Analyze the Prognostic Value of Current Imaging Biomarkers in Neovascular Age-Related Macular Degeneration

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Purpose: To evaluate the potential of machine learning to predict best-corrected visual acuity (BCVA) outcomes from structural and functional assessments during the initiation phase in patients receiving standardized ranibizumab therapy for neovascular age-related macular degeneration (AMD).

Design: Post hoc analysis of a randomized, prospective clinical trial.

Participants: Data of 614 evaluable patients receiving intravitreal ranibizumab monthly or pro re nata according to protocol-specified criteria in the HARBOR trial.

Methods: Monthly spectral-domain (SD) OCT volume scans were processed by validated, fully automated computational image analysis. This system performs spatially resolved 3-dimensional segmentation of retinal layers, intraretinal cystoid fluid (IRF), subretinal fluid (SRF), and pigment epithelial detachments (PED). The extracted quantitative OCT biomarkers and BCVA measurements at baseline and months 1, 2, and 3 were used to predict BCVA at 12 months using random forest machine learning. This approach was also used to correlate OCT morphology to BCVA at baseline (structure–function correlation).

Main Outcome Measures: Accuracy (R^2) of the prediction models; ranking of input variables.

Results: Computational image analysis enabled fully automated quantitative characterization of neovascular lesions in a large-scale clinical SD-OCT data set. At baseline, OCT features and BCVA were correlated with $R^2 = 0.21$. The most relevant biomarker for BCVA was the horizontal extension of IRF in the foveal region, whereas SRF and PED ranked low. In predicting functional outcomes, the model's accuracy increased in a linear fashion with each month. If only the baseline visit was considered, the accuracy was $R^2 = 0.34$. At month 3, final visual acuity outcomes could be predicted with an accuracy of $R^2 = 0.70$. The strongest predictive factor for functional outcomes at 1 year was consistently the individual BCVA level during the initiation phase.

Conclusions: In this large-scale study based on a wide spectrum of morphologic and functional features, baseline BCVA correlated modestly with baseline SD-OCT, whereas functional outcomes were determined by BCVA levels during the initiation phase with a minor influence of fluid-related features. This finding suggests a re-evaluation of current diagnostic imaging features and a search for novel imaging approaches, where machine learning is a promising approach. *Ophthalmology Retina 2017;■:1–7 © 2017 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Supplementary files available at www.ophthalmologyretina.org.

Intravitreal anti–vascular endothelial growth factor (anti-VEGF) therapy is the current standard of care for neovascular age-related macular degeneration (AMD).[1] In the pivotal clinical trials, patients receiving anti-VEGF treatment gained on average 1 to 2 lines in best-corrected visual acuity (BCVA) from baseline at 1 year of therapy.[2,3] However, the functional response to treatment on an individual patient level is markedly heterogeneous and difficult to predict clinically. For instance, in the large-scale Comparison of AMD Treatments Trials, at year 1, roughly 30% of patients showed a BCVA gain of 3 lines or more, whereas about 10% of patients experienced a BCVA loss of 1 line or more.[4] Therefore, to counsel patients appropriately, and also to provide more reliable end points for clinical trials, identification of precise and robust methods to predict BCVA outcomes on an individual patient level represents an important goal of research.

Extensive research efforts have been directed at the discovery of structural parameters ("imaging biomarkers") that would allow a more accurate functional prognosis in the management of neovascular AMD.[5] In general, the BCVA level at baseline has become an established prognostic factor for functional gains and final BCVA outcomes.[5] Although patients with higher initial BCVA achieve, on

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average, less relative BCVA gain than individuals with pronounced pre-existing BCVA loss (a phenomenon known as the "ceiling effect"), best absolute BCVA outcomes are observed in patients with high baseline BCVA. Concerning imaging biomarkers with relevance for vision outcomes, mainly OCT-based features such as the presence and extent of intraretinal cystoid fluid (IRF) or photoreceptor signal loss have been demonstrated to correlate with BCVA outcomes, along with other markers such as size of the choroidal neovascularization (CNV) lesion on fluorescein angiography.[6,7]

Machine learning is a subfield of computer science that constructs automated algorithms to empirically recognize pathognomonic and prognostic patterns in large-scale multivariable datasets, rather than relying on predefined hypotheses.[8] The spectrum of potential variables extracted from different morphologic and functional data sources is therefore unlimited. Methods from this field of artificial intelligence are currently introduced into ophthalmology in a pioneering effort to predict recurrence of disease or therapeutic needs in anti-VEGF therapy, to predict progression in atrophic AMD, but also to construct realistic segmentation algorithms for morphologic features.[9–11]

The aim of this study is to introduce machine learning methodology to, first, correlate morphologic OCT parameters at baseline to the corresponding visual function in active neovascular disease; and second, predict final BCVA levels after 1 year of standardized anti-VEGF therapy from functional and structural parameters acquired during the initiation phase in a large-scale randomized clinical trial setting.

Methods

In this post hoc analysis of a comprehensive clinical trial database, prospectively collected BCVA data and spectral-domain (SD) OCT images of patients enrolled in the HARBOR trial were included.[12] The study was conducted in compliance with the Declaration of Helsinki. Approval was obtained by the Ethics Committee at the Medical University of Vienna as well as at each participating center for the HARBOR trial. Patients provided written informed consent for inclusion into the HARBOR trial. The HARBOR trial is registered at clinicaltrials.gov (identifier NCT00891735).

Study Design and Inclusion and Exclusion Criteria

The study design and main outcomes of the HARBOR trial have been published previously.[12] In brief, patients with treatment-naïve subfoveal CNV secondary to AMD as diagnosed by a retina specialist using fluorescein angiography and SD-OCT were included. Eligibility for the study was confirmed by a central reading center. Patients had to be aged 50 years or older and were eligible if BCVA was between 20/40 and 20/320 (Snellen equivalent). At baseline, all patients were randomized 1:1:1:1 to receive intravitreal ranibizumab 0.5 mg monthly, ranibizumab 0.5 mg pro re nata (PRN; after a 3-monthly initiation phase), ranibizumab 2.0 mg monthly, or ranibizumab 2.0 mg PRN. At each monthly visit, patients underwent BCVA testing using Early Treatment Diabetic Retinopathy Study (ETDRS) charts by certified examiners after formal refraction. SD-OCT was performed by certified operators using the Cirrus HD-OCT III instrument (Carl Zeiss Meditec, Dublin, CA), having 512 × 128 × 1024 voxels with a size of 11.7 × 47.2 × 2.0 μm^3, covering a volume of 6 × 6 × 2 mm^3.

Computational Image Analysis

Of the HARBOR dataset (n = 1095), 70% were randomly selected for analysis. The remaining 30% were kept for future studies. All SD-OCT images from baseline to month 3 underwent a standardized analysis for imaging biomarkers at a certified reading center (Vienna Reading Center, Vienna, Austria). A validated, fully automated computational image analysis

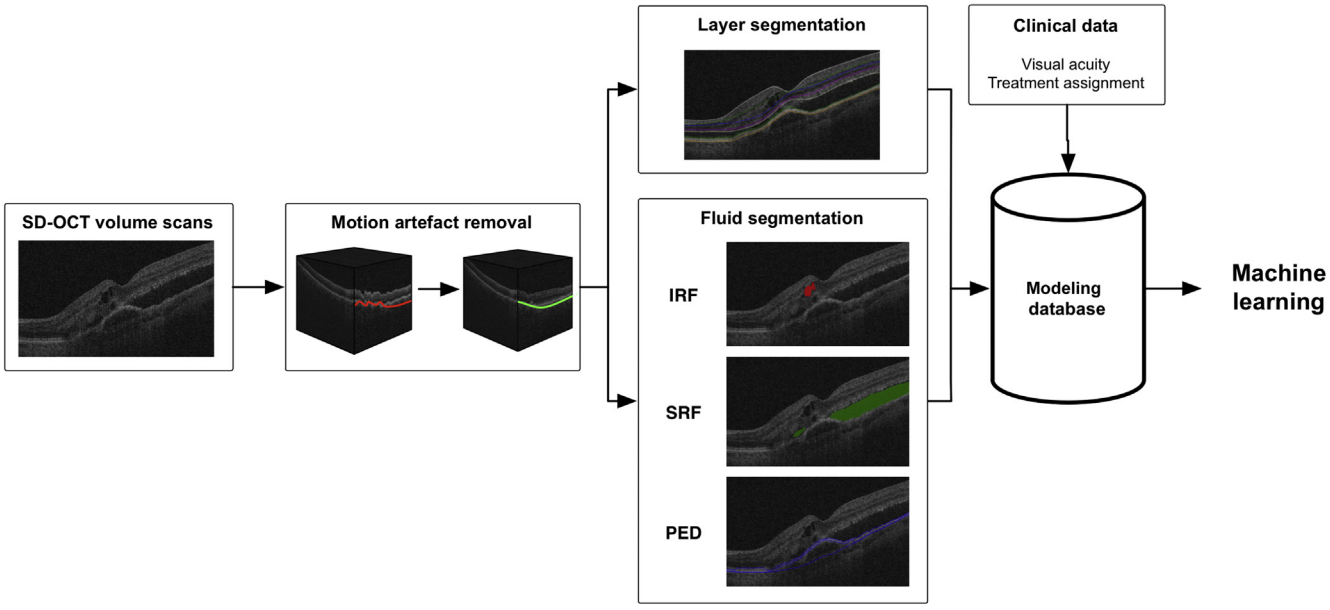

Figure 1. Image analysis pipeline. IRF = intraretinal fluid; PED = pigment epithelial detachment; SRF = subretinal fluid.