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Deep Learning–Based Algorithms in Screening of Diabetic Retinopathy: A Systematic Review of Diagnostic Performance

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Topic: Diagnostic performance of deep learning–based algorithms in screening patients with diabetes for diabetic retinopathy (DR). The algorithms were compared with the current gold standard of classification by human specialists.

Clinical Relevance: Because DR is a common cause of visual impairment, screening is indicated to avoid irreversible vision loss. Automated DR classification using deep learning may be a suitable new screening tool that could improve diagnostic performance and reduce manpower.

Methods: For this systematic review, we aimed to identify studies that incorporated the use of deep learning in classifying full-scale DR in retinal fundus images of patients with diabetes. The studies had to provide a DR grading scale, a human grader as a reference standard, and a deep learning performance score. A systematic search on April 5, 2018, through MEDLINE and Embase yielded 304 publications. To identify potentially missed publications, the reference lists of the final included studies were manually screened, yielding no additional publications. The Quality Assessment of Diagnostic Accuracy Studies 2 tool was used for risk of bias and applicability assessment.

Results: By using objective selection, we included 11 diagnostic accuracy studies that validated the performance of their deep learning method using a new group of patients or retrospective datasets. Eight studies reported sensitivity and specificity of 80.28% to 100.0% and 84.0% to 99.0%, respectively. Two studies report accuracies of 78.7% and 81.0%. One study provides an area under the receiver operating curve of 0.955. In addition to diagnostic performance, one study also reported on patient satisfaction, showing that 78% of patients preferred an automated deep learning model over manual human grading.

Conclusions: Advantages of implementing deep learning–based algorithms in DR screening include reduction in manpower, cost of screening, and issues relating to intragrader and intergrader variability. However, limitations that may hinder such an implementation particularly revolve around ethical concerns regarding lack of trust in the diagnostic accuracy of computers. Considering both strengths and limitations, as well as the high performance of deep learning–based algorithms, automated DR classification using deep learning could be feasible in a real-world screening scenario.

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Fellow Eye Status Is a Biomarker for the Progression Rate of Geographic Atrophy: A Systematic Review and Meta-analysis

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Topic: Systematic review and meta-analysis of how fellow eye status predicts the progression rate of geographic atrophy (GA).

Clinical Relevance: The status of age-related macular degeneration (AMD) in the fellow eye has been used as an indicator of the GA progression rates in primary eyes, but the reported growth rates vary widely in prior clinical studies.

Methods: We searched MEDLINE, EMBASE, Cochrane Library, Clinicaltrials.gov, and PubMed up to September 12, 2018, for studies that classified treatment-naive GA patients based on different AMD manifestations in the fellow eyes and that monitored GA progression in the primary eyes. Three fellow eye statuses were analyzed: (1) no GA or choroidal neovascularization (CNV) in the fellow eye, (2) GA in the fellow eye, and (3) CNV in the fellow eye. To account for the patients' different entry times, we introduced a horizontal translation factor to shift each dataset within each group. We determined the translation factor by adjusting it 1 month at a time until the r^2 in weighted least squares regression (r^2_{WLS}) was maximized for the cumulative linear trend line of all datasets. Heterogeneity and study quality were assessed using the I^2 statistic and Newcastle–Ottawa scale, respectively. Publication bias was evaluated by funnel plots, the Egger test, and the Begg test.

Results: We included 9 studies with 2134 eyes from 1835 patients. After the introduction of translation factors, the datasets in each fellow eye group fit along a straight line with a high r^2_{WLS}. The GA radius growth rate in fellow eyes with GA (0.179±0.003 mm/year) and fellow eyes with CNV (0.159±0.015 mm/year) was significantly higher than that in fellow eyes without GA or CNV (0.110±0.009 mm/year; $P < 0.001$ and $P = 0.02$, respectively). We found no significant difference in the GA radius growth rates between fellow eyes with GA and fellow eyes with CNV ($P = 0.42$).

Conclusions: We confirmed that the presence of advanced AMD in the fellow eye, defined as GA or CNV, can serve as a biomarker of the GA enlargement rate in the primary eye. This may assist the design of clinical trials and may shed light on the natural history of GA expansion.

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Distribution of OCT Features within Areas of Macular Atrophy or Scar after 2 Years of Anti-VEGF Treatment for Neovascular AMD in CATT

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Purpose: Macular atrophy and scar increase in prevalence during treatment for neovascular age-related macular degeneration and are associated with poor visual acuity. We sought to identify the distribution of spectral-domain OCT (SD-OCT)-determined features and subretinal lesion thicknesses at sites of macular scar or atrophy after 2 years of treatment in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT).

Design: Cross-sectional analysis.

Participants: CATT participants with SD-OCT, color photographic (CP) and fluorescein angiogram (FA; CP/FA) images at year 2.

Methods: Sixty-eight study eyes at year 2 in CATT were selected based on image quality and CP/FA determined predominant presence of the following: geographic atrophy (GA, n = 25), non-GA (NGA, n = 44), fibrotic scar (FS, n = 26), or non-FS (NFS, n = 7). The CP/FA components were delineated by CP/FA readers; SD OCT morphologic features and thicknesses were delineated by OCT readers. Using custom software and graphic user interfaces, images were registered, overlaying features and components per pixel; differences were analyzed across groups.

Main Outcome Measures: OCT features, CP/FA components, and retinal and subretinal lesion thicknesses at each pixel of regional overlays.

Results: SD-OCT assessment of registered areas of pathology revealed the following: (1) retinal pigment epithelium atrophy (with or without residual lesion material) covered 75% of pixels designated as GA, 22% of NGA, 24% of NFS, and 46% of FS ($P < 0.001$). (2) Photoreceptor layer thinning covered 85% of GA, 42% of NGA, 33% of NFS, and 59% of FS ($P < 0.001$). (3) Subretinal lesion features covered 31% of GA, 42% of NGA, 85% of NFS, and 92% of FS ($P < 0.001$). Mean thickness of the subretinal lesion complex (measured in microns ± standard deviation) differed among GA (48±25 μm), NGA (61±35 μm), NFS (83±17 μm), and FS (151±74 μm) ($P < 0.001$). In eyes with GA, the thickness was greater in areas with residual lesion (51.4±27 μm) than in those without (27.2±9 μm).

Conclusions: Retinal pigment epithelium atrophy and photoreceptor layer thinning are common not only in areas of macular atrophy but also in areas of FS. Photoreceptor loss extends beyond the areas of clinically apparent atrophy and FS. Subretinal lesion components were common in areas of scar, but they were also present in nearly one-third or more of areas of macular atrophy.

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Imaging Characteristics of Choroidal Neovascular Lesions in the AREDS2-HOME Study: Report Number 4

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Purpose: To characterize choroidal neovascular (CNV) lesions and the corresponding change in visual acuity (VA) in eyes that converted to neovascular age-related macular degeneration (AMD) in the Age-Related Eye Disease Study 2−HOme Monitoring of the Eye Study. (AREDS2−HOME Study).

Design: Cohort study.

Participants: A total of 1520 participants at risk of developing CNV were enrolled, each of whom contributed 1 or both study eye(s) that had a best-corrected VA letter score of ≥54 letters (Snellen equivalent 20/60) and ≥1 large (≥125 mm) macular druse in the absence of neovascular AMD or central geographic atrophy.

Methods: A multicenter clinical trial comparing standard care (SC) versus SC plus ForeseeHome (FH; Notal Vision, Manassas, VA) monitoring strategy in the detection of neovascular AMD. Fluorescein angiograms (FA) and OCT were evaluated by an independent reading center (RC) from the visit in which the ophthalmologist identified progression to CNV (n = 82 eyes).

Main Outcome Measures: Development of CNV on OCT, FA, or both.

Results: The RC confirmed CNV in 67 of 82 eyes (82%); lesions were confirmed in 42 of 70 eyes (60%) with FA, 59 of 72 eyes (82%) with OCT, and on both images in 34 of 67 eyes (51%). Among the FA-confirmed cases, the median lesion size was 0.82 disc area (DA); lesions were subfoveal in 40.5%, occult CNV composition was present in 54.8%, and associated hemorrhage in 50%. Median (interquartile range [IQR]) lesion size on FA was 0.23 (0.0−0.91) DA versus 0.70 (0.0−1.50) DA, $P = 0.051$) in the FH and SC eyes, respectively. Among the OCT-confirmed cases median (IQR) center point thickness was 209 (175−274) μm, retinal pigment epithelial lesion complex was present in 86.4%, and subretinal fluid (SRF) was present in 76.3%. The median change in VA from baseline was −4.0 letters and −10.0 letters in the FH and SC eyes ($P = 0.008$) confirmed as CNV at the RC.

Conclusions: Incident CNV lesions were more prevalent on OCT images than on FA; however, the use of both OCT and FA enhanced detection of incident lesions. Lesions were smaller and associated with less vision loss among eyes in the FH group.

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Driving and Visual Acuity in Patients with Age-Related Macular Degeneration

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Purpose: To assess driving status, habitual visual acuity (VA) in the better-seeing eye, and self-reported driving difficulty among patients diagnosed with age-related macular degeneration (AMD).

Design: Cross-sectional cohort study of 553 AMD patients' habitual VA, self-reported driving status, and driving difficulty at time of interview.

Participants: Patients diagnosed with AMD and recruited into the University of Colorado registry.

Methods: Measurement of habitual VA by median logarithm of the minimum angle of resolution (logMAR) and Snellen equivalent, as well as 3 categories: 20/40 or better, 20/50 or 20/60, and worse than 20/60. Driving difficulty was self-reported on the 25-item National Eye Institute Visual Function Questionnaire.

Main Outcome Measures: Self-reported driving status and driving difficulty.

Results: A total of 394 patients (71.2%) reported currently driving at time of study interview. Drivers were significantly younger than nondrivers (mean age, 76.7 years vs. 83.9 years; $P < 0.0001$) and were more likely to be men (42.6% vs. 25.8%; $P = 0.0002$). Median habitual VA in the better-seeing eye was better among drivers: 0.097 logMAR (Snellen equivalent, 20/25) versus 0.301 logMAR (Snellen equivalent, 20/40) for nondrivers ($P < 0.0001$). Among drivers, habitual VA was 20/40 or better for 87.6% of patients, 20/50 to 20/60 for 9.6% of participants, and worse than 20/60 for 2.8% of participants. Driving patients with habitual VA in the better-seeing eye of 20/40 or better reported less difficulty driving compared with patients with 20/50 or worse VA.

Conclusions: In our study, most patients with AMD who were currently driving had at least 20/40 VA in the better-seeing eye. However, 12.4% of patients had VA of 20/50 or worse and reported more difficulties with driving. As the aging population continues to grow with increasing lifespan, the number of patients with AMD will increase, and discussion of driving and VA will become more clinically and legally pertinent.

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Accuracy of Detection and Grading of Diabetic Retinopathy and Diabetic Macular Edema Using Teleretinal Screening

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Purpose: To determine the accuracy of a county teleretinal screening program of detecting referable diabetic retinopathy (DR) and treatable diabetic macular edema (DME), as well as to evaluate patient compliance with clinic follow-up after referral from teleretinal screening.

Design: Retrospective observational study.

Participants: Patients in the Harris Health System (HHS, Houston, TX) older than 18 years of age who underwent teleretinal screening between July 2014 and July 2016.

Methods: Teleretinal imaging (TRI) consisting of single-field 45-degree nonmydriatic color fundus photography with referral thresholds of severe nonproliferative DR, proliferative DR, and significant DME. Teleretinal imaging results for all referred subjects were obtained and cross-referenced with dilated fundus examination findings with regard to DR severity and the presence of DME. Follow-up status was also noted. Subjects underwent OCT if deemed necessary by the examining specialist. Agreement between TRI and dilated fundus examination (DFE) findings was determined by calculating the Cohen κ coefficient.

Main Outcome Measures: The primary outcome measure is agreement between TRI results and DFE findings with regard to DR severity and the presence of DME. The secondary outcome measure is compliance with follow-up.

Results: Of 1767 patients who were screened and referred for clinical examination, 935 (52.9%) attended their clinic appointment. Overall agreement between DFE and TRI was moderate (weighted κ 0.45) in terms of DR severity. There was agreement within one DR severity level in 86.2% of patients. The positive predictive value for detecting referable disease was 71.3%. Of patients referred for DME, 30.4% were deemed to have treatable DME.

Conclusions: The HHS teleretinal screening program demonstrates a high level of accuracy in the detection and classification of referable DR, but a lesser degree of accuracy in the detection of treatable DME. Only slightly more than half of participants were compliant with follow-up after a TRI referral. This large-scale study provides insight into the utility of teleretinal screening in a county health care system.

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Longitudinal Wide-Field Swept-Source OCT Angiography of Neovascularization in Proliferative Diabetic Retinopathy after Panretinal Photocoagulation

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Purpose: Wide-field swept-source (SS) OCT angiography (OCTA) was compared with ultrawide-field (UWF) fluorescein angiography (FA) for evaluating neovascularization (NV) before and after panretinal photocoagulation (PRP) in eyes with treatment-naive proliferative diabetic retinopathy (PDR).

Design: Prospective, observational, consecutive case series.

Participants: Patients with treatment-naive PDR.

Methods: Patients were imaged using the SS OCTA 12 × 12-mm field of view (PLEX Elite 9000; Carl Zeiss Meditec, Inc, Dublin, CA) at baseline and at 1 week, 1 month, and 3 months after PRP. Select eyes were imaged with 5 SS OCTA 12 × 12-mm scans to create posterior pole montages. Ultrawide-field fundus photography and UWF FA were obtained at baseline and 3 months after PRP.

Main Outcome Measures: Neovascularization visualized using wide-field SS OCTA and UWF FA.

Results: From January through May 2018, wide-field SS OCTA was performed on 20 eyes with treatment naïve PDR from 15 patients. The en face SS OCTA 12 × 12-mm vitreoretinal interface (VRI) slab images showed NV at baseline in 18 of 20 eyes (90%). Of the remaining 2 eyes, the posterior pole montage captured peripheral NV in one eye, and in the other eye, no evidence of NV was detected with either UWF FA or SS OCTA. After PRP, both SS OCTA and FA demonstrated similar progression or regression of NV, but SS OCTA provided more detailed visualization of the vascular changes.

Conclusions: Neovascularization in PDR can be identified at baseline and imaged serially after PRP using wide-field SS OCTA. In patients with a high clinical suspicion for PDR, wide-field SS OCTA likely will be the only imaging method needed for diagnosis and longitudinal evaluation of NV.

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Yearly Treatment Patterns for Patients with Recently Diagnosed Diabetic Macular Edema

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Purpose: To describe the treatment patterns and the predictors of different treatment standards in recently diagnosed diabetic macular edema (DME) patients in a nationally representative sample.

Design: A retrospective cohort study using administrative claims data from January 1, 2007, through March 31, 2015. Patients were grouped into yearly cohorts.

Participants: A total of 96 316 patients were included.

Methods: Patients with a diagnosis of DME were identified using International Classification of Diseases, Ninth Edition, Clinical Modification, codes. Predictors of anti−vascular endothelial growth factor (VEGF) use and number of anti-VEGF injections per patient were assessed using generalized linear regression (logistic and negative binomial, respectively), and yearly trends in different treatments were analyzed with Mann-Kendall tests.

Main Outcome Measures: Predictors of anti-VEGF treatment and of anti-VEGF injections per patient and the changes in relative use of DME therapies per cohort.

Results: Among those with any treatment, the odds of being prescribed anti-VEGF therapy increased by 700% from 2009 to 2014 and by 154% for those seen by a retina specialist. Those in the cohort of year 2014 received 3.5 times more injections than those in 2009, whereas those covered by Managed Medicare, Medicaid, and Medicare received 31%, 24%, and 11% less injections. Anti-VEGF were 11.6% of all DME treatments in 2009 increasing to 61.9% in 2014, while corticosteroids and focal laser procedures dropped from 6.1% to 3% and 75% to 24%, respectively. Procedures per patient (PPP) were much lower than those observed in clinical trials of anti-VEGF. Procedures per patient increased in the cases of aflibercept (from 1 in 2011 to 2.20 in 2014), bevacizumab (from 1.84 in 2009 to 3.40 in 2014), and ranibizumab (from 3.11 in 2009 to 4.48 in 2014), whereas applications of laser procedures and corticosteroids per patient remained roughly stable.

Conclusions: Year of diagnosis and being seen by a retina specialist were important predictors of receiving anti-VEGF therapy, and after one received such therapy, the number of additional injections was smaller for those with government-provided insurance. Anti-VEGF therapy has become a mainstay in DME treatment, with PPP, although relatively low, also increasing.

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Reflectance and Thickness Analysis of Retinal Layers in Patients with Epiretinal Membranes Using Spectral-Domain OCT before and after Vitrectomy with Membrane Peeling

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Purpose: To compare thickness and reflectance of retinal layer findings in patients with idiopathic epiretinal membranes (ERMs) before and after surgery with those of normal controls.

Design: Retrospective study.

Participants: Patients with ERMs before and after surgery and healthy controls.

Methods: Spectral-domain (SD) OCT imaging of eyes with ERMs before and after surgery and of healthy eyes were analyzed for morphologic appearance and using a customized algorithm to measure retinal layer reflectance and thickness. Findings were correlated with visual acuity outcomes.

Main Outcome Measures: Retinal layer thickness and reflectance.

Results: Thirty-four ERM and 12 healthy eyes were identified. Mean preoperative best-corrected visual acuity (BCVA) improved from 0.53±0.31 logarithm of the minimum angle of resolution (logMAR; Snellen equivalent, 20/68) to 0.41±0.25 logMAR (Snellen equivalent, 20/51) after surgery ($P = 0.030$). Differences in reflectance and thickness of retinal layers were identified among the preoperative ERM, postoperative ERM, and healthy eyes. High preoperative reflectance of the internal limiting membrane (ILM) to outer plexiform layer (OPL) was correlated with better postoperative BCVA ($r = -0.451$; $P = 0.007$). A larger improvement in BCVA was correlated with preoperative thick measurements of the outer nuclear layer ($r = 0.514$; $P = 0.002$), high reflectance of the group of layers from the ILM to the OPL ($r = 0.426$; $P = 0.012$), and low reflectance of the photoreceptor layer ($r = -0.453$; $P = 0.007$). Using linear regression analysis, better postoperative BCVA was associated with better preoperative vision (standardized regression coefficient, 0.553; $P = 0.001$) and high reflectance of the group of layers from the ILM to OPL (standardized regression coefficient, −0.526; $P = 0.001$). A larger improvement in BCVA was associated with worse preoperative BCVA (standardized regression coefficient, −0.539; $P < 0.001$) and high reflectance of the group of layers from the ILM to OPL (standardized regression coefficient, −0.428; $P = 0.001$).

Conclusions: Quantitative differences in reflectance and thickness among preoperative, postoperative, and normal SD OCT imaging allow assessment of retina layer changes secondary to ERMs. High reflectance of the ILM to OPL correlated with and was associated with better postoperative BCVA and improvement in BCVA.

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